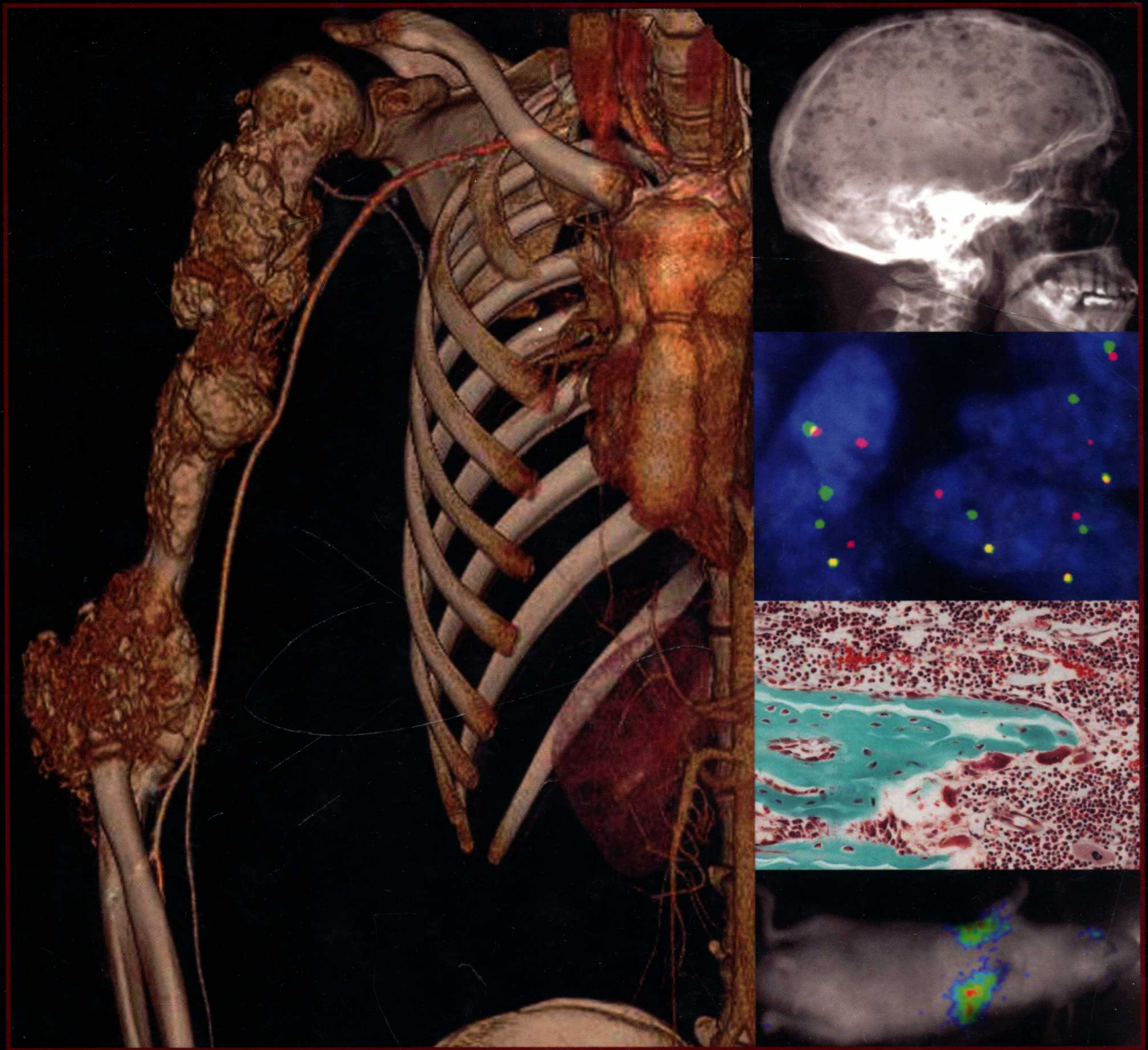


# BONE CANCER

## 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

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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.

Professor Dominique Heymann, PhD  
Professor Gérard Karsenty, MD PhD  
Department of Genetics and Development  
College of Physicians and Surgeons  
Columbia University  
New York, New York, USA



## 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 (osteoclasts, 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 deriving 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.

