Diagnostic Strategy for Bone Tumours

Jacob Bickels

Abstract

Bone tumours are relatively rare and their diagnosis requires a staged multidisciplinary approach using clinical, radiographic, and histological analyses, when required. Patient's history and plain radiographs remain the key factors in establishing the correct diagnosis in the majority of these cases. Anatomical location of the lesion, pattern of bone destruction, and nature of the tumoural matrix can be assessed by plain radiographs and allow categorization of most lesions. Biopsy, when required, should be performed only at the conclusion of the clinical and radiological staging.

Identifying the histological type of a bone tumour is a critical step for its diagnosis and management. The differential diagnosis of a musculoskeletal neoplasm must be precise, and it is achieved by a staged multi-disciplinary approach using clinical, radiographic, and histological analyses, as appropriate. In a 1958 publication, Jaffe stated that a biopsy should be regarded as the final diagnostic procedure, not as a shortcut to diagnosis, and that biopsy must be preceded by careful clinical evaluation and analysis of the imaging studies [9]. The final diagnosis of a musculoskeletal lesion is based on those three parameters, and it must be questioned when all three do not match [1, 9]. Bone tumours are classified as either benign (latent, active, or aggressive – Table 1) or malignant (primary malignant tumours of bone or metastatic lesions).

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Biological Behaviour of Bone Tumours

Bone tumours are relatively rare and include a wide spectrum of histological types, ranging from lesions that usually heal spontaneously and convert to normal bone tissue (e.g., non-ossifying fibroma) to neoplasms that invade and destroy neighboring tissues and organs, metastasize early

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Table 1 Stages of benign musculoskeletal neoplasms

Latent	Remains static or heals spontaneously	Non-ossifying fibroma Enchondroma Osteochondroma
Active	Progressive growth but limited by natural barriers	Fibrous dysplasia Osteoid osteoma
Locally aggressive	Progressive growth, not limited by natural barriers	Giant cell tumor Aneurysmal bone cyst Osteoblastoma Chondroblastoma Chondromyxoid fibroma Eosinophilic granuloma

during the course of the disease and ultimately become life-threatening (e.g., Ewing's sarcoma). Tumours that arise from the mesenchymal elements of the musculoskeletal system exhibit certain characteristics that set them apart from other groups. Although each histological type has its own peculiar microscopic appearance, all histological types share some features in their biological behaviour, which reflect their common derivation.

Benign bone tumours grow in a centripetal fashion and spread as a ripple on a pond. The most immature tissue is found at the growing edge, i.e., at the periphery of the tumour. Lesions arising within bone are encapsulated by the fine connective tissue elements of the marrow, the endosteum, and periosteum. As the lesion extends along paths of least resistance between trabeculae and along haversian canals, the tumour remains separated from the bone by a thin, compressed layer of fibrous connective tissue. The presence of the tumour triggers a mesenchymal response at its periphery: the mesenchymal proliferation surrounding an intra-osseous lesion will mature unto reactive bone, whereas the mesenchymal response will be fibrous if the lesion penetrates into the soft tissues. This reactive tissue forms a pseudocapsule. Pseudocapsules associated with high-grade sarcomas may be invaded by nodules of neoplastic cells known as "satellites". High-grade sarcomata may also present with tumour nodules that grow outside the reactive rim but within the same anatomical compartment in which the lesion is located ("skip lesions") (Fig. 1) [7]. Unlike sarcomata, carcinomas usually infiltrate, rather than push, the surrounding tissues and ordinarily do not induce the

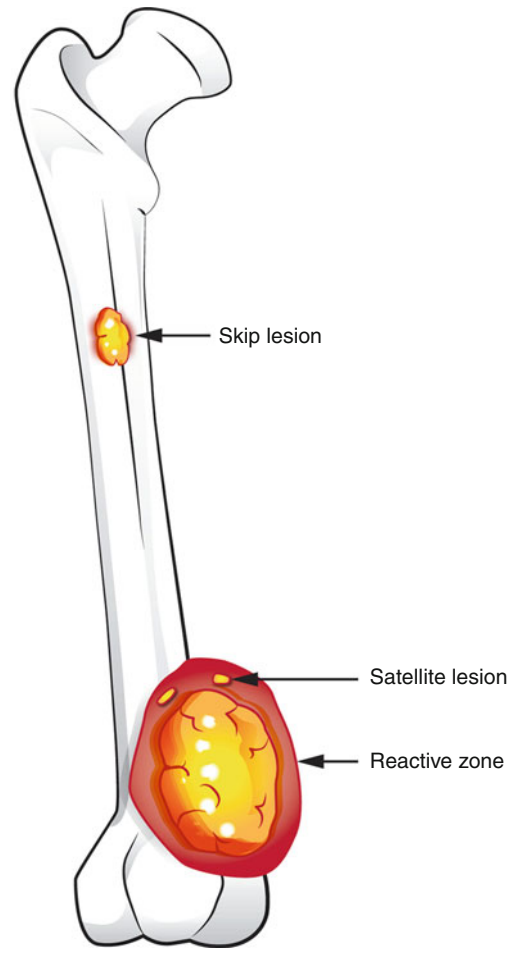

Fig. 1 Growth pattern of bone sarcomata. Sarcomata grow in a centripetal fashion, with the most immature part of the lesion at the growing edge. A reactive zone is formed between the tumour and the compressed surrounding normal tissues and may be invaded by tumour nodules that represent micro extensions of tumour (satellites) and not a metastatic phenomenon. High-grade sarcomas may present with tumour nodules that grow outside the reactive zone ("skip lesions") but within the same anatomical compartment in which the lesion is located

formation of a reactive zone and pseudocapsule. Metastatic disease from bone sarcomata is site-specific, first manifested by lung involvement in its early stage and by bone involvement later on.

