Oncology

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An Evidence-Based Approach

With 346 Figures in 501 Parts

Edited by

Alfred E. Chang, MD
Hugh Cabot Professor of Surgery; Chief, Division of Surgery Oncology; Department of Surgery, University of Michigan, Ann Arbor, Michigan

Patricia A. Ganz, MD
American Cancer Society Clinical Research Professor, Director, Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center at UCLA, Professor, Schools of Public Health and Medicine, University of California, Los Angeles, Los Angeles, California

Daniel F. Hayes, MD
Clinical Director, Breast Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan

Timothy J. Kinsella, MD
Vincent K. Smith Professor and Chairman, Department of Radiation Oncology, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio

Harvey I. Pass, MD
Professor and Chief of Thoracic Surgery, Department of Cardiothoracic Surgery, Head, Thoracic Oncology, New York University School of Medicine and Comprehensive Cancer Center, New York, New York

Joan H. Schiller, MD
Melanie Heald Professor of Medical Oncology, Department of Medicine, University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin

Richard M. Stone, MD
Associate Professor, Department of Medicine, Harvard Medical School, Clinical Director, Adult Leukemia Program, Dana-Farber Cancer Institute, Boston, Massachusetts

Victor J. Strecher, PhD, MPH
Professor and Director, Health Media Research Laboratory, Department of Health Behavior and Health Education, University of Michigan School of Public Health, Associate Director, Cancer Prevention and Control, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan

Foreword by Gabriel N. Hortobagyi, MD, FACP

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Alfred E. Chang, MD
Hugh Cabot Professor of Surgery
Chief, Division of Surgery Oncology
Department of Surgery
University of Michigan
Ann Arbor, MI, USA

Daniel F. Hayes, MD
Clinical Director, Breast Oncology Program
University of Michigan Comprehensive Cancer Center
Ann Arbor, MI, USA

Harvey I. Pass, MD
Professor and Chief of Thoracic Surgery
Department of Cardiothoracic Surgery
Head, Thoracic Oncology
New York University School of Medicine and Comprehensive Cancer Center
New York, NY, USA

Richard M. Stone, MD
Associate Professor, Department of Medicine
Harvard Medical School
Clinical Director, Adult Leukemia Program
Dana-Farber Cancer Institute
Boston, MA, USA

Patricia A. Ganz, MD
American Cancer Society Clinical Research Professor
Director, Division of Cancer Prevention and Control Research
Jonsson Comprehensive Cancer Center at UCLA
Professor, Schools of Public Health and Medicine
University of California, Los Angeles
Los Angeles, CA, USA

Timothy J. Kinsella, MD
Vincent K. Smith Professor and Chairman
Department of Radiation Oncology
University Hospitals of Cleveland
Case Western Reserve University
Cleveland, OH, USA

Joan H. Schiller, MD
Melanie Heald Professor of Medical Oncology
Department of Medicine
University of Wisconsin Comprehensive Cancer Center
Madison, WI, USA

Victor J. Strecher, PhD, MPH
Professor and Director, Health Media Research Laboratory
Department of Health Behavior and Health Education
University of Michigan School of Public Health
Associate Director, Cancer Prevention and Control
University of Michigan Comprehensive Cancer Center
Ann Arbor, MI, USA

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I would like to dedicate this book to all of our cancer patients. They are the ones who have taught us about living, coping, and how to be better physicians.
AEC

Producing a new textbook is a little like designing a clinical protocol by committee: we had specific aims, with some proposed methods, and we got a pretty good result. I appreciate the team work of my co-editors, and especially the contributions of my colleagues who helped to launch survivorship as a recognized component of an oncology text.
PAG

To I. Craig Henderson, M.D., who first taught me the importance of scientifically-based clinical evidence for decision-making, and to my wife, Jane, who has provided so much so that I can pursue my whim: academic medicine.
DFH

Dedicated to my wife Susan and children for their unending support; also dedicated to my oncology mentors Sam Hellman, George Canellos and Eli Glatstein.
TJK

To my family, Helen, Ally, and Eric, who always put up with my tendency to get overextended, but always have time to make me feel loved
HIP

To my parents, my husband George, and my children Quintin, Craig, and Lindsey, all of whom have been incredibly supportive over the years
JHS