Professor Dominique Heymann, PhD  
Nantes University Faculty of Medicine  
INSERM  
Nantes, France



# List of Contributors

---

**Kosei Ando, MD**

Department of Orthopaedic Surgery, Shiga University of Medical Science, Shiga, Japan

**Coskun Arslanemir, MD**

Department of Nuclear Medicine, University Hospital, Kiel, Germany

**Walter C. Bell, MD**

University of Alabama at Birmingham, Birmingham, AL, USA

**Ariane Berdal, Professor, DDS-PhD**

Centre de Recherche des Cordeliers, Oral Facial Biology and Pathology, Paris, France

**Dominik Berthold, MD**

Centre Phiridisciplinaire d'Oncologie—Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

**Bheem M. Bhat, PhD**

Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA, USA

**Ramesh A. Bhat, PhD**

Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA, USA

**Sudeepa Bhattacharyya, PhD**

Center of Orthopaedic Research, Department of Orthopaedic Surgery and Physiology and Biophysics, UAMS College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

**Julia Billiard, PhD**

Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA, USA

**Frederic Blanchard, PhD**

INSERM, Université de Nantes, Nantes Atlantique Universités, Laboratoire de Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, EA3822, Nantes, France

**Peter V.N. Bodine, PhD**

Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA, USA

**Tom Böhling, MD**

Department of Pathology, Haartman Institute, University of Helsinki, Finland

**Aymann Bouattour, DDS**

Centre de Recherche des Cordeliers, Oral Facial Biology and Pathology, Odontology Department, Pitié-Salpêtrière Hospital, Paris, France

**Corinne Bouvier, MD, PhD**

Service d'Anatomie et Cytologie Pathologiques, Hôpital La Timone, Faculté de Médecine de Timone, Marseille, France

**Bénédicte Brounais, PhD student**

INSERM, Université de Nantes, Nantes Atlantique Universités, Laboratoire de Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Nantes, France

**Giacomina Brunetti, PhD**

Department of Human Anatomy and Histology, University of Bari Medical School, Bari, Italy

**Stephanie Byrum, PhD**

Center of Orthopaedic Research, Department of Orthopaedic Surgery and Physiology and Biophysics, UAMS College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

**Daniel Chappard, MD, PhD**

INSERM, U922-LHEA, Bone Remodeling and Biomaterials, Faculté de Médecine, Angers, France

**Edward Chow, MBBS, PhD, FRCPC**

Department of Radiation Oncology, University of Toronto, Rapid Response Radiotherapy Program, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada



**Philippe Clezardin, PhD**

INSERM, Laennec School of Medicine, Lyon,  
France

**Gregory A. Clines, MD**

Division of Endocrinology and Metabolism,  
Department of Medicine, University of Virginia,  
Charlottesville, VA, USA

**Denis R. Clohisy, MD**

Department of Orthopedic Surgery and Cancer Center,  
School of Medicine, University of Minnesota, Minneapolis,  
MN, USA

**Silvia Colucci, MD**

Department of Human Anatomy and Histology, University  
of Bari Medical School, Bari, Italy

**Emmanuelle David, PharmD**

INSERM, Université de Nantes, Nantes Atlantique  
Universités, Laboratoire de Physiopathologie de la  
Résorption Osseuse et Thérapie des Tumeurs Osseuses  
Primitives, Nantes, France

**Gonzague de Pinieux, MD, PhD**

Service d'Anatomie et Cytologie Pathologiques, Hôpital  
Trousseau, Faculté de Médecine, Université François  
Rabelais, Tours, France

**Vianney Descroix, DDS, PharmD, PhD**

Centre de Recherche des Cordeliers, Oral Facial Biology  
and Pathology, Odontology Department, Pitié-Salpêtrière  
Hospital, Paris, France

**Sara DeDosso, MD**

Oncology Institute of Southern Switzerland, Medical  
Oncology, Bellinzona, Switzerland

**William C. Dougall, PhD**

Amgen Washington, Seattle, WA, USA

**Lauren K. Dunn, MD**

Division of Endocrinology and Metabolism,  
Department of Medicine, University of Virginia,  
Charlottesville, VA, USA

**Alysa Fairchild, BSc, PGDip (Epi), MD, FRCPC**

Department of Radiation Oncology, University of Alberta,  
Cross Cancer Institute, Alberta, Canada

**Stefano Ferrari, MD**

Chemotherapy unit, Department of Musculoskeletal  
Oncology, Istituti Orthopedici Rizzoli, Bologna,  
Italy

**Luis Filgueira, MD**

University of Western Australia, Crawley, WA, Australia

**Adrienne M. Flanagan, MB, PhD**

University College London, Department of Histopathology,  
Royal National Orthopaedic Hospital, Middlesex, United  
Kingdom

