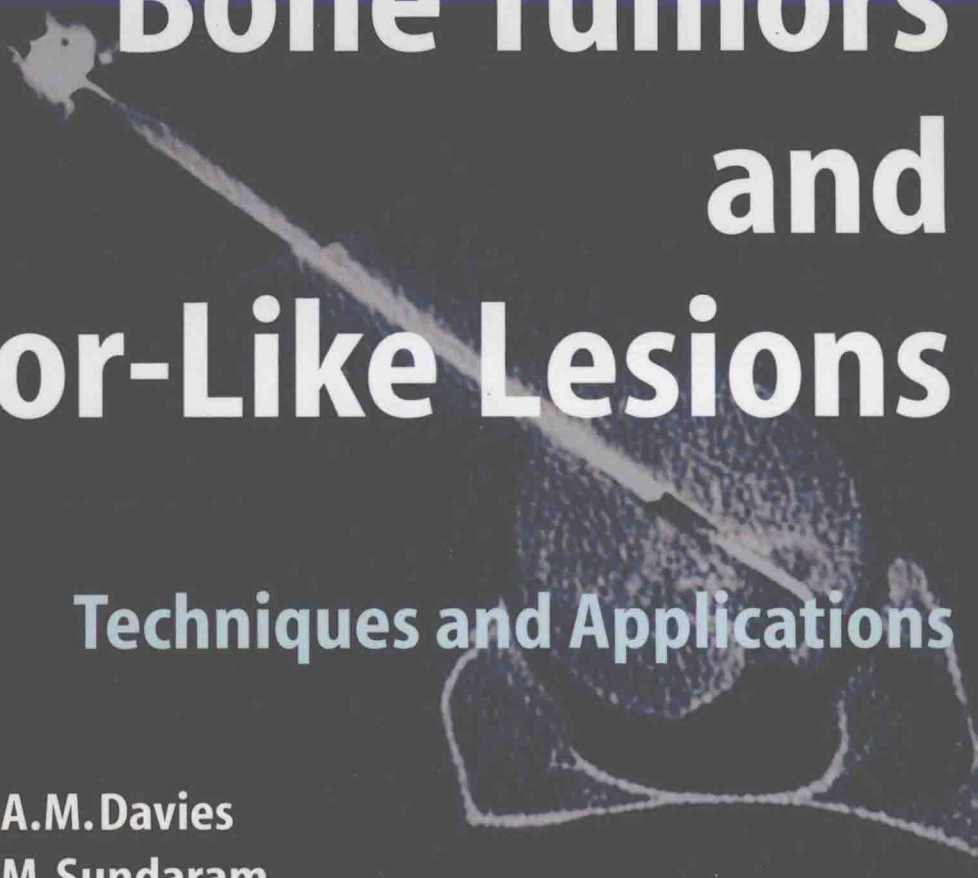
MEDICAL RADIOLOGY

Diagnostic Imaging

A. L. Baert
M. Knauth

Imaging of Bone Tumors and Tumor-Like Lesions

Techniques and Applications



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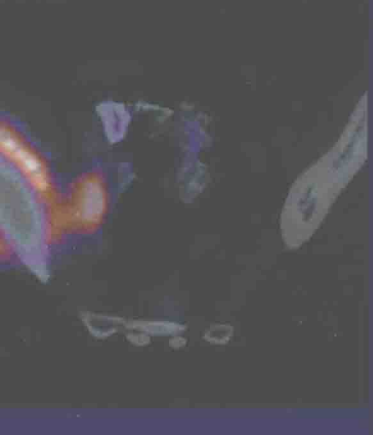

