
Bone Metastases from Prostate Cancer

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Editors

Bone Metastases from Prostate Cancer

Biology, Diagnosis and Management

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Foreword

Would you like to know everything that there is to know about bone metastases from prostate cancer? Prostate cancer is the second most diagnosed malignancy and the sixth cause of cancer-related death worldwide and is one of the cancers that most frequently metastasizes to the bone. Would you like to be knowledgeable about all of the new imaging techniques and treatments available for bone metastases? This textbook is not only on bone metastases but is an up-to-date review on everything the clinician needs to know about prostate cancer.

This book was conceived with the intention to emphasize bone pathology and metastases, critical to prostate cancer. You will learn about the complex histology, high heterogeneity, and bone matrix-derived factors. Each chapter is thorough, well written, and up to date. There is a section devoted to markers of bone turnover in bone metastasis and new markers. Many chapters contain beautiful illustrations and images of bone metastases. You will learn about non-osteoclastic bone, bone resorption mediated by metalloproteases, periostin, bone sialoprotein, osteopontin, and other emerging markers. You will acquire the ability to compare new markers with “classic” bone markers.

You are invited to improve your knowledge of bone homing and metastasis, the result of a multistep process that requires an interaction between tumor cells and the bone microenvironment that starts with tumor malignant progression and invasion through the extracellular matrix and leads to bone metastases. You will gain knowledge about the role of epithelial-mesenchymal plasticity in bone homing, the role of chemokines and their receptors, and the role of microRNAs. You will also understand the many signaling pathways implicated in the development of prostate cancer bone metastases.

There is an increasing need for validated, reliable circulating tumor markers. PSA is discussed in great detail and the clinical settings, in which it is most useful, with an exhaustive summary of recommendations as to its predictive use in staging, and detection of recurrence.

You will learn about the different methodologies in detecting circulating tumor cells (CTCs). CTCs can provide valuable information about disease heterogeneity, clonal evolution, disease progression, and response and development of resistance to therapies such as novel AR-directed treatments.

Conventional imaging methods are inadequate for the assessment of changes in bone metastases in response to various treatments. PET with various targeted radiotracers is required. There are several chapters devoted to distinguishing among the different imaging methodologies: ^{99m}Tc -biphosphonates planar scintigraphy or SPECT/CT, ^{18}F -FDG PET, ^{18}F -NaF PET/CT, $^{11}\text{C}/^{18}\text{F}$ choline PET/CT, and ^{68}Ga -PSMA PET/CT. You will learn about the different sensitivities and insensitivities of these modalities in identifying disease and capturing degrees of biological response and the challenges such as flare phenomenon. PSMA-based PET imaging agents fall into three categories. Consider also the auspicious performance of ^{18}F -FACBC, ^{68}Ga -PSMA PET/CT for investigating prostate cancer patients with biochemical recurrence.

Radiation therapy techniques are continually evolving, not only for treating the prostate. Careful attention is paid to new techniques for the palliation of bone metastases. There is an excellent summary of randomized trials comparing single versus multiple fractions in the palliative setting, data on stereotaxic irradiation for oligometastatic disease, and much more.

This book discusses classic hormonal therapy, first-generation antiandrogens, and novel second-generation antiandrogens. You will learn about AR splice variants, such as AR-V7 and AR567e, and their predictive and prognostic value. The cross-resistance between abiraterone and enzalutamide are important topics.

Chemotherapy with docetaxel and cabazitaxel plays an important role in patients with prostate cancer. The trials that have further investigated these agents in CRPC are reviewed. You will learn about Radium-223 that can not only decrease symptomatic skeletal events but also increases survival.

A hot topic in CRPC is molecular profiling. Studies have shown that around 90% of mCRPC patients harbor clinically actionable molecular alterations and 23% harbor DNA repair pathway aberrations that may respond to PARP inhibitors or platinum. The clinical trials in hormone-sensitive prostate cancer are also reviewed in great detail, as is the treatment of oligometastatic disease with radiation or surgery.

Nociceptive and neuropathic pain, pain assessment, pain syndromes in prostate cancer bone pain, and treatment of cancer-induced bone pain are extensively reviewed as well as simultaneous palliative care.