**Yannick Fortun, PhD**

INSERM, Université de Nantes, Nantes Atlantique  
Universités, Laboratoire de Physiopathologie de la  
Résorption Osseuse et Thérapie des Tumeurs Osseuses  
Primitives, Nantes, France, Université d'Angers, IUT,  
France

**Pierrick Fournier, PhD**

Division of Endocrinology and Metabolism, Department of  
Medicine, University of Virginia, Charlottesville, VA, USA

**Sonia Ghoul-Mazgar, DDS-PhD**

Laboratoire d'Histologie-Embryologie, Faculté de  
Médecine Dentaire de Monastir, Tunisia

**Panagiotis D. Gikas, BSc(Hons), MBBS(Hons),  
MRCS(Engl)**

Academic Clinical Fellow, Trauma and Orthopaedic  
Surgery, Royal National Orthopaedic Hospital, Stanmore,  
Middlesex, United Kingdom

**Georg Gosheger, MD**

Klinik and Poliklinik für Allgemeine Orthopädie  
Universitätsklinikum Münster, Münster, Germany

**François Guoin, MD, PhD**

INSERM, Physiopathologie de la Résorption Osseuse et  
Thérapie des Tumeurs Osseuses Primitives, Faculté de  
Médecine, Nantes, France

**Maria Grano, PhD**

Department of Human Anatomy and Histology, University  
of Bari Medical School, Bari, Italy

**Theresa A. Guise, MD**

Division of Endocrinology and Metabolism, Department of  
Medicine, University of Virginia, Charlottesville, VA, USA

**Jendrik Hardes, MD**

Klinik and Poliklinik für Allgemeine Orthopädie  
Universitätsklinikum Münster, Münster Germany

**Esther I. Hauben, MD, PhD**

Department of Pathology, University of Leuven, Leuven,  
Belgium

**Eric J. Heffernan, MD**

Vancouver General Hospital, Department of Radiology,  
Vancouver, BC, Canada

**Monica Herrera, MD**

Department of Pharmacology, College of Medicine,  
University of Arizona, Tucson, AZ, USA

**Fernanda G. Herrera, MD**

Oncology Institute of Southern Switzerland, Radiation  
Oncology, Bellinzona, Switzerland

**Dominique Heymann, PhD**

INSERM, Physiopathologie de la Résorption Osseuse  
et Thérapie des Tumeurs Osseuses Primitives Faculté de  
Médecine, Nantes, France

**David G. Hicks, MD**

Department of Pathology and Laboratory Medicine,  
University of Rochester, Rochester, NY, USA

**Amanda Hird, BSc**

Rapid Response Radiotherapy Program, Odette Cancer  
Centre, Sunnybrook Health Sciences Centre, Toronto,  
Ontario, Canada

**Pancras C.W. Hogendoorn, MD, PhD**

Department of Pathology, Leiden University Medical  
Center Leiden, The Netherlands

**Ingunn Holen, PhD**

Academic Unit of Clinical Oncology, School of Medicine  
and Biomedical Sciences, University of Sheffield,  
Sheffield, United Kingdom

**Juan Miguel Jimenez-Andrade, MD**

Department of Pharmacology, College of Medicine,  
University of Arizona, Tucson, AZ, USA

**Robert G. Jones, MRCP(UK), FRCR**

Vancouver General Hospital, Department of Radiology,  
Vancouver, BC, Canada

**Joseph Khoury, MD**

Department of Pathology, Nevada Cancer Institute, Las  
Vegas, NV, USA

**Sakari Knuutila, MD**

Department of Pathology, Haartman Institute, University of  
Helsinki, Finland

**Udo Kontny, MD**

Division of Pediatric Hematology and Oncology, Center for  
Pediatrics and Adolescent Medicine, University Medical  
Center, Freiburg, Germany

**François Lamoureux, PhD**

INSERM, Physiopathologie de la Résorption Osseuse et  
Thérapie des Tumeurs Osseuses Primitives, Faculté de  
Médecine, Nantes, France

**Ching C. Lau, MD, PhD**

Texas Children's Cancer Center, Baylor College of  
Medicine, Houston, TX, USA

**Nathan Lawrentschuk, MD**

University of Melbourne, Department of Surgery, Urology  
Unit, Austin Hospital; Heidelberg, Melbourne, Australia