Clinical and Radiological Evaluation

The age of the patient is associated with the nature of a given bone lesion. For example, primary sarcomata of bone are usually diagnosed in the second decades of life, while a destructive bone lesion in patients older than 50 years should be considered as being metastatic until proven otherwise. Latent bone lesions can be detected as incidental findings at any age: non-ossification of the distal femur may be detected on plain radiographs of the knee of a 9-year-old boy following a trauma to that site, while enchondroma at the same location may be detected on plain radiographs of a 60-year-old female.

Latent bone lesions are mostly asymptomatic and are usually detected incidentally on an imaging study done for another purpose. In contrast, benign-aggressive and malignant bone tumours are associated with pain that is distinctive by having an insidious onset that gradually becomes unremitting, progressive, and unresponsive to change in position or bed rest in most cases [2]. When these tumours are located in the pelvic girdle and lower extremities, the pain may be exacerbated upon weight-bearing and ambulation.

Despite advances in imaging techniques, a plain radiograph remains the key study in evaluating the nature of a given bone lesion. The cardinal principle in the diagnosis of solitary bone lesions is that the radiological appearance reflects the underlying pathology of the abnormal tumour tissue and its interplay with the host bone. All bone lesions can be described by the following parameters:

1. anatomical location,
2. interaction with the host bone, and
3. the characteristics of their matrix. Based on those features, it was claimed that the categorization of a lesion (latent, benign-aggressive, and malignant) and even its specific histological type can be made by a computer or telephonically without the diagnostician having to see the actual radiological image [12].

Anatomical Location

The anatomical location of the lesion within the host bone can be described as being confined to either the epiphysis, metaphysis, or diaphysis. Specific lesions have a typical anatomical location within the host bone: enchondroma is typically located within the diaphysis, osteochondroma and osteosarcoma in the metaphysis, giant cell tumour in the metaphyseal-epiphyseal region, and chondroblastoma in the epiphysis (Fig. 2).

Interaction with the Host Bone

A given bone lesion's interaction with its host bone is evaluated by two parameters: the pattern of bone destruction (e.g., geographic, permeative, or moth-eaten) and the nature of bone reaction at the host bone-lesion interface.

Pattern of Bone Destruction

In a *geographic* pattern of bone destruction, the tumour creates a large and well-circumscribed hole in the bone which is surrounded by normal spongy bone (Fig. 3). A *moth-eaten* pattern appears as multiple and confluent lytic areas (Fig. 4). In a *permeative* pattern, the spongy bone and adjacent cortices are invaded by numerous very small lytic lesions that do not modify their gross contours on imaging (Fig. 5). There generally is a correlation between the pattern of bone destruction and the rate of tumour growth, with the geographic pattern having been shown as being consistent with slow growth, the permeative pattern consistent with the most rapid rate, and the moth-eaten pattern consistent with an intermediate growth rate [12, 13].

Response of the Host Bone

The presence of a tumour within the host bone may induce a reparative process at its periphery. Reparative reactions are usually limited to cancellous bone, but they may also occur in the cortex