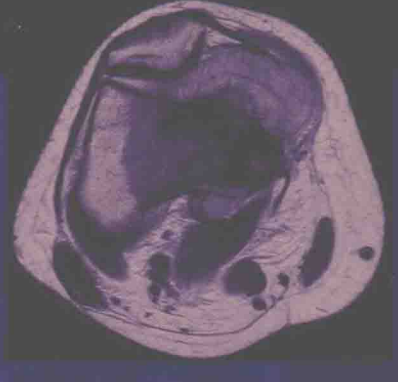

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A. M. Davies · M. Sundaram · S. L. J. James
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Imaging of Bone Tumors and Tumor-Like Lesions

Techniques and Applications

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MEDICAL RADIOLOGY

Diagnostic Imaging

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Foreword

Detection and characterization of bone tumors with imaging remains a big challenge for every radiologist notwithstanding the impressive progress achieved by the introduction of several new imaging modalities. Moreover, new concepts in surgical and oncological treatment of these lesions require from the radiologist appropriate and focused answers to the specific questions asked by the referring physicians in order to choose the best therapeutic approach for the individual patient.

This comprehensive textbook describes in detail the possibilities and limits of all modalities, including MRI, CT, nuclear medicine and interventional radiological procedures, employed for the modern imaging of tumoral and tumor-like lesions of bone. Their role in the diagnosis, surgical staging, biopsy and assessment of response to therapy is discussed in detail, covering all tumor subtypes as well as their specific anatomical location.Well selected and technically impeccable illustrations strongly enhance the didactic value of this work.

I am very much indebted and grateful to the three editors: A. Mark Davies, Murali Sundaram and Steven L. J. James, world authorities in musculoskeletal radiology, for their superb scientific achievement in preparing and editing this wonderful volume as well as for their individual chapters. I would also like to thank the large international group of collaborating authors, who are also widely acknowledged for their specific expertise in the area of bone tumors, for their outstanding contributions.

I am convinced that this unique book will be of great help to certified radiologists and radiologists in training to assist them in their daily clinical duties. However, orthopedic surgeons and oncologists also will find it extremely helpful to guide them in the therapeutic management of their patients.

I have no doubt that it will meet great success with the readership of this book series.

Leuven

Albert L. Baert
Series Editor

Preface

As our understanding of the complex subject of bone tumours improves, there is a need for the continuous updating of radiologists, orthopaedic surgeons, oncologists and other professionals working in this area. This book takes a multifaceted approach to the subject.

After an initial introductory chapter covering classification and epidemiology the first section acquaints the reader with the range of techniques available for imaging bone tumours. These five chapters cover magnetic resonance imaging, computed tomography, ultrasound, interventional techniques and nuclear medicine. The expanding role of PET scanning is included in this last chapter. The next six chapters apply these techniques to the general diagnosis and management of bone tumours including image-guided biopsy techniques, surgical staging and assessment of tumour response to different treatments. The third and largest section comprises 18 chapters detailing the salient clinical and imaging features of all the important tumour subtypes (cartilaginous, osteogenic etc.). The fourth section reviews the types of tumours that may be found at particular anatomical sites such as the ribs, scapula, spine and so on. Finally there is a chapter covering the important topic of compartmental anatomy and a further chapter giving potted biographies of those whose names over the past 150 years have become synonymous with bone tumours.

The editors are grateful to the international panel of authors for their contributions to this book, which aims to provide a comprehensive overview of current imaging of tumours and tumour-like lesions of bone.

Birmingham, UK — A. Mark Davies
Cleveland, US — Murali Sundaram
Birmingham, UK — Steven L. J. James

Contents

Bone Tumors: Epidemiology, Classification, Pathology

1

Lars Gunnar Kindblom

CONTENTS

KEY POINTS

- Primary bone tumors are rare; non-neoplastic conditions, metastatic disease, and lymphohematologic malignancies, which may simulate primary bone tumors, by far outnumber genuine bone tumors.
- Excluding myeloma and lymphoma, malignant primary bone tumors constitute only 0.2% of all malignancies in adults and approximately 5% of childhood malignancies.
- Bone tumor classification is based on morphologic findings: cell type, architecture, and matrix production. The morphologic features of benign and malignant as well as non-neoplastic conditions and true tumors may overlap.
- Many bone tumor entities show a striking consistency in clinical setting and age and anatomic site distribution.
- The final diagnosis of bone tumors should be based on a synthesis of histopathologic findings, clinical presentation, and imaging characteristics, preferably in the setting of a multidisciplinary team conference.
- Adjunctive immunohistochemical and genetic/molecular genetic techniques are important for the definite classification of certain bone tumors.
- A number of congenital, hereditary, and non-hereditary syndromes are associated with increased risk of bone tumors.