To my wife Jane and my children Ben, Rebecca, Sarah, and Harry
RMS

For Jeri, Rachael, and Julia
VJS

Foreword

Compared to more traditional subspecialties, oncology is a young, vibrant, and progressive branch of medicine that has relatively few ties to a dogmatic past. Perhaps for this reason many innovations in oncology have occurred as a consequence of rapid cultural changes within the specialty, and continued change remains an accepted and integral part of our field. While most other practitioners of medicine learned a "standard of practice" and some dedicate their practice to clinical and/or basic research, research has been an integral and inseparable part of oncology since its inception. Consequently, virtually all oncologists consider clinical trials and experimental therapeutics as bread and butter and as necessary components of an ongoing progress. The broad acceptance of the necessity of prospective clinical trials and the continued testing of new drugs, strategies, and concepts highlights the need for differentiating hypothesis from fact, experience from experimental results, and opinion from fact. Such separation is the basis of evidence-based medicine, and oncology is one of the specialties with perhaps the richest tradition of practicing it. Considering that medicine has relied almost exclusively on clinical observation, anecdotal series, and uncontrolled personal experience for the past many centuries, such rapid adoption of evidence-based medicine is somewhat surprising and attests to the scientific orientation of our discipline.

For the past three decades several excellent textbooks on oncology were developed. The leading examples are multiauthored volumes that summarize the results of clinical trials placed in clinical context by experts on the field. These are encyclopedic textbooks in the best tradition of medicine, and several have progressed through multiple editions. In that context, what will the current textbook contribute to the field and how is it different from other volumes in the crowded field of oncology? Multiple answers to this question emerge from a careful review of this textbook. First, this book reflects a mature field of oncology; in addition to descriptions of natural history, clinical course, and the value of commonly used therapeutic strategies, much emphasis is placed on the cost, in terms of unwanted effects or toxicities associated with treatments. In addition to detailed presentations of acute side effects and their management, there is careful presentation of long-term effects, most of which are irreversible and some, potentially lethal. Only such careful assessment and tabulation of quantifiable therapeutic affects placed on the balance along with acute and long-term toxicities can provide a true picture of the therapeutic ratio of an intervention, which can then be translated in the context of each patient's clinical situation, risk of progression, recurrence, or death. Second, the book presents a systematic approach to issues of survivorship. Physicians with a major interest in survivorship describe some of these, while survivors themselves describe others, providing a poignant perspective not found in books entirely authored by medical specialists. This aspect is the logical consequence of the increasing integration of users in breast cancer research and allocation of resources. Patient perspectives have contributed in a major way to identification of research fund over the past decade, and their participation in the activities of multiple research groups have contributed to identification of important questions to be addressed and the prioritization of research activities in cancer centers, SPOREs, and other multi-investigator activities. Such contributions are irreplaceable and of great importance to reaching the ultimate goals of cancer research: improvements in quality and duration of life.

The third, and perhaps most important contribution of this volume, is the emphasis on determining the quality of evidence in the integration of research results into guidelines or recommendations for patient care or design of subsequent research. The first chapter is dedicated to the definitions of research quality, systematic approaches to quantify levels of evidence, and providing examples of such systematic approach to grading quality of cancer investigation. It is no accident that the editor in chief of the *Journal of the National Cancer Institute*, dedicated for many years to the assessment of the quality of research publications is the senior author of this chapter. In

earlier decades, assessment of the quality of research was an intuitive process, and most seasoned oncologists based their enthusiasm for specific reports or research results on their subjective assessment of the research in question. Such subjective assessments were based, in part, on the name recognition of the reporting investigator(s), the reputation of the center or group behind the research, the sample size, and often the biases of those engaged in the assessment. The systematic approach to assigning specific levels of evidence to research reports goes a long way toward removing subjectivity from these assessments, focusing more on the methodology and the inherent strengths and weaknesses of any particular research approach than on the concordance of the results with preconceived biases or favored hypothesis. Identifying reports with the highest levels of evidence often clarifies seemingly confusing collections of data and often points out the glaring weaknesses or deficiencies of specific fields of interest. Sometimes it becomes apparent that despite decades of accepted treatment approaches, no evidence exists on which to base such approaches. It is apparent from such application of evidence-based scrutiny that modern medicine is still a hybrid filed, where evidence-based approaches coexist and often comingle with old observations, qualitative personal experiences, opinions, and anecdotes. It is amply clear that the generation of high-quality evidence requires time and resources, including the willing participation of users, in this case, research subjects and patients. It is also clear that in many situations, physicians will have to continue using clinical judgment, extrapolate from related evidence and utilize common sense in the day-to-day management of clinical problems, because only a relatively small proportion of oncological treatments have been subjected to strict, controlled, prospective clinical trials, and not every question will be the subject of high-quality clinical trials in the future. Limitations in time and resources and the ongoing supply of high-priority biological questions will always displace questions of lower priority.