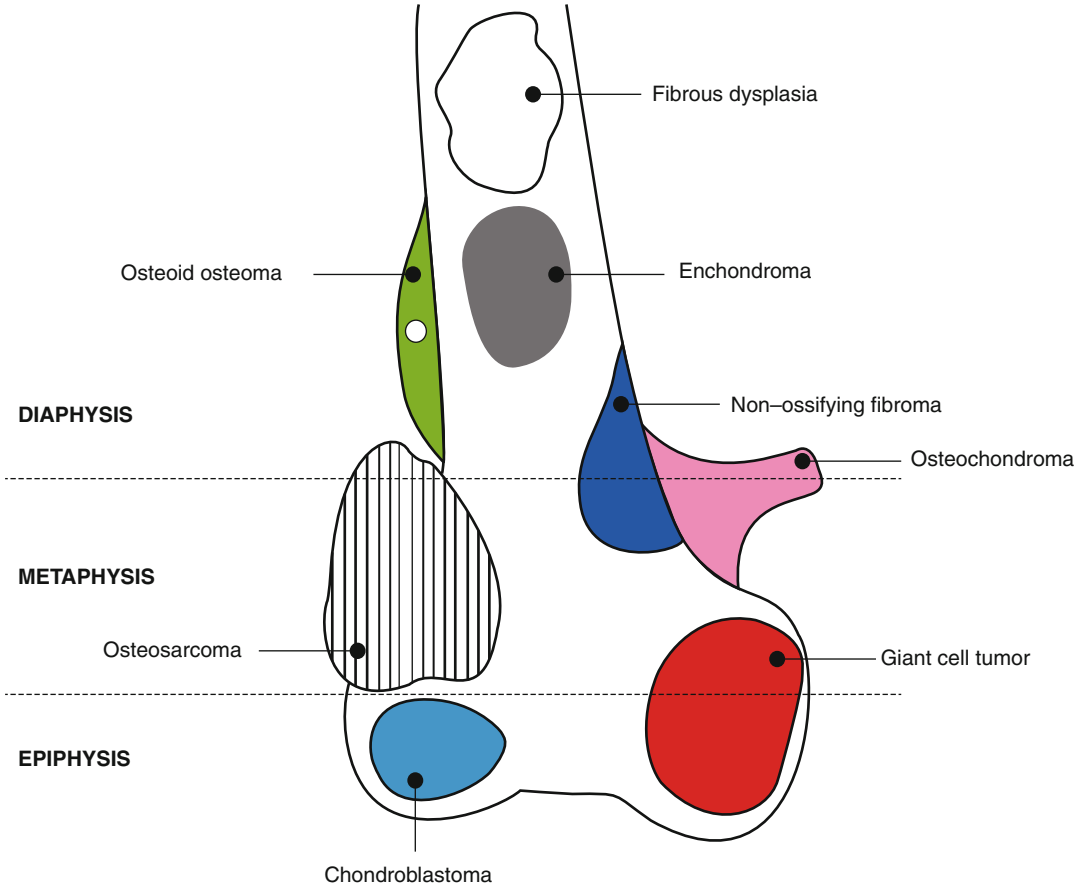

Fig. 2 The anatomical location of the lesion within the host bone can be a clue to its histological type

and in the overlying periosteum. As the tumour grows within the medullary cavity, the adjacent cancellous bone and inner surface of the cortex are resorbed by osteoclastic activity. The formation of new bone along the surface of the lesion is induced as the result of reciprocal and enhanced osteoblastic activity. In a latent or very slow-growing lesion, this osteoblastic activity results in the formation of a clear and thick sclerotic rim around the lesion (Fig. 6). Lesions that grow at a moderate pace allow a remodelling process that results in the expansion of the contour of the host bone, thus creating an expanded cortical shell (Fig. 7). Rapidly growing tumours erode the surrounding bone and do not provide the time required for new bone formation, resulting in the loss of the cortex and the characteristic patterns of a periosteal reaction, which is another form of host-bone response.

The periosteum is a labile structure that is capable of responding to pressure from an advancing tumour or from the presence of actual tumoral tissue by depositing new bone. The radiographic patterns of this osteoblastic response reflect the rate of aggressiveness of the process. Slow-growing tumours provoke the formation of a solid buttress of bone at their borders under the periosteum. More rapid growth of a tumour penetrating through an eroded cortex stimulates the formation of a lamellated periosteal new bone that may be either parallel to the cortical surface (“onion-skin”) or perpendicular to it (“spiculated” or “sun-ray”). The latter pattern usually indicates very aggressive tumour growth. In rapidly advancing neoplastic processes with cortical destruction and periosteal elevation of considerable degree, the separation of the periosteum

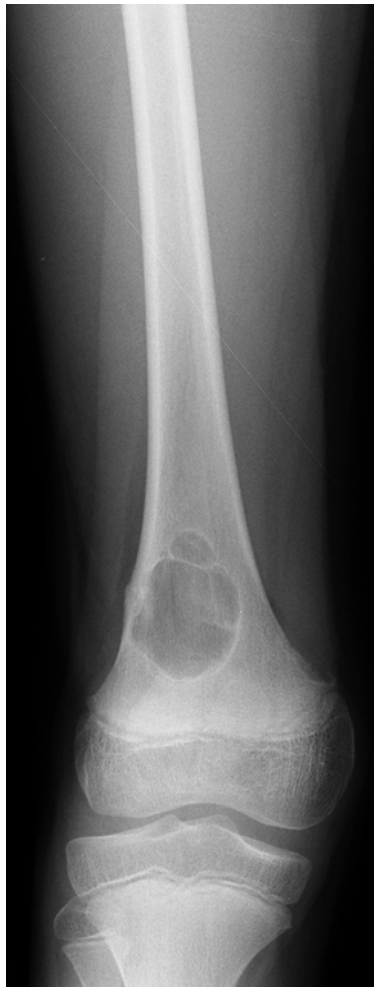

Fig. 3 Plain radiograph of the distal femur showing non-ossifying fibroma, causing a *geographic* pattern of bone destruction