**Michelle A. Lawson, PhD**

Academic Unit of Bone Biology, School of Medicine and  
Biomedical Sciences, University of Sheffield, Sheffield,  
United Kingdom

**Jiyun Lee, MD**

Genetics Laboratory, Department of Pediatrics at the  
University of Oklahoma Health Sciences Center, Oklahoma  
City, OK, USA

**Frederic Lezot, DDS-PhD**

Centre de Recherche des Cordeliers, Oral Facial Biology  
and Pathology, Paris, France

**Shibo Li, MD**

Genetics Laboratory, Department of Pediatrics at the  
University of Oklahoma Health Sciences Center, Oklahoma  
City, OK, USA

**Robert D. Loberg, PhD**

Department of Internal Medicine and Urology, University  
of Michigan Comprehensive Cancer Center, The University  
of Michigan, Ann Arbor, MI, USA

**Tsz-Kwong Man, PhD**

Texas Children's Cancer Center, Baylor College of  
Medicine, Houston, TX, USA

**Patrick W. Mantyh, PhD**

Department of Pharmacology, College of Medicine,  
University of Arizona, Tucson, AZ, USA

**Mallory Martin, MD**

Genetics Laboratory, Department of Pediatrics at the  
University of Oklahoma Health Sciences Center, Oklahoma  
City, OK, USA

**Yoshitaka Matsusue, MD**

Department of Orthopaedic Surgery, Shiga University of  
Medical Science, Shiga, Japan

**Mario Mercuri, MD**

Fifth Division of Orthopaedic Surgery, Department of  
Musculoskeletal Oncology, Istituti Orthopedici Rizzoli,  
Bologna, Italy

**Kanji Mori, MD, PhD**

Department of Orthopaedic Surgery, Shiga University of  
Medical Science, Shiga, Japan

**Peter L. Munk, MD**

Vancouver General Hospital and University of British Columbia, Department of Radiology, Vancouver, BC, Canada

**Richard J. Murrills, PhD**

Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA, USA

**Marc Padrines, PhD**

INSERM, Faculté de Médecine, Nantes, France

**Emanuela Palmerini, MD**

Chemotherapy Unit, Department of Musculoskeletal Oncology, Istituti Orthopedici Rizzoli, Bologna, Italy

**Paul C. Park, MD, PhD**

Department of Pathology and Molecular Medicine, Richardson Labs, Queen's University, Kingston, Ontario, Canada

**Alexander HG Paterson, MD**

Department of Medicine, Tom Baker Cancer Centre, University of Calgary, Alberta, Canada

**Gaëlle Picarda, Engineer**

INSERM, Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Faculté de Médecine, Nantes, France

**Kenneth J. Pienta, MD**

Department of Internal Medicine and Urology, University of Michigan Comprehensive Cancer Center, The University of Michigan, Ann Arbor, MI, USA

**Nieroshan Rajarubendra, MD**

University of Melbourne, Department of Surgery, Urology Unit, Austin Hospital; Heidelberg, Melbourne, Australia

**Pulivarthi H. Rao, PhD**

Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA

**Faisal Rashid, MD**

Vancouver General Hospital, Department of Radiology, Vancouver, BC, Canada

**Françoise Rédini, PhD**

INSERM, Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Faculté de Médecine, Nantes, France

**Carl D. Richards, PhD**

Professor, Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada

**John A. Robinson, PhD**

Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA, USA

**Julie Rousseau, PhD student**

INSERM, Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Faculté de Médecine, Nantes, France

**Blandine Ruhin, MD, PhD**

Centre de Recherche des Cordeliers, Oral Facial Biology and Pathology, Stomatology and Maxillofacial Surgery Department, Pitié-Salpêtrière University Hospital, Pierre et Marie Curie University, Paris, France

**Velasco C. Ruiz, MD**

INSERM, Université de Nantes, Nantes Atlantique Universités, Laboratoire de Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Nantes, France

**Ma'Ann C. Sabino, DDS, PhD**

Division of Oral and Maxillofacial Surgery, School of Dentistry, University of Minnesota, University of Minnesota, Minneapolis, MN, USA

**Suvi Savola, MD**

Department of Pathology, Haartman Institute, University of Helsinki, Finland

**Holger Schirrmeister, MD**

Department Head, Department of Nuklearmedizin Westküstenklinikum Heide, Heide, Germany

**Markus J. Seibel, MD, PhD**

PhD, FRACP, ANZAC Research Institute, The University of Sydney, Concord Campus, Sydney, Australia