Let us examine then other features of this remarkable book. The first few chapters review the basic approaches to treat cancer. Surgery, radiotherapy, and chemotherapy are carefully presented, with a clear description of mechanisms of action and in the context of modern biological understanding of the malignant process. The chapter about radiation therapy is an example of the enormous progress made in our understanding of this highly technological branch of cancer treatment and the major progress that has occurred in this specialty over the past few years. Targeted therapy is the latest addition to our armamentarium, but it is one of the most exciting aspects of systemic treatments because it is based on clear understanding of the molecular underpinnings of the biological advantage of certain malignant cells over their normal components, biological characteristics that drive the proliferation, invasion, metastasis, and survival of such cells. The recent success of specific forms of targeted therapies (imatinib, trastuzumab, bevacizumab, and the endocrine agents) emphasize the enormous potential of this approach in the development of more specific treatments with fewer expected consequences on nonmalignant tissue. This chapter also highlights the many challenges encountered in the development of targeted agents, such as the need to validate molecular targets, to demonstrate in vivo that the agent accomplishes its desired effect on the target and, in consequence, can be expected to produce a specific clinical effect. These challenges have proved to be major obstacles in the case of certain targets, yielding easily in the case of others.

Tumor markers are an inherently attractive concept. Would it not be desirable to have a marker of disease extent, activity or malignant potential that one can identify and quantify in a minimally invasive or noninvasive manner? Would it not be helpful to relay on such markers to determine the efficacy of therapy early in a therapeutic intervention? The author of Chapter 7 is a recognized expert in this field and has contributed to our conceptual systematization of the tumor marker field with the development of clear criteria for validating markers and guidelines for their utilization, as well as recommendations to avoid obvious pitfalls in this area.

Much of the high-level evidence we have today was derived from prospective clinical trials. The chapter describing these master tools is authored by enormously experienced clinical trials who have contributed both conceptually and practically to the definition, implementation and analysis of randomized clinical trials. This chapter provides an excellent roadmap for current and future investigators.

The ethics of human experimentation are a critical subject for all investigators and patients. Decades of controversy have refined our approach to randomized trials,

no treatment or placebo controls, and defined optimal approaches for analysis and release of trial results. High-quality evidence can only be generated in the context of a highly ethical trial design. Screening and early diagnosis present particular challenges, largely because they relate to asymptomatic subjects, most of whom will not need nor benefit from these interventions. Therefore, these approaches benefit a few, while exposing many to potential risks. Trial design, ethics, and economics meet and often collide in this field.

As increasing emphasis has been placed on patient autonomy and as the population at large has gained increasing access to medical information, issues related to alternative and complementary therapies have also become prominent. This field includes IT, where assessment of levels of evidence can provide enormous benefits to our patients and also to healthcare providers, who often have only a passing knowledge of such popular, but often untested approaches, to the treatment of cancer or its symptoms. The lead author is clearly one of the most knowledgeable experts on this field and provides a broad overview of the issues.

Outstanding contributions cover the potential etiologies of cancer, as well as the basic biological principles of malignant transformation, invasion, and metastases. The role of the immune system is receiving increasing attention, as greater effort is being expended on the development of vaccines and other immunological approaches to cancer control.

One of the outstanding examples of the application of evidence-based medicine is Chapter 23. The authors describe the complexity of research that brings together epidemiology, basic sciences, and chemoprevention trials, in a field where isolated causes of cancer are seldom identified and where control of all variables is an unrealistic expectation. These issues are highlighted in examples of dietary intervention or the use of specific components of the human diet, such as vitamins, minerals, and other micronutrients.