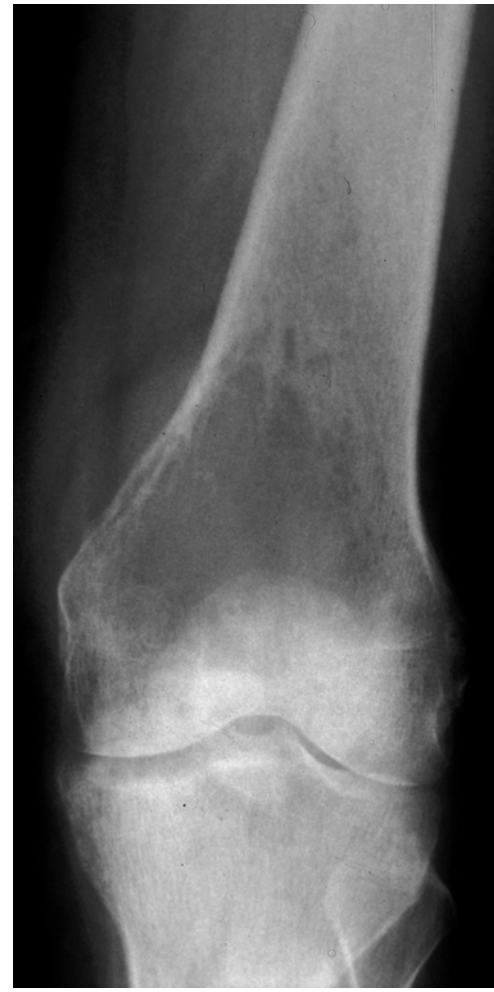

Fig. 4 Plain radiograph of the distal femur showing multiple myeloma, causing a *moth-eaten* pattern of bone destruction

from the still-intact cortex forms an acute angle with an open end towards the tumour's epicenter (Codman's triangle). This is most often present in malignant lesions and is an indicator for rapid cortical penetration with periosteal detachment (Fig. 8).

Tumour Matrix

The matrix of a mesenchymal tumour, which is its intercellular product, may assist in its correct identification. The matrix can accept mineral deposition in the form of calcification or ossification, thus allowing the distinction between bone- and cartilage-forming lesions. It is usually possible to differentiate between cartilage and bone matrix mineralization by the presence of stippled focal densities or as rings or arcs of peripheral calcifications in more lobulated cartilage areas. Osteoid mineralization can usually be recognized as amorphous densities when the bone is immature, or when it is trabecular in when ossification is more advanced. An extensively ossified matrix is referred to as a blastic lesion, and a lytic lesion is one in which the matrix has little or no ossification (Fig. 9). Fibrous dysplasia has a typical ground-glass matrix, which is the result of a mix-

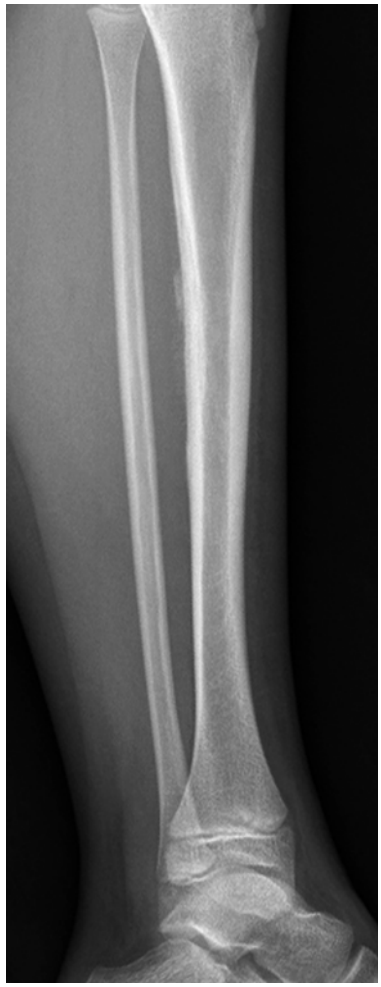

Fig. 5 Lateral plain radiograph of the leg showing Ewing's sarcoma of the mid-tibial diaphysis, causing a *permeative* pattern of bone destruction

ture of bone and fibrous elements (Fig. 10). Thus, the nature of a given bone lesion can be defined by the above-mentioned parameters of tumour-host bone interaction

Biopsy of Bone Tumours

Biopsy is the final and definitive step in the diagnosis of bone tumours. Anatomical alteration following a biopsy may interfere with a proper diagnosis and may even impair the possibility of performing a limb-sparing tumour resection. Biopsy of a musculoskeletal lesion should be performed only at the conclusion of staging accord-

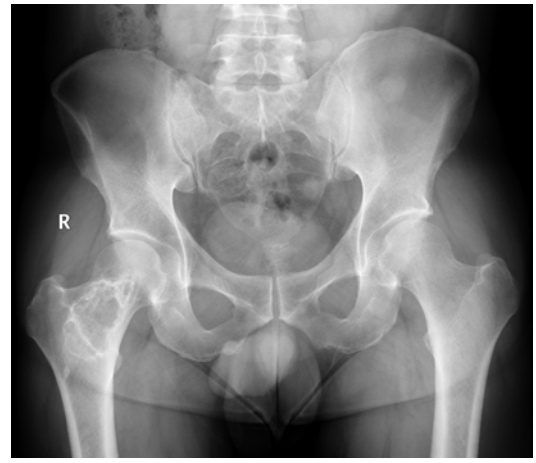

Fig. 6 Plain radiograph showing a latent cystic bone lesion of the right femoral neck surrounded by a thick sclerotic rim

