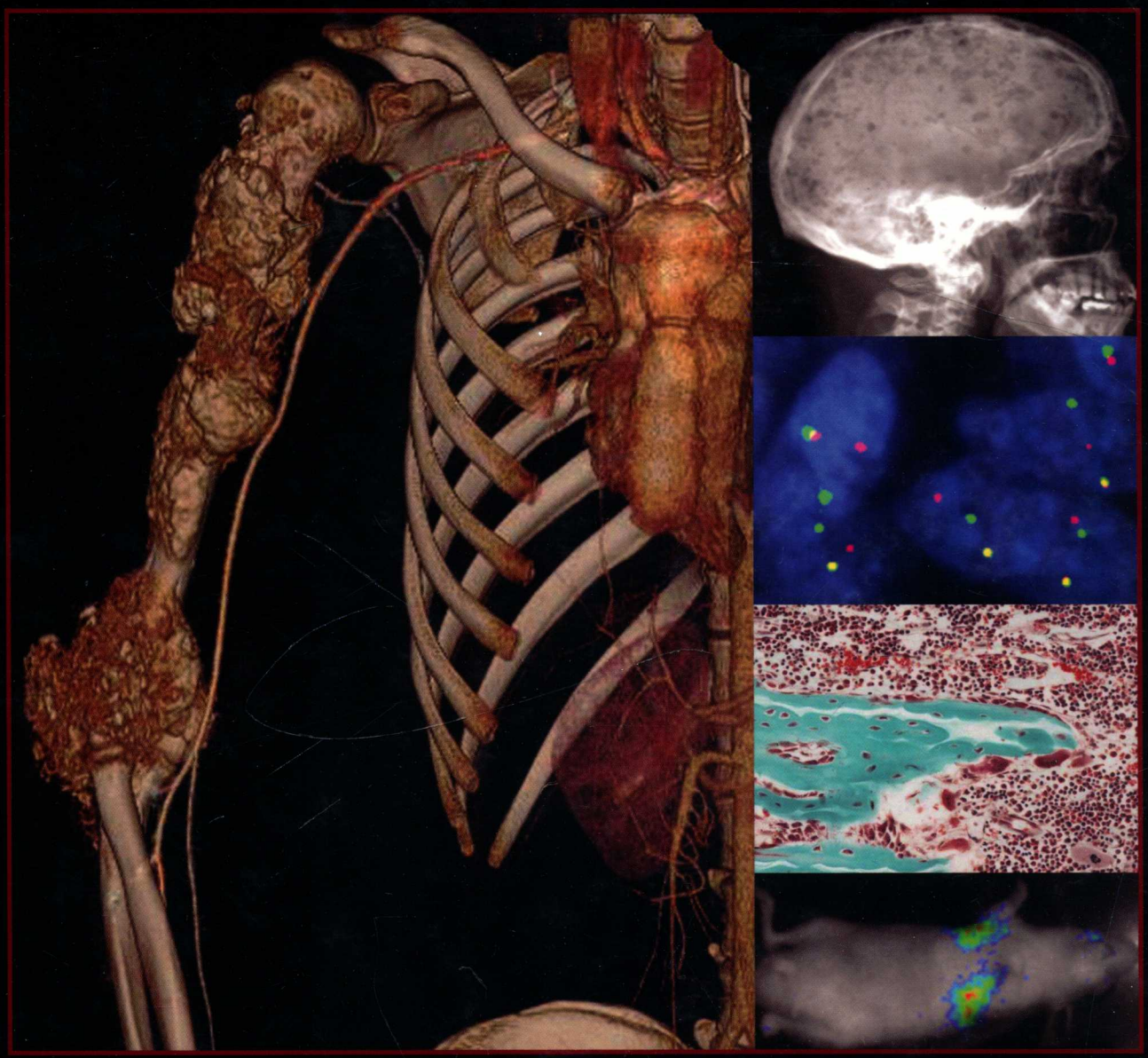
Bone Cancer

Progression and Therapeutic Approaches



Edited by

Dominique Heymann

BONE CANCER

PROGRESSION AND THERAPEUTIC APPROACHES

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DOMINIQUE HEYMANN

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Foreword

Our understanding of bone malignancies is following, with only a slight delay, that of the molecular bases of cell differentiation and function in the skeleton. As a result, it is increasing steadily and rapidly. What this timely book (edited by Dr. Heymann) does is to set the records straight and to define the questions and problems that bone biologists can now tackle through the use of modern molecular approaches and appropriate model organisms.