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1.1 Introduction

Primary bone tumors are fairly rare. Conditions that may simulate primary bone tumors, such as metastasis and non-neoplastic conditions such as inflammatory processes, bone cysts, fibrous dysplasia, non-ossifying fibroma, Paget's disease of bone, etc., by far outnumber the cases of true bone tumors. Compared to other malignancies, primary malignant bone tumors are very rare. The three most common genuine primary bone malignancies (osteosarcoma, chondrosarcoma, and Ewing's sarcoma) account for only 0.2% of all malignancies in the UK and USA; however, in children (< 15 years) malignant bone tumors account for approximately 5% of all malignancies (Dorfman and Czerniak 1995, 1998; Unni et al. 2005). This chapter reviews the epidemiology and pathologic classification of bone tumors. In addition, it gives an overview of the pathologist's role in diagnosis and management.

1.2 Epidemiology

The vast majority of primary bone tumors are benign and since many are non-symptomatic they remain undetected or are detected only incidentally at radiographic examinations for other reasons. The true incidence of benign bone tumors has therefore been difficult to determine. The incidence of primary bone malignancies is, in contrast, fairly well documented in various national cancer registries. Excluding the most common lymphohematopoietic malignancies (particularly plasma cell tumor/myeloma and malignant lymphoma, more rarely leukemia) that are of bone marrow origin rather than true bone tumors, the yearly incidence in the USA has been estimated to be $8/10^6$. This corresponds well with the approximately 500 cases diagnosed yearly in the UK and some 2,500 cases in the USA. More than 75% of malignant bone tumors are osteosarcoma, chondrosarcoma, and Ewing's sarcoma (Table 1.1). The incidence of malignant bone tumors shows a striking age-specific distribution: in the age group 0–40 years, there is an incidence peak between 10 and 20 years (primarily osteosarcoma and Ewing's sarcoma) and for the age group above 40 years there is a steady increase in incidence up to 80 years (primarily chondrosarcoma and to a lesser degree Paget's related osteosarcoma) (Dorfman and Czerniak 1995, 1998; Unni et al. 2005).

Benign bone tumors and many bone simulating, non-neoplastic conditions also show a striking age distribution. This together with a likewise striking site distribution for both benign and malignant bone tumors is most helpful in the diagnosis of bone lesions. The combined information of age, site, and imaging findings can in reality in many instances indicate a definite diagnosis, sometimes to the point that morphologic confirmation is considered unnecessary (such as in cases of bone cysts, fibrous dysplasia, non-ossifying fibroma, Paget's disease of bone). For the pathologist, awareness of these age and site distributions is essential; when a suggested morphologic diagnosis occurs at a highly unusual site or in "the wrong" age group, the definite diagnosis should be carefully reevaluated. The age and anatomic site distributions of some of the most common bone tumors are summarized in Tables 1.2 and 1.3.

