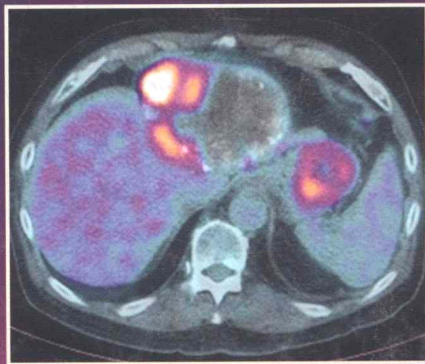
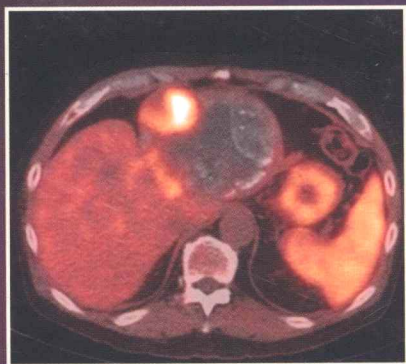


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Nuclear Oncology



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Foreword by Heinrich R. Schelbert



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NUCLEAR ONCOLOGY

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To my wife, Miriam Goldsmith, who dedicated her life to our family, to my professional goals, and to me. Her love made possible the life that I have been fortunate enough to have lived.

Stanley J. Goldsmith, MD

To Mustafa Kemal Ataturk, the founder of Republic of Turkey, who established the foundations of modern scientific education in my country.

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FOREWORD

Nuclear Medicine has grown at an astonishing pace. When I first became involved in Nuclear Medicine, imaging had just transitioned from rectilinear scanners to gamma cameras; planar imaging of the brain, of perfusion and ventilation of the lung, of colloid uptake in the liver and spleen, of gall bladder function and renal blood flow and function dominated the daily nuclear medicine fare. Imaging of the cardiovascular system was in its infancy and nuclear oncology consisted bone imaging and an occasional gallium uptake study.

The introduction of cross-sectional imaging with computed tomography (CT) and later with magnetic resonance imaging (MRI) profoundly transformed the field of diagnostic imaging. In fact, the arrival of CT was feared to threaten the very existence of nuclear medicine; radionuclide procedures like the many brain scans soon began to disappear from the daily nuclear medicine schedule as CT became clinically available.

Yet, nuclear medicine has proved itself to be astoundingly resilient. With single photon emission tomography (SPECT) and positron emission tomography (PET), nuclear medicine joined cross-sectional imaging, yet in a unique and specific way by focusing on assays of tissue function and biology rather than on anatomy. Combined with anatomic imaging with PET/CT or PET/MRI today, molecular and cellular events visualized on radionuclide images can now be localized precisely. Even more importantly, as these images display biologic properties of anatomic alterations, hybrid function/structure imaging has gained growing clinical interest and importance. Accordingly, nuclear medicine schedules have dramatically changed. Today, they are dominated by qualitative and quantitative image-based tissue assays with SPECT/CT and especially PET/CT for cancer diagnosis and staging, prediction of clinical outcomes, and monitoring therapy responses, for planning radiation therapy and for identifying treatment targets.

Nuclear medicine owes much of this change to impressive advances in cancer research which have led to an improved and more detailed understanding of cancer biology, including tumor growth and angiogenesis, growth receptor function and intracellular signaling chains, and cancer survival strategies. They have also defined key regulatory steps as potential treatment targets. These advances have driven the development of highly targeted imaging probes for the noninvasive visualization of molecular and cellular events ranging from substrate utilization to amino acid metabolism and cell growth, angiogenesis and perfusion as well as cell membrane receptors regulating cell growth and replication. Labeled with radionuclides, many of these targeted imaging probes, tested and validated in the research laboratory, are now entering the clinical environment. They arm both, the nuclear medicine physician and the oncologist with specific tools for the image-based detection of cancer, estimation of its severity and extent, prediction of tumor progression and outcome and, importantly, measurements of therapy responses. With these tools, the nuclear medicine physician participated as "nuclear oncologist" in the care of cancer patients.

With this book, Drs. Cumali Aktolun and Stanley J. Goldsmith, well-known authorities in nuclear medicine, have enlisted many internationally known specialists to present, for the first time, a much needed comprehensive account of today's nuclear oncology. This "inventory" of today's nuclear oncology appropriately proceeds with a series of reviews of organ-related malignancies and of system-wide cancers, to practical issues in cancer imaging and, finally, to image-based assays of cancer biology and radionuclide therapy. Each chapter on organ-related or system-wide tumors presents the current knowledge of molecular cancer pathogenesis and development, early tumor manifestations and tumor spread, established and emerging therapeutic strategies and clinical outcomes. Advantages and limitations of diagnostic approaches are critically assessed, including biomarkers and image-based technologies for cancer diagnosis and staging, for cancer recurrence and therapy response. Nuclear medicine approaches like planar and SPECT imaging are included but applications of modern PET/CT imaging are emphasized appropriately. Their utility is fully integrated with that of more conventional imaging technologies like ultrasound, CT, and MRI for optimizing the diagnostic approach to cancer diagnosis and characterization. Importantly, the "inventory of nuclear oncology" extends into more specific topics like cancer in the pediatric population, image-based monitoring of treatment responses but also of chemotherapy-related adverse effects, to image-based target identification and targeted radionuclide therapeutic strategies ("theranostics") and the role of nuclear medicine in response-adapted treatment strategies. Each topic is abundantly illustrated with high quality mostly color renditions of cancer-specific findings made with CT, MR, SPECT, and PET/CT. Beyond these diagnostic radionuclide approaches largely implemented in today's clinical practice, the "nuclear oncology inventory" ventures into emerging approaches and thus offers a view of what may lie ahead. This prospect of the future includes radionuclide technologies employed primarily in the research environment but attests to future clinical possibilities for targeting specific aspects of molecular cancer biology such as for example growth receptors, hypoxia, cell replication, angiogenesis, extracellular matrix formation, and apoptosis.