Most of the bone metastases are osteolytic, the main exception being prostate cancer bone metastases that form new bones. Thus, understanding the pathogenesis of bone metastases relies, to a very large extent, on understanding osteoclast differentiation. As very well illustrated in this volume, our knowledge of this aspect of bone biology has greatly progressed through the identification of RANKL as a master osteoclast differentiation factor, through the identification of its receptor, and of the complex signal transduction pathways it triggers in osteoclast progenitor cells. This body of work has also greatly advanced our understanding of bone metastases. This alone, however, would not have been enough. What is allowing us to get a better understanding of bone metastases is the more and more generalized ability to perform cell-specific and sometimes time-specific gene deletion in mice. These two types of advances, molecular and genetic, also supported by the progress of bioinformatics, are the pillar of the modern study of bone metastases. Going forward, it is likely that new aspects of molecular biology, such as the emerging biology of small RNAs, will join the group.

Molecules like RANKL, osteoprotegerin and PTHrP, tumor suppressor genes such as p53 and Rb are now central players in the study of osteoclast differentiation and proliferation. Furthermore, what is progressively emerging, beyond these genes and their functions are partial but nevertheless useful genetic pathways. In the face of this steady increase in knowledge one can ask: what is the use of such a book? As a matter of fact, and as a bone biologist not working directly on metastases, such a volume is extremely timely for several reasons. Firstly, it provides a very good picture of the state of the knowledge on this part of bone biology in 2009; secondly, and just as importantly, in doing so it also puts together a list of questions and problems that are now facing the field. It was always humbling and difficult to make a statement, as a book is, about a field that is still developing rapidly. In that respect, what Dr. Heymann and his co-workers have done is outstanding and certainly very useful. They deserve congratulations for this work which, I am sure, will generate a lot of interest in our community.

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Preface

The past decade has witnessed an explosion in the field of bone biology. The topic of bone biology over this period has been marked by significant advances that have opened up entirely new areas for investigation. Indeed, the molecular mechanisms that control bone remodeling have been extensively investigated and some scientific fields have emerged. This is the case for osteoimmunology after identification of a set of molecules, allowing communication between bone cells (ostoclasts, osteoblasts) and immune cells (monocytes, lymphocytes, dendritic cells). Similarly, concepts based on the neuronal regulation of bone mass have emerged. Unfortunately, genetic or environmental deregulations lead to the development of bone cancer diseases such as primary bone tumors (osteosarcoma, Ewing's sarcoma, chondrosarcomas, giant cell tumors, etc.) that originate from bone cells or from mesenchymal stem cells. Bone is also a privileged site for metastases due to the migration and development of tumor cells derivating from non-bone cells such as breast cancer cells or prostate carcinomas cells. Some tumor cells such as myeloma cells initially proliferate in bone sites and then induce a deregulation of the bone apposition and resorption balance in favor of an osteolytic process.

This book gives an overview of the most up-to-date epidemiological data of these tumors and their biology including molecular aspects (protein and gene) allowing clear identification of new therapeutic targets and approaches. As well as the biological aspects of bone tissue, primitive bone tumors and bone metastases well described in this book, the clinical aspects are also addressed: histopathology, imaging of bone tumors, management of bone pain and conventional therapeutic care. Finally, better understanding of biological mechanisms associated with the development of many pre-clinical models allows the emergence of new therapeutic approaches of bone tumors. Therefore, this book, describing bone tumors, from their fundamental aspects to their clinical aspects, is specifically dedicated to medical students and scientists, to health professionals, researchers and teachers working in the osteo-articular domain and interested in the more recent data available. This review book consists of 38 chapters resulting from the work of 26 professional teams from 11 countries and who are specializing in the pathophysiology of bone. I would like to thank the authors for the work performed and to give their expertise to the students, to our colleagues and to all readers.