The economic impact of prostate cancer bone metastases and skeletal-related events is also explored. This book concludes with discussions on the importance of a multidisciplinary team approach to prostate cancer and the importance and benefits of well-organized prostate cancer units.

This textbook is a must for anyone who is interested in prostate cancer. It is well written, up to date, and highly relevant.

Cora N. Sternberg, MD, FACP

Preface

Skeletal metastases affect more than 80% of men with metastatic prostate cancer, and they are the main cause for patients' poor quality of life, morbidity, and mortality. In the recent years, there was a tremendous improvement in the options of treatment for patients with metastatic prostate cancer. New hormonal, cytotoxic, immunotherapeutic drugs and new therapeutic radiation-based strategies have been developed. These approaches achieved very important results also in terms of overall survival and appear to be suitable for a large number of patients with metastatic prostate cancer, either those affected by hormone-naïve prostate cancer (HNPC) or those affected by castration-resistant prostate cancer (CRPC). One could say that while in the past the majority of patients, especially those affected by CRPC, were candidate only to best supportive care, at present most of them can afford upon different treatment choices able to impact favorably both with their life expectancy and their quality of life as well as upon novel therapeutic options and new combination strategies which promise to further improve patient outcomes.

In view of the increasing interest and number of scientific contributions in this area, we have conceived the idea to invite a number of distinguished colleagues to summarize the state of the art and to examine the new perspectives from their different points of view on the most important topics related to bone metastases in prostate cancer, starting from the physiopathological background of bone metastatization and the biological mechanisms involved in bone remodeling and in skeletal homing of cancer cells, which are the premises to a rational approach to the disease. Markers of these phenomena are described and analyzed in view of their clinical applications in everyday clinical practice. A special focus was given to the putative role of circulating cancer cells, circulating markers of bone metabolism, and markers of prostatic cancer. The metabolic relevance of the mechanisms involved in bone metastatization is also described in the perspective of the technological advancements of metabolic imaging that visualizes bone metastases through new radiopharmaceuticals capable to target bone changes caused by metastasis or directly prostate cancer cells. New modalities of metabolic imaging, such as ^{18}F -fluoride, $^{18}\text{F}/^{11}\text{C}$ -choline, and ^{18}F -FDG positron emission tomography (PET)/computed tomography (CT), are reported, including the most recent experimental tracers like ^{68}Ga -prostate specific membrane antigen (^{68}Ga -PSMA). In the radiological area, the contribution of the multimodality

magnetic resonance imaging (MRI) in improving the accuracy of CT has been critically discussed, also in terms of availability of this technique and relative costs. As a logical consequence of an adequate diagnosis and staging, attention was moved to the available treatment options for patients with prostate cancer bone metastases (hormonal therapy, chemotherapy, chemotherapy associated with hormonal manipulations, bone targeted drugs, surgery, external beam therapy, and radio-metabolic therapy). The evaluation of treatment response in bone metastatic prostate cancer is one of the key points addressed in the textbook due to the limits of currently available tools, namely, radiology and nuclear medicine imaging. The putative advantages of one or more techniques over the others have been specifically analyzed. The putative role in implementing the definition of tumor response at the bone level by the dosage of markers of bone turnover and of prostate-specific antigen (PSA) has been also considered. The performances and limitations of the criteria adopted in the most important clinical trials and which are currently recommended by the Guidelines of the Scientific Societies have also been critically reviewed. A look at other issues that are strictly correlated with the management of the patients affected by bone metastases has been provided. The abovementioned issues include bone pain palliation and prevention of major adverse skeletal events as well as the social and economic impact of bone metastases, which intuitively is not limited to the costs more directly related to patient care. The necessity of addressing this increasingly important health problem through a multidisciplinary team of clinicians able to intercept all the patient needs and to provide an appropriate answer to all of them has also been addressed, with the hope that this model could become standard for the majority of the centers involved in the management of prostate cancer. Our ambition, as editors of this volume, was to provide the readers with a complete but clear-cut information about the most relevant results achieved in the different areas concerning the topic as well as a look at the researches that are still going on and that promise to further change the course of the disease and of its management. Let's hope we have reached the scope, thanks to the efforts of the authors who have accepted to actively provide their contributions and to the editor staff who trusted in this task and whose help and assistance was essential to complete it.

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