**Shamini Selvarajah, PhD**

Center for Medical Oncologic Pathology, Dana-Farber Cancer Institute, Boston, MA, USA

**Gene P. Siegal, MD, PhD**

Robert W. Mowry Endowed Professor of Pathology and Director, Division of Anatomic Pathology, Exec. Vice-Chair of Pathology – UAB Health System, Sr. Scientist, UAB Comprehensive Cancer Center and the Gene Therapy Center, Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA

**Eric R. Siegel, MS**

Center of Orthopaedic Research, Department of Biostatistics, UAMS College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

**David Smyth, MD**

Professor, Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada



**Jeremy A. Squire, PhD**

Director of Translational Laboratory Research, NCIC-Clinical Trials Group, Research Chair in Molecular Pathology, Kingston General Hospital, Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada

**Eric L. Staals, MD**

Fifth Division of Orthopaedic Surgery, Department of Musculoskeletal Oncology, Istituti Orthopedici Rizzoli, Bologna, Italy

**Arne Steitbueger, MD**

Klinik and Poliklinik für Allgemeine Orthopädie, Universitätsklinikum Münster, Münster, Germany

**Larry J. Suva, PhD**

Center of Orthopaedic Research, Department of Orthopaedic Surgery and Physiology and Biophysics, UAMS College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

**Ping Tang, MD, PhD**

Department of Pathology and Laboratory Medicine, University of Rochester, Rochester, NY, USA

**Roberto Tirabosco, MD, FRCPath**

Royal National Orthopaedic Hospital, Stanmore, Middlesex, United Kingdom

**Valérie Trichet, PhD**

INSERM, Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Faculté de Médecine, Nantes, France

**Marina Vardanyan, MD**

Department of Pharmacology, College of Medicine, University of Arizona, Tucson, AZ, USA

**Maria Zielenska, PhD**

Genetics and Genome Biology, Department of Pediatric Laboratory, Medicine and Pathobiology, The Hospital for Sick Children, Toronto, Ontario, Canada, Kingston General Hospital, Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada



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# Epidemiology of Primary Bone Tumors and Economical Aspects of Bone Metastases

Department of Pathology, University of Leuven, Leuven, Belgium

Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

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Primary bone tumors are rare and as such they form a difficult category of tumors for appropriate acquisition and classification both for clinicians as well as pathologists. They account for less than 0.1% of the malignancies registered in the SEER database [1]. The occurrence of bone sarcoma 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 hence missed by patients and their doctors. Therefore, benign bone tumors are most likely underestimated. But nevertheless they are, like other benign tumors, a rare event. Another confounding factor is the high discrepancy rate in histological review of bone tumors, which make that population-based series remain scarce available [2]. On the other hand, consultation series or expert center series are likely to over-report differential rates.

Bone tumors can occur spontaneously. However, a substantial number of them do occur in the context of a

secondary disorder that might bring 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 incidence 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 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 and lymphomas.

### I. INCIDENCES OF PRIMARY BONE TUMORS

The incidence of bone tumors—especially primary bone cancers—compared to malignant tumors—in general is very low. Review of large series revealed that approximately 0.1% of all neoplasms are bone sarcomas [10-12]. In France about two new primary bone sarcomas arise per 100,000 persons a year. Interestingly, if childhood there is a peak with its frequency of occurrence over the age span [13]. From the first year of life the incidence increases from 0.9 per million to a peak of 642.9 per 100,000 at the age of fifteen [14]. The archives of the Netherlands Committee of Bone Tumors contain details of over 10,000 cases of bone tumors and a population where the percentages of the sarcomas are approximately in the order of frequency for malignant bone diseases: osteosarcoma (32%), chondrosarcoma (22.6%), fibrosarcoma (11.2%), liposarcoma/malignant fibrous histiocytoma (10.9%), Ewing-Moserkin's lymphoma of bone (0.9%), rhabdomyosarcoma (0.8%), and chondroblastoma (0.8%) [10].





# Epidemiology of Primary Bone Tumors and Economical Aspects of Bone Metastases

ESTHER I. HAUBEN<sup>1</sup> AND PANCRAS C.W. HOGENDOORN<sup>2</sup>

<sup>1</sup>Department of Pathology, University of Leuven, Leuven, Belgium

<sup>2</sup>Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

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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].



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, Langerhans cell 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 epiphyseal 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 metaphyseal and diaphyseal 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 epiphyseal location is restricted for chondroblastoma, osteoblastoma and dysplasia epiphysealis 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