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Contents

Section I. Epidemiology and Economical Aspects of Bone Cancer

CHAPTER 1

Epidemiology of Primary Bone Tumors and Economical Aspects of Bone Metastases

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Contents

Primary bone tumors are rare and as such they form a difficult category of tumors for appropriate recognition and classification both for clinicians as well as pathologists. They account for less than 0.2% of the malignancies registered in the SEER database [1]. The occurrence of bone sarcomas ranges between 0.8 and 2 cases per person per year [1]. However, particularly children and adolescents are affected, which means that bone tumors have a major impact on the life of patients and their immediate surroundings. The incidence of benign bone tumors may be considerably higher, but a number of these are asymptomatic and often missed by patients and their doctors. Therefore, benign bone tumors are most likely underreported. But nevertheless they are, like other benign tumors, a rare event. Another confounding factor is the high discrepancy rate at histological review of bone tumors, which make most population-based series somewhat unreliable [2]. On the other hand, consultation series or expert center series are likely to over-report difficult/unusual cases.

Bone tumors can occur spontaneously. However, a substantial number of them do occur in the context of a hereditary disorder thus implicating a detailed family history in every new case. If a hereditary context is suspected, then a proper follow-up, often in close collaboration with clinical geneticists, is mandatory [3,4]. This hereditary aspect might explain the higher incidences in some regional populations.

A subgroup of primary bone malignancies occurs secondary to benign precursor lesions in the bone such as in a case of Ollier disease, fibrous dysplasia or Paget's disease of bone [5–9], so the incidence adds up to the occurrence of the primary condition in the population. For instance, there is a well-known regional incidence difference for Paget's disease of bone.

Both benign as well as malignant primary tumors of bone are greatly outnumbered by metastases to the bone from epithelial cancers or melanoma and hematological disorders like multiple myeloma/plasmacytoma.

I. INCIDENCES OF PRIMARY BONE TUMORS

The incidence of bone tumors—especially primary bone sarcomas compared to malignant tumors—in general is very low. Review of large series revealed that approximately 0.2% of all neoplasms are bone sarcomas [10–12]. In Europe about two new primary bone sarcomas arise per 100,000 persons a year. Interestingly, at childhood there is a steep shift in frequency of occurrence over the age span [13]. From the first year of life the incidence increases from 3.9 per 100,000 to a peak of 142.9 per 100,000 at the age of fifteen [13]. The archives of the Netherlands Committee of Bone Tumors hold details of over 14,000 cases of bone tumors and tumor-like lesions where the percentages of the sarcomas are given in decreasing order of frequency for malignant bone tumors: osteosarcoma (37%), chondrosarcoma (23.6%), Ewing sarcoma (12.2%), fibrosarcoma/malignant fibrous histiocytoma (10.9%), Non-Hodgkin's lymphoma of bone (3.3%), malignancy in giant cell tumor (2.3%), Paget's sarcoma 1%, and adamantinoma (0.8%) [10].

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Fibrosarcoma and malignant fibrous histiocytoma are diagnoses which are infrequently encountered these days. This is reflected by a change of methods used to classify these tumors, which in practice commonly appear to be poorly differentiated osteosarcoma, or dedifferentiated chondrosarcoma. For benign tumors, enchondroma is the most frequent (27.7%) followed by giant cell tumors (21.5%), osteochondroma (14%), osteoid osteoma (10.5%), chondroblastoma (9%) and osteoblastoma (5.7%) [10]. However, an age-dependent frequency difference is present [13], as discussed below.