The identification of genes involved in cancer predisposition has dramatically changed our approach to familial cancer syndromes. Our ability to precisely identify subjects at risk for certain malignant tumors has also placed in evidence complex social, psychological, financial, and ethical issues that need to be addressed with subjects potentially eligible for genetic screening or preventive interventions. Such advances have also uncovered potential leads for identifying other genes that influence the development of more common, apparently sporadic cancers in the population, and eventually point to future therapeutic strategies.

The chapters dedicated to specific malignant tumors bring together updated information about epidemiology, carcinogenesis, natural history, diagnostic procedures, and therapeutic interventions. The book highlights, in general, that optimal care requires close interdisciplinary collaboration, both in the diagnostic process and therapeutic strategies. There is much emphasis on the results of randomized trials, as the major theme of the book would indicate. It is painfully clear, however, that for common adult malignancies there is much evidence generated from prospective randomized trials that allows the development of evidence-based treatment guidelines; however, this is often not the case for less common tumors, especially those most resistant to systemic treatments. For these, treatment strategies are often based on observational or single-arm prospective trials. The recent identification of molecular targets for some of these tumors (renal cell or pancreatic cancers) has led to renewed interest and some notable successes in recent clinical trials.

Chapter 63 is an excellent example of how the editors envision the presentation of systematic knowledge about a specific disease condition. The authors synthesized an enormous body of information derived from clinical trials if patients with acute leukemia or myelodysplastic syndromes. The highest quality evidence, based on multiple phase III trials, is presented first, followed in descending order of quality by other types of evidence.

The stepwise development of therapeutic interventions, comparing the best "standard" to an investigational approach, is a logical candidate for evaluation in prospective randomized trials. Patient selection can be predetermined, and, in general, treatments can be compared on relatively homogeneous groups of patients. That is clearly not the case for complications of malignancy or treatment; such events occur at different times of the clinical course of the disease, and of course, patients cannot be selected a priori. Rather, the development of the complication selects the patients and treatments must be adjusted to the patients' circumstances.

For these reasons it is all the more satisfying to review Chapter 71 about acute CNS complications. Such complications are almost always dramatic and require prompt intervention. It is, therefore, all the more admirable to find level I evidence and Grade A recommendations for the management of an oncological emergency. The secondary message of these results is that appropriate controlled trials can be ethically developed in almost every circumstance in the oncological patient, and high level evidence can be generated for optimal management of subsequent patients.

Another excellent chapter, Chapter 76, summarizes current knowledge and therapeutic approaches to infectious complications of malignant disease and their treatments. While not presented with detailed assessment of levels of evidence, this chapter highlights current approaches to common and uncommon infections, the appropriate use of antibiotics and hematopoietic growth factors, and introduces methods to prevent or reduce the risk of infectious complications. It is gratifying how, from the number one cause of treatment-related mortality a few decades ago, infectious complications have become a much more manageable, and in fact, almost completely preventable complications of cancer treatment, especially in patients with solid tumors.

Chapter 83 focuses on a difficult field of research, the assessment, management, and prevention of nausea and emesis. While a common side effect of cancer treatment, especially chemotherapy and radiotherapy, nausea and emesis are difficult research subjects because of the major subjective component, interindividual variability, and the lack of external, validated, hard endpoints, short of counting the numbers of emetic episodes. Despite these obstacles, multiple prospective randomized have been conducted, comparing antiemetics with placebo or no treatment, or two antiemetics, or single antiemetics with combination therapy. The tables not only describe the results of such research, but list them in the order of higher to lower level of evidence. Such ranking facilitate the assessment of relative value of information derived from different clinical trials and also identifies opportunities to conduct additional research to clarify or complement existing evidence.

Other fields of research, especially those in the psychosocial and behavioral disciplines, have made less progress in the implementation of levels of evidence to research results. This observation is largely based on the predominantly "soft" endpoints utilized in many of these disciplines—endpoints that lend themselves less to easy quantification. As validated instruments are developed and employed in prospective research, this is also likely to change, and we can expect an increasing emphasis on evidence-based recommendations and guidelines in these fields too.