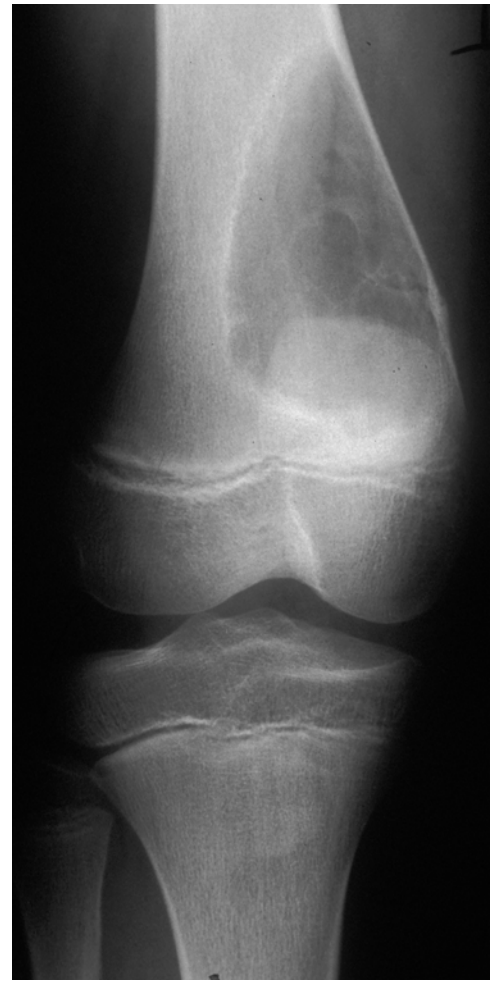

Fig. 7 Plain radiograph of the distal femur showing aneurysmal bone cyst, creating an expanded cortical shell

ing to the imaging studies that are essential for determining the characteristics and local extent of the tumour as well as the presence of metastatic disease. Staging helps determine the exact anatomical approach to the tumour, and delineates the region of the tumour that represents the underlying disease. A final and compelling reason for deferring biopsy until staging is complete is that biopsy superimposes both real and artificial radiological changes at the biopsy site and can thereby alter the interpretation of the imaging studies.

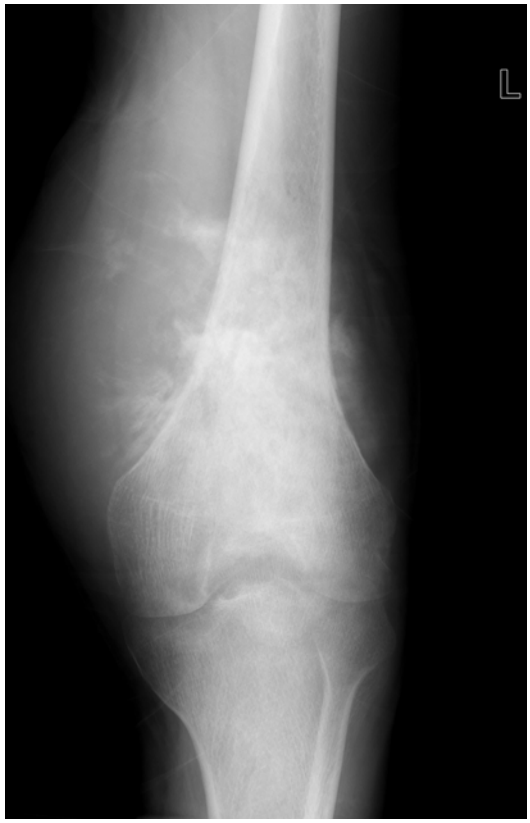

Fig. 8 Plain radiograph of the distal femur showing osteosarcoma, causing a spiculated periosteal elevation

Staging studies for a high-grade sarcoma of bone include computerized tomography (CT) and magnetic resonance imaging (MRI) scans of the affected bone in order to evaluate the local tumour extent, and chest CT and positron emission tomography (PET) scan to rule out the presence of metastatic disease. The CT scan provides anatomical data on the extent of bone involvement, and the MRI scan provides data on tumour extent within the medullary canal and in the surrounding soft tissues. As such, these two imaging studies provide complementary information and are both required to evaluate the full anatomical extent of a given bone tumour. A PET scan using fluorine-18-fluorodeoxyglucose (FDG) was shown to be as effective as the conventional imaging modalities in detecting the primary tumour, and superior to them in detecting bone manifestations and lymph node involvement of the disease [18]. However, PET-FDG was shown to be less accurate than CT in detecting lung metastases [18]. Complete staging is only required when the diagnosis of high-grade sarcoma of bone is in question. Benign-aggressive tumours do not require a metastatic work-up, and metastatic tumours are evaluated for the purpose of determining their specific histological type.