Table 1.1. Relative frequency of most common primary bone malignancies (excluding myeloma/malignant lymphoma) (Dorfman and Czerniak 1995)

Primary bone malignancy	Frequency (%)
Osteosarcoma	35.1
Chondrosarcoma	25.8
Ewing's sarcoma	16.0
Chordoma	8.4
Malignant fibrous histiocytoma	5.7
Angiosarcoma	1.4
Unspecified	1.2
Other	6.4

Table 1.2. Classification of primary benign bone tumors, peak age, and most common sites distribution

Histologic type	Peak age (years)	Most common sites	Comments
Cartilage tumors			
Osteochondroma	10–30	Distal femur, proximal tibia, proximal humerus, rarely from flat bones	> 2 cm cartilage cap may indicate malignant transformation
Enchondroma	10–40	Hands, feet, long tubular bones	
Periosteal chondroma	10–40	Proximal humerus, distal femur, hip region, and pelvis	Sharply demarcated from cortex
Chondroblastoma	10–30	Distal femur, proximal tibia and humerus, calcaneus	Typically epiphyseal
Chondromyxoid fibroma	10–30	Proximal tibia, distal femur, pelvis, feet (metatarsal)	
Osteogenic tumors			
Osteoid osteoma	5–25	Proximal femur, any long bones	Distinguished from osteoblastoma by size and imaging
Osteoblastoma	10–40	Spine, long tubular bones, jaws	
Fibrogenic tumors			
Desmoplastic fibroma	10–30	Mandible, femur, pelvis	Very rare; distinction from FD, low-grade osteosarcoma, and fibrosarcoma may be difficult
Fibrohistiocytic tumors			
Benign fibrous histiocytoma	20–60	Pelvis, femur	Diaphyseal or metaphyseal; rarely used concept, distinguished from non-ossifying fibroma only by clinical setting
Giant cell tumor	20–45	Distal femur, proximal tibia, distal radius, sacrum	Epiphyseal; pulmonary metastases occur in 2%; very rarely transformation to high-grade sarcoma
Vascular tumors			
Hemangioma (cavernous, capillary, epithelioid, etc.)	Classic hemangiomas, usually adults	Craniofacial bones, vertebrae	Hemangiomas are often multicentric
Angiomatosis, lymphangioma(tosis)	Often children	Highly variable	
Glomus tumor	Usually adults	Hands, distal phalanx	
Hemangiopericytoma	Usually adults	Pelvis	
Epithelioid hemangioendothelioma	Adults	Long tubular bones, spine	
Soft tissue type tumors			
Lipoma	Adults	Femur, calcaneus	All very rare
Schwannoma		Sacrum, mandible	
Leiomyoma		Mandible, tibia	

FD fibrous dysplasia

Table 1.3. Classification of primary malignant bone tumors, peak age, and most common sites distribution

Histologic type	Peak age (years)	Most common sites	Comments
Chondrosarcoma			
Primary	50–80	Pelvis, proximal/distal femur, proximal humerus, ribs	Usually large, intraosseous; very rarely periosteal
Secondary	20–60	Ex osteochondroma(tosis): pelvis, hip and shoulder	In Ollier's/Maffucci's at any site affected
Dedifferentiated chondrosarcoma	50–70	Pelvis, femur, humerus	Usually small component of low-grade chondrosarcoma juxtaposed with high-grade osteo-, spindle cell-, MFH-, or other sarcoma
Clear cell chondrosarcoma	25–60	Proximal femur, humerus	Typically epiphyseal location
Mesenchymal chondrosarcoma	10–40	Jaws, ribs, pelvis, spine	20–30% occur in soft tissues
Osteosarcoma			
Conventional	10–30	Distal femur, proximal tibia, hip and shoulder	Typically metaphyseal
Telangiectatic osteosarcoma	10–30	Femur, tibia, humerus	Typically metaphyseal; ABC-like, purely lytic
Low-grade central osteosarcoma	20–40	Distal femur, proximal tibia	May dedifferentiate to high grade
Parosteal osteosarcoma	20–50	Posterior distal femur, proximal humerus	May invade the bone, may dedifferentiate to high grade
Periosteal osteosarcoma	10–30	Femur, tibia	Diaphyseal, surface lesion, predominantly chondroblastic, intermediate grade
High-grade surface	10–40	Distal femur, shoulder	Diaphyseal or metaphyseal
Secondary osteosarcoma			
Paget's associated	50–90	Pelvis, hip and shoulder, craniofacial	High-grade osteosarcoma
Post-radiation	50–80	Pelvis, craniofacial, hip and shoulder, chest wall	High-grade osteosarcoma
Other conditions	40–70	Bones affected by FD, bone infracts, chronic osteomyelitis, etc.	
Ewing´s sarcoma, PNET	5–30	Pelvis, longbones of lower and upper extremities	
Fibrosarcoma, MFH, spindle cell sarcoma	40–70	Knee, hip and shoulder regions, pelvis	
Malignant giant cell tumor	20–60	Knee region, pelvis, shoulder region	High-grade sarcoma arising in GCT; classic GCT may rarely metastasize
Chordoma	30–80	Sacrococcygeal, skull base, vertebrae	May rarely dedifferentiate