II. AGE

Bone tumors have an age-related presentation. There are two age-specific peaks in frequency in bone sarcomas. The first peak occurs in the second decade of life and consists of osteosarcoma and Ewing's sarcoma in cases of malignant tumors and osteochondroma in the benign group [13]. The second peak, slightly increasing from the fourth decade, peaks after the sixth decade and includes chondrosarcomas, MFH, chordoma and osteosarcoma, including Paget's and radiation-induced sarcomas. Chondrosarcomas are somewhat equally distributed over all decades, although rarely found in someone younger than 20, and slightly increasing thereafter. Malignant progression of osteochondroma, as in multiple osteochondroma, only presents itself a number of years after closure of the growth plate and can be recognized by a regrowth of the cartilaginous cap of a pre-existent osteochondroma [14].

The majority of benign bone tumors and tumor-like lesions in young patients are seen in the first and second decades of life. In about half, the median age occurs in the second decade (solitary bone cyst, aneurysmal bone cyst, non-ossifying fibroma, fibrous cortical defect, enchondroma, Langerhanscell histiocytosis, osteochondroma, chondroblastoma, osteoblastoma and osteoid osteoma). The median age incidence of the rest is not specifically age-related and may be seen in the first decade of life, extending even into the sixth or seventh decade (i.e. juxtacortical chondroma, parosteal osteosarcoma, desmoplastic fibroma). Giant cell tumors occur almost exclusively after closure of the epiphysial plate.

III. GENDER

The male–female ratio has little diagnostic contribution for most bone tumors, as in general there is no striking difference and both sexes are roughly equally affected. In osteosarcoma the male–female ratio is 1:1. In Ewing's sarcoma, Paget's sarcoma, chordoma and primary osseous non-Hodgkin lymphoma there is a higher prevalence in males (2:1). There is some male predominance seen in a number of benign lesions like osteochondroma, chondroblastoma, osteoid osteoma, solitary bone cyst, or osteoblastoma. Whether this correlates to a higher incidence of trauma in males which attracts attention to an underlying, previously asymptomatic tumor, is unknown.

IV. RACIAL DIFFERENCES IN INCIDENCES OF PRIMARY BONE TUMORS

While there are some differences reported in incidences between different national registries in the frequency of occurrence, most striking racial differences are reported with regard to Ewing's sarcoma [15] and giant cell tumor of the bone [16]. There is, as yet, an unexplained, extremely low, incidence of Ewing's sarcoma in those of African descent; while giant cell tumors of the bone tend to occur more frequently in the Asian population.

V. SITE DISTRIBUTION

Bone tumors have a preference for the long bones of the extremities. The metaphysis is the preferred site for malignant bone tumors; especially the metaphysis of the distal and proximal femur, the proximal tibia and proximal humerus, which are the affected sites in more than 80% of instances of osteosarcoma. Depending on the extent of the tumor, the epiphysis, and even diaphysis, might be affected as well.

The majority of central chondrosarcoma are restricted to the long bone marrow space, mostly in metaphysial and diaphysial locations. Malignant fibrous histiocytomas arise and extend mostly in the metaphysis, like osteosarcoma, prompting us to question whether this should be regarded as a poorly differentiated form of osteosarcoma. Ewing's sarcoma tends to arise more frequent in the diaphysis but may also extend in the metaphysis. Chordomas are sited exclusively in the sacrum, vertebra and skull, except for very rare casuistic presentations in the long bones. Sites other than the long bones for sarcomas are the flat bones like pelvis, scapula and ribs (chondrosarcoma and Ewing's sarcoma) and craniofacial bones (osteosarcoma). Adamantinoma is almost pre-eminently sited in the tibia and sometimes the fibula.

In benign tumors the epiphysial location is restricted for chondroblastoma, osteoblastoma and dysplasia epiphysialis hemimelica. Solitary and aneurysmal bone cysts occur metaphysically, usually close to the epiphysis. All osteochondroma originate in the metaphysis of long bones and increase the distance to the epiphysis during growth. Fibrous dysplasia can occur at all sites in all bones. Lesions