The presence of a bone lesion does not necessarily mandate a biopsy. The combination of medical history, thorough physical examination, laboratory data, and appropriate imaging studies allows accurate diagnosis of most bone tumours. Clinically and radiologically benign-appearing lesions do not require a biopsy. In contrast, a biopsy is indicated in benign-aggressive, malignant, and questionable lesions to confirm the clinical diagnosis and accurately classify the lesion before the initiation of definitive treatment (Fig. 11).

In 1982, Mankin et al. [14] evaluated 329 patients who underwent biopsy for bone or soft-tissue sarcomata. The rate of major errors in diagnosis was 18.2 %, and the rate of complications was 17.3 %. Unnecessary amputations were performed in 4.5 % of these patients [14]. These events occurred with far greater frequency when the biopsy was performed in a referring institution rather than in a specialized oncology centre. In addition to technical recommendations (discussed below), it was recommended that the patient should be referred to a specialized treating centre before the biopsy is done if a surgeon or an institution is not equipped to perform accurate diagnostic studies or definitive surgery and adjunctive treatment of musculoskeletal tumors [14]. In 1996, Mankin et al. reported a second study on 597 patients [15]. They documented

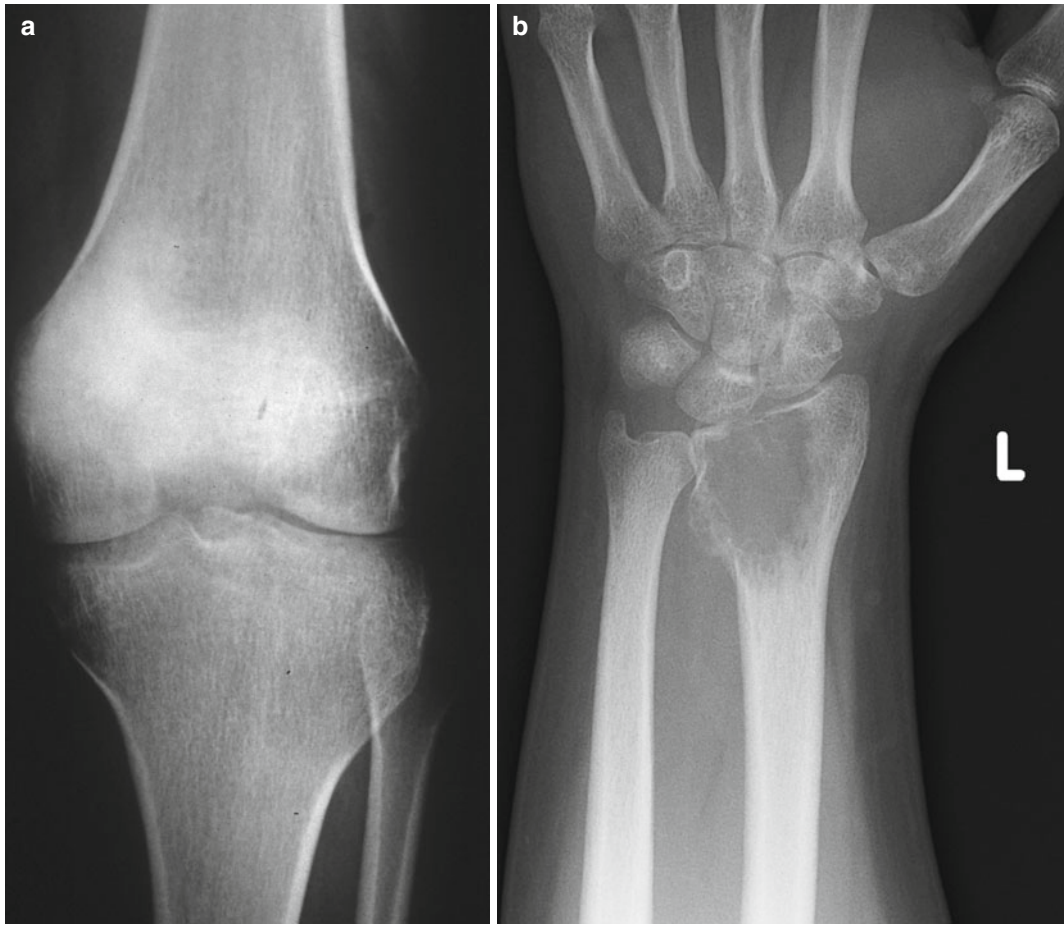

Fig. 9 Plain radiographs showing (**a**) osteosarcoma of the distal femur with a blastic matrix, (**b**) giant cell tumour of the distal radius with a lytic matrix

major errors in diagnosis in 13.5 % of the patients, a complication rate of 15.9 %, and unnecessary amputations in 3 %. The differences in outcome between referring and oncology centres were unchanged, and their recommendations were identical [15].