ABC aneurysmal bone cyst, *FD* fibrous dysplasia, *GCT* giant cell tumor, *MFH* malignant fibrous histiocytoma, *PNET* primitive neuroectodermal tumor

Table 1.3. *(continued)* Classification of primary malignant bone tumors, peak age, and most common sites distribution

Histologic type	Peak age (years)	Most common sites	Comments
Angiosarcoma	20–70	Spine, pelvis, hip and shoulder regions	May be multicentric
Other soft tissue type sarcomas	20–70	Long bones, around major joints	Rare examples of leiomyosarcoma, liposarcoma, extraskeletal myxoid chondrosarcoma, synovial sarcoma, rhabdomyosarcoma, etc.
Adamantinoma	10–40	Tibia, rarely ulna, radius and fibula	Typically diaphyseal

ABC aneurysmal bone cyst, *FD* fibrous dysplasia, *GCT* giant cell tumor, *MFH* malignant fibrous histiocytoma, *PNET* primitive neuroectodermal tumor

1.3 Morphologic Diagnosis of Bone Tumors

The pathologic diagnosis of primary bone tumors poses particular problems:

1. Their rarity prevents most pathologists from gaining sufficient diagnostic experience.
2. There is an unusual need for the pathologist to be familiar with and to integrate clinical, laboratory, and imaging findings in the final diagnosis.
3. Despite their rarity, there is a wide spectrum of bone lesions with overlapping morphologic features.
4. The distinction between neoplastic, reactive/inflammatory, and metabolic bone lesions as well as some developmental disorders is sometimes difficult.
5. The diagnosis of malignant bone tumors, which frequently involve children or young adults, often has dramatic consequences in terms of surgical and adjuvant treatment. Moreover, there are a number of rare hereditary and non-hereditary conditions associated with increased risk of developing bone tumors that the pathologist needs to be aware of.

Even if clinical presentation and imaging studies are very often highly suggestive of a particular diagnosis, it is the morphologic findings that form the basis for the definite diagnosis of bone tumors. It is expected that the pathologists reporting primary bone malignancies participate in multidisciplinary team conferences and appropriately integrate clinical, laboratory, and imaging findings in the final diagnosis. Within these teams the pathologists have the important role to establish the correct diagnosis, to arrange for and interpret required adjunctive diagnostic tests (immunohistochemistry, cytogenetic/molecular analyses), to provide prognostic information, to identify patients that should be considered for adjuvant treatment protocols or trials, and to assess treatment response.

The possibility for the pathologist to correctly diagnose a bone tumor depends to a large extent on the completeness of the clinical and imaging information provided. The request forms for bone tumors should therefore contain information regarding pertinent clinical history, family history, laterality and exact anatomic site of tumor, whether the patient has solitary or multicentric disease or clinical evidence of metastatic disease, information on type and timing of any preoperative treatment, type of surgical procedure (fine-needle aspiration, core needle biopsy, open surgical biopsy, curettage, resection, amputation, etc.), and nature of specimen and, if indicated, orientation markers on specimen.