The text succeeds in merging basic and clinical sciences in oncology with knowledge in nuclear imaging and therapy. As such, it is of considerable interest to both, the clinician and the imager. Importantly, it is destined to intensify and broaden interactions and collaborations between nuclear and clinical oncologists.

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The Journal of Nuclear Medicine

PREFACE

This volume, *Nuclear Oncology*, is a compendium of the state of the art of Nuclear Medicine procedures relevant to the current practice of Oncology, primarily diagnostic imaging and to some extent to targeted radionuclide therapy when appropriate.

Over a decade ago, both of the editors of this volume had previously individually coedited a volume on *Nuclear Oncology*. Since that time, a great deal of progress has occurred; SPECT has evolved from SPECT to SPECT/CT and PET to PET/CT; ^{18}F -FDG PET/CT has revolutionized the practice of oncology; PET/MR has been emerging as a clinical technology; and the scope of molecular imaging has remarkably expanded to the point that many new molecules have gained acceptance as an imaging or therapeutic tracer.

It would not be an overstatement to say that ^{18}F -FDG PET/CT is essential for the current practice of oncology including the determination of the extent of disease, evaluation of treatment response, surveillance following treatment, and on some occasions, even contributing to the diagnosis by differentiating benign from malignant lesions or at least characterizing the metabolic activity.

Currently, we are on the brink of introducing into clinical practice other tracers such as ^{18}F -fluorocholine, ^{18}F -fluorothymidine, and a host of ^{68}Ga - or ^{89}Zr -labeled molecules to recognize specific tumor characteristics. SPECT/CT is increasingly being applied to imaging single photon emission tracers, thus improving both sensitivity and specificity. Instrumentation, too, is on the brink of another giant step forward: The development and application of MRI/PET devices that will perform, in this case, simultaneous acquisition of MRI anatomic data and PET images of the underlying metabolic process being imaged depending upon the tracer.

There is no doubt that image fusion increases overall accuracy; it also improves the ability to communicate findings to clinicians who are not imaging specialists and to physicians in training. There has also been considerable growth in the number of targeted radionuclide therapy agents, but the data published in this volume are limited since more detailed descriptions have recently been published.

The editors, taking into consideration the above advances in the field of Nuclear Oncology, have tasked our authors to prepare reviews of the current applications of the available tracers using these techniques but also to include information on techniques in development and, when possible, to suggest likely future developments or needs.

All aspects of Nuclear Oncology including topics directly related to the practice of Oncology such as diagnostic and therapeutic radionuclide techniques are compiled in a single volume, but experimental molecular imaging techniques and newest trac-

ers and technology are also detailed in plain language, emphasizing their clinical potential in future practice. Up-to-date clinical, experimental, and technical data are presented by expert authors practicing or researching in the subject they described in their chapters. The volume is divided into 5 parts and 43 chapters. Nineteen chapters are devoted to malignancies involving specific organs such as the Brain, Breast, Lungs, Prostate, etc. Five additional chapters are devoted to malignancies that may be found virtually anywhere in the body, such as Lymphoma and Neuroendocrine Tumors. In addition, there are nine chapters on special topics, such as Pediatric Tumors and Cancer of Unknown Primaries. Eight chapters are devoted to investigational aspects of Tumor Biology and Molecular Imaging, such as Imaging of Multi-drug Resistance, Annexin, Human Epidermal Receptors, Integrins and Hypoxia, as well as two chapters on Technical Issues, Instrumentation, Radiochemistry, and Radiopharmaceuticals. Pediatric tumors, the role of bone mineral densitometry in oncology, sentinel lymph node imaging, assessment of lymph node involvement, response to antineoplastic treatment, non-FDG PET/CT imaging, emerging role of PET/CT in radiotherapy planning, angiogenesis, tumor cell proliferation, and apoptosis are given special emphasis in separate chapters. All chapters are delightfully comprehensive. The editors are grateful to our chapter authors for their expertise and conscientious effort to communicate these complex ideas so thoroughly and clearly.

Although our past efforts were inclusive of physicians and scientists from many nations, this volume is even more diverse in the sources of expertise drawn upon to provide readers with a view of Nuclear Oncology as it is perceived on a worldwide canvas. We are pleased also that we were able to include many younger physician-scientists who are bringing new ideas and renewed energy to research and practice of nuclear medicine in oncology. In editing the chapters as they were completed, we were pleased with the knowledge and wisdom contained in the texts and touched by the conscientious efforts of so many individuals from all around the world to provide comprehensive and authoritative reviews of the history and current status of these diverse topics in Nuclear Oncology.

Truly, we are fortunate to have been able to assemble the contributors who have enabled us to bring this remarkable volume to our readers: Nuclear medicine and oncology physicians, scientists, and trainees. We are hopeful that this volume will contribute to further utilization of nuclear medicine diagnostic and therapeutic procedures and to improved management and clinical outcomes in the care of patients with malignant diseases.

Stanley J. Goldsmith, MD, and Cumali Aktolun, MD, MSc

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Cumali Aktolun and Stanley J. Goldsmith