The site of biopsy within the lesion is of major significance because bone and soft tissue tumours may have regional morphological variations. As a result of that heterogeneity, multiple samples are required to establish a diagnosis. In contrast, carcinomas are commonly homogeneous, and a single tissue core or aspirate is sufficient for diagnosis. The term "sampling error" refers to an incorrect or inconclusive diagnosis, which occurs because the biopsy specimen was taken from a region that does not represent the underlying primary disease. Before performing a biopsy, the clinical findings and imaging studies must be evaluated by the surgeon and a radiologist who must be familiar with the biological and radiological findings of musculoskeletal tumours. The questions that must be answered before biopsy are the part of the lesion that needs to be biopsied, and the safest anatomical route to that site. Despite serious concerns regarding the potential of accelerated growth or metastatic dissemination of a malignant tumour after biopsy, there is no well-founded, objective evidence to show that biopsy promotes either adverse event. The real

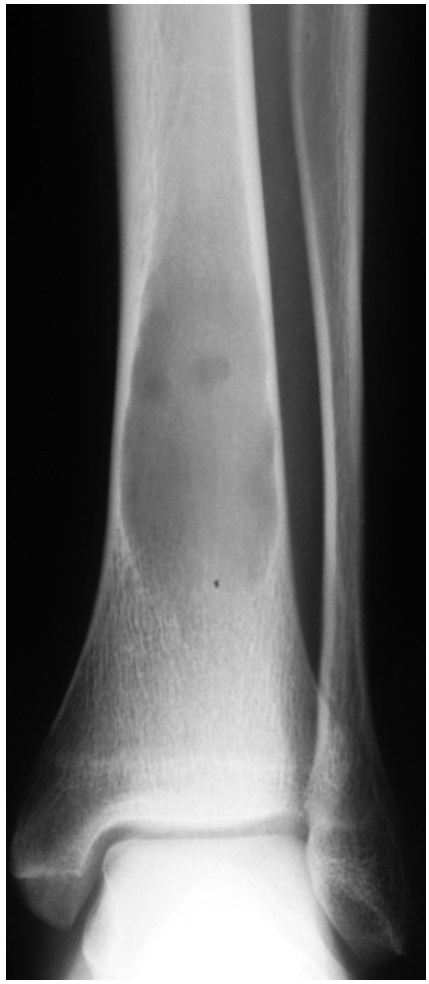

Fig. 10 Plain radiograph of the distal tibia showing fibrous dysplasia with its typical "ground-glass" matrix

risk of open and needle biopsies is that they may spread tumour cells locally and facilitate local tumour recurrence. The actual risk of local recurrence after biopsy is not well documented, but it is reasonable to assume that it is higher in open biopsy than in needle biopsy and that it is related to the width of the biopsy tract and adequacy of haemostasis.

A closed biopsy is relatively non-invasive, and the specimen is obtained after skin puncture by a needle or trephine. In contrast, an open biopsy is obviously an invasive procedure. It can be incisional, for which only a representative specimen is removed from the lesion, or excisional, for which the lesion is excised en bloc. Any surgical procedure, even the most minor one, is accompanied by a risk of complications, which may include iatrogenic injury to blood vessels or nerves, complicated wound healing, wound infection, and tumour cell contamination along the biopsy tract and subsequent local recurrence.

Open incisional biopsy is a reliable diagnostic method because it allows the pathologist to evaluate cellular morphological features and tissue architecture from different sites of the lesion. In addition, it provides material for performing ancillary studies, such as immunohistochemical analysis, cytogenetics, molecular genetics, and flow cytometric analysis. Needle biopsy of mesenchymal tumours had initially been criticized because the quantity of biopsy material was often considered to be insufficient for a routine histopathological evaluation and the ancillary studies that also require tissue. However, CT-guided core needle biopsies were shown to be safe and accurate in the diagnosis of bone tumours [16, 19]. Fine needle aspirations were also shown to have similar reliability in allowing accurate diagnosis in the majority of patients who have high-grade sarcomata [8]. Open biopsies may be unavoidable in cases when needle aspiration has not provided a clear diagnosis or in cases where the clinical-radiological diagnosis is inconsistent with a known histological entity.

In planning the definitive surgery, it was traditionally assumed that the biopsy tract is contaminated with tumour cells and that it should therefore be resected with the same safety margins as the primary tumour (i.e., wide margins). Binitie et al. reported 59 adult patients who had a deep and large soft-tissue sarcoma of the extremities and for which a core needle biopsy was done [3]. Definitive surgery in these patients did not include the biopsy tract and there was no increase in local tumour recurrence in those study patients compared with previously published data on local tumour recurrence when the biopsy tract was removed en bloc with the tumour [3]. Kaffenberger et al. reported similar observations among their 388 patients who underwent fine needle aspiration biopsy for high-grade sarcoma