Whenever practically possible, it is advantageous if malignant bone tumor specimens are delivered fresh and unfixed to the pathology laboratory with the shortest possible delay. This will enable the pathologist to obtain material for studies that require fresh, unfixed tissue, to decide on the most appropriate way to obtain material from surgical margins, to decide on techniques for decalcification procedures, and to decide when dealing with large specimens if sectioning of skin, soft tissues, and bone is required to facilitate fixation.

1.4 Types of Bone Tumor Specimens

1.4.1 Intraoperative Procedures/ Frozen Sections

There are inherent problems with intraoperative diagnosis of bone tumors: hard, bony specimens cannot be processed since decalcification is needed, the pathologist needs to be familiar with the artifacts introduced by freezing specimens, and the overlapping morphologic features of different entities may be difficult to correctly interpret in frozen sections. However, where this technique is widely used, specialized bone tumor pathologists can acquire a very high degree of expertise. Frozen sections may be particularly helpful in determining if the biopsy is representative of the lesion and can help to immediately distinguish primary genuine bone tumors from inflammatory processes, other non-neoplastic conditions, metastases, and lymphohematologic malignancies.

1.4.2 Fine-needle Aspiration Biopsy

With the exception of Scandinavia, there are few bone tumor centers that have adopted this technique as a routine in the diagnosis of bone tumors. The reluctance to apply fine-needle aspiration biopsy (FNAB) is explained by the lack of experienced cytopathologists in this field, the limitations of the technique to obtain material from bony, calcified components, the loss of architecture and matrix characteristics, and the limited volume of tissue obtained (prohibiting extensive immunohistochemical and cytogenetic/molecular workup). In the hands of experienced cytopathologists, FNAB has, however, proven practically useful. For example, it is a very quick method to identify a lesion as a cartilage-producing neoplasm or hematologic malignancy (lymphoma/myeloma) and helps to distinguish osteosarcoma from Ewing's sarcoma and metastatic disease from primary bone tumors (Willen 1997). There are also reports of the diagnostic FNAB characteristics of many individual bone tumor entities such as osteosarcoma, chondrosarcoma, Ewing's sarcoma, and chordoma (Dahl et al. 1986; Walaas and Kindblom 1990, 1991; Walaas et al. 1990; Willen 1997).

1.4.3 Biopsy

Today "closed" transcutaneous, core needle biopsy techniques are widely used, often assisted by radiographic imaging techniques. Material can be obtained from both soft tissue components (preferable when possible) and intraosseous components, and the material obtained is usually sufficient for adjunctive studies such as immunohistochemistry and cytogenetic/molecular genetic analyses. If RNA-based molecular analyses are to be carried out it is important that decalcification processes if required are adjusted to allow such techniques (formic acid can be used, not nitric acid!) (Mangham et al. 2006). When for various reasons "closed" biopsy techniques cannot provide material sufficient for a definite diagnosis an open surgical biopsy has to be performed. It is important that decalcification techniques are not routinely applied on all bone lesion specimens since many specimens need no decalcification at all or at least parts of the biopsy can be processed without such procedures. The decalcification procedure has also to be adjusted for each specimen in order not to overdecalcify the tissue, which can severely hamper the possibilities to reach a correct diagnosis.

1.4.4 Curettage

A bone lesion can be curetted as a one-step diagnostic and treatment procedure or as definite treatment after previous biopsy. Generous sampling for microscopic examination is essential and the same principles for decalcification procedures should be applied as for biopsies.

1.4.5 Resections and Amputations

Resections and amputations are performed as part of curative definite treatment of bone tumors. For a correct approach to dissection of such specimens it is important that the pathologist can review pertinent radiographic images and that that the surgeon has indicated orientation if necessary. In addition to a correct histopathologic diagnosis, the examination of such specimens should include assessment of tumor size (three dimensions), margins (tissue type and dimensions), involvement of the marrow, cortex, periosteum, joints, surrounding soft tissues, etc., and possible vascular invasion. If preoperative treatment has been given, the response should be assessed based on a detailed mapping of the tumor.

1.5 Adjunctive Diagnostic Techniques

1.5.1 Histochemistry, Immunohistochemistry, and Electron Microscopy

These techniques have helped to better define many bone tumors but are, with some important exceptions, not required in routine diagnosis. For the vast majority of bone tumors the diagnosis is based on the histologic appearance in routine-stained sections with appropriate consideration of clinical setting and imaging findings. Immunohistochemical characterization, however, is of special importance for classification of metastatic bone disease (identification of primary sites if unknown) and for the subclassification of lymphohematologic malignancies and small round cell malignancies, in particular Ewing's sarcoma. Other examples where immunohistochemical findings may be helpful include the diagnosis of chordoma in biopsies, the recognition of endothelial differentiation in poorly differentiated angiosarcomas, and for the distinction between osteofibrous dysplasia (OFD) and OFD-like adamantinoma.

1.5.2 Cytogenetic/Molecular Genetic Techniques

Genetic characterization of various bone tumors has helped to better understand their nature and the pathogenetic mechanisms involved and has also given additional support for the morphology-based classifications. Examples of this include the identification of the role of the EXT 1 and 2 genes in the development of osteochondroma, osteochondromatosis, and secondary chondrosarcomas (Bovée et al. 1999). Another example is the identification of the CDH11-USP6 fusion gene caused by a 16; 17 translocation in aneurysmal bone cysts, suggesting that these lesions are probably of neoplastic nature (Oliveira et al. 2004). Other genetic findings have also made the distinction between what in the past were considered non-neoplastic, developmental disorders, such as fibrous dysplasia and Paget's disease, and true neoplasia less clear. There are even some genetic observations suggesting that synovial chondromatosis and pigmented villonodular synovitis may represent neoplastic conditions (Fletcher et al. 2002).

In a few instances karyotyping and molecular genetic techniques (such as FISH and RT-PCR techniques) have provided highly valuable diagnostic tools. The most striking example is the identification of the Ewing's sarcoma-specific translocation between the long arms of chromosomes 11 and 22 involving a fusion of the EWS gene (or rarely the FUS gene) with various other genes of the ETS transcription factor family; mostly these translocations involve the FLI1 gene, less frequently the ERG, ETV1, E1A-F, FEV or ZSG genes. FISH- and/or RT-PCR-based techniques, designed to identify these gene translocations, are today widely applied in the routine diagnosis of Ewing's sarcoma and its distinction from other small round cell malignancies (Fletcher et al. 2002; Mangham et al. 2006; Unni et al. 2005).

1.6 Classification of Bone Tumors

The histologic classification of bone tumors is based on cytologic findings (in particular cell type such as osteocyte/osteoblast, chondrocyte/chondroblast, osteoclast, etc.), architecture, and type of matrix produced by the tumor. Despite the rarity of bone tumors there is a very wide spectrum of entities with sometimes overlapping features; the current WHO classification (2002) includes a total of 45 main bone tumor types. For some malignant bone tumors, such as osteosarcoma and chondrosarcoma, malignancy grading is important, while for others such as Ewing's sarcoma and chordoma the degree of malignancy is implicated in the diagnosis. In addition to correct classification and in some cases grading, the pathologist has to report on margins, relation of tumor to cortex, periosteum, surrounding soft tissues, joints, etc., and the presence of vascular invasion as well as give information of importance for staging (Dorfman and Czerniak 1998).

The current classifications of benign and malignant bone tumors are summarized in Tables 1.2 and 1.3 and the most common non-neoplastic bone tumor-simulating conditions in Table 1.4.

1.7 Comments on the Morphologic Classification of Bone Tumors

1.7.1 Cartilage Tumors

The morphologic diagnosis of cartilage tumors poses particular problems. The distinction between benign cartilage lesions and chondrosarcoma is tradition-