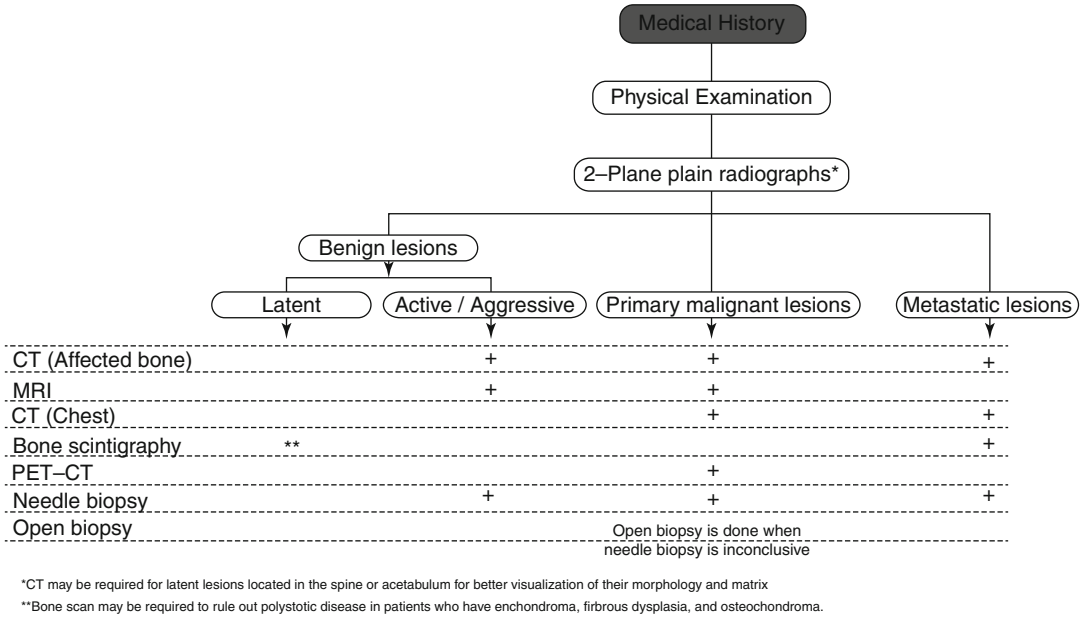

Fig. 11 Clinical and radiological processing algorithm of a bone lesion

[10]. A reasonable policy, therefore, would be to remove only the biopsy tracts that remain following an open biopsy (Fig. 12).

Important and meaningful advances have been made in mesenchymal tumour cytogenetics during the last two decades. Chromosomal translocation analysis has evolved from conventional chromosomal karyotyping and southern blot studies to more sophisticated molecular diagnostic techniques. Techniques such as reverse transcription-polymerase chain reaction and fluorescence in situ hybridization have become important tools for evaluating musculoskeletal neoplasms and for increasing the diagnostic accuracy of histopathological classification. Novel methodologies with diagnostic potential continue to emerge, such as cDNA micro-array and expression profiling [11]. A number of bone and soft tissue tumours have been shown to have recurrent and specific chromosomal changes, ranging from point mutations to chromosomal translocations. These changes not only serve as aids in the diagnosis and classification of bone and soft-tissue tumours – especially in the differential diagnosis of those of a confusing nature – but they have also guided molecular studies in establishing the underlying genes that are involved in tumour origin and progression. A number of tumour-specific gene fusions have been identified to date, and many have been shown to encode aberrant transcription factors [5, 11]. Knowledge obtained from these studies has translated into diagnostic, prognostic, and therapeutic applications for patient management [5, 11].

Conventional karyotyping depends on the availability of fresh, sterile tumour tissue, the success of tumour cell growth in culture, and the quality of metaphase cell preparations. It requires skilled personnel, which is mostly available in large centralized laboratories, and remains time-consuming, even with automated karyotyping systems. Although chromosomal abnormalities have been identified in a large variety of latent, benign, and malignant bone tumours, the vast majority is still accurately diagnosed on the basis of clinical, radiographic, and basic histopathological techniques [4, 6, 17]. The most common histological types in which chromosomal translocations are used for diagnosis include small blue round cell tumours, such as Ewing's sarcoma/primitive neuroectodermal tumour (PNET), poorly differentiated embryo-

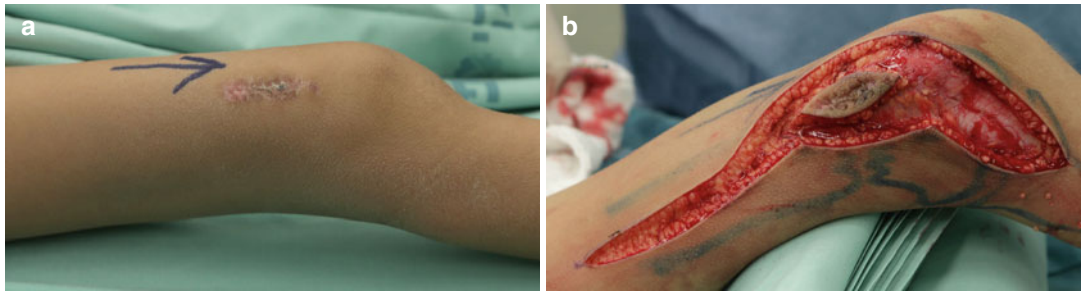

Fig. 12 Clinical photographs of a patient with osteosarcoma of the distal femur undergoing the definitive surgery of tumour resection showing (**a**) a biopsy incision along the medial aspect of the distal thigh, (**b**) biopsy scar, surrounding skin, and biopsy tract are kept adhered to the tumour and will be removed en bloc with it

nal rhabdomyosarcoma, and solid-alveolar rhabdomyosarcoma.

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