Much progress has been made since the War on Cancer was declared in 1971. Some of it was the result of the outstanding laboratory based research conducted with the support of the National Institutes of Health, National Cancer Institute, American Cancer Society, and multiple foundations, and resulted in marked improvement in our understanding of the basic biological underpinnings of malignant disease and the processes that give it its life-threatening characteristics. Some progress was derived from the technological progress in developing new diagnostic methods, refining our ability for early diagnosis, staging, and focusing of therapeutic interventions. Some progress was the result of successful drug development resulting in more effective therapeutic interventions that reduced markedly the probability of recurrence and mortality for patients diagnosed with several common human solid tumors and hematological malignancies. However, progress has been costly in financial terms, infrastructure building, and human resources. With more than 1800 new oncological drugs in the pipeline, and almost half of them at some stage of clinical development, resources are becoming even scarcer and more precious. It behooves us, as a community, to find or develop more effective and more cost-effective methods to assess the efficacy of drugs and procedures, to identify patients more and less likely to benefit from a specific intervention, and to minimize waste in the utilization of the multiple diagnostic and therapeutic approaches we have available to us today. Such urgent need for cost-effective approaches is even more dramatically highlighted by the plight of the majority of countries with limited resources around the globe. Squandering precious resources in poorly designed healthcare strategies limits access to life saving procedures. Our best hope is the increasingly stringent application of high-level evidence to decision making at the level of public health officials but also at the level of each individual physician. To enhance our probability of success, we need to speak in the language of evidence, think of levels of evi-

dence in the design of research projects and clinical trials, and increasingly limit our recommendations to those interventions supported by the highest levels of evidence. Anything less will limit access to high-quality care and dilute our efforts to serve our patients. We hope that this textbook and subsequent editions of it will lead the way towards the implementation of evidence-based oncology and set the tone for future textbooks in other medical fields.

Gabriel N. Hortobagyi, MD, FACP
Professor and Chair
Department of Breast Medical Oncology
Director of the Multidisciplinary Breast Cancer Research Program
The University of Texas
M. D. Anderson Cancer Center

Preface

A new textbook in oncology?! What is different about this book compared to other established texts that have already been published? Why do we need a new book? For anyone in the market for a textbook, the main reason is to keep pace with the knowledge base that is growing ever so rapidly in oncology, a field that is evolving faster than all other medical fields. This book does not attempt to be an encyclopedic summary of that information. Rather, this textbook strives to organize that knowledge into a unified approach that categorizes and summarizes the evidence that is currently available. We realize that clinicians are too busy to keep up with the literature that is published in the many available journals. Therefore, a key feature of this book is the evidence-based tables that collate the best available evidence from the literature, enabling the reader to make decisions on the basis of data. We have chosen current experts to create evidence-based chapters on topics that span the field from basic and translational science to prevention to clinical practice, and ultimately to survivorship, totaling 113 chapters written by more than 250 contributors. The tone of this book is established in the first chapter, "Evidence-Based Approach to Oncology," which reviews the history of evidence-based medicine and describes the different levels of evidence. This book will be informative to residents, fellows, practicing clinicians, and allied health professionals.

This book has several unique features. Section One, "Principles of Oncology," contains several chapters that discuss areas that have only recently matured. The topics include the biologic principles of hematopoietic stem cell therapies; informatics infrastructure; economics of cancer care; and, patient decision making. The section on "Translational Basic Science," includes chapters that review the basic concepts of cancer biology; these are written from the perspective of clinical translational science and how it is relevant to the physician. The chapter entitled "Technologies in Molecular Biology: Diagnostic Applications" is both timely and concise, while exploring the application of genomics to daily clinical practice. In the section on "Cancer Prevention and Control," the chapter, "Behavioral Modification" is unique in the literature. Similarly, the section on "Cancer Imaging" has a chapter on the "Imaging of Gastrointestinal Stromal Tumor," which is not found in current oncology textbooks. The chapter on PET imaging investigates the promise of that modality. In the "Practice of Oncology" section, several chapters discuss the care of subpopulations of patients who pose different challenges to the clinician: immunosuppressed patients; elderly patients; patients with organ dysfunction; and pregnant women. Foremost, an entire section of 13 chapters is devoted to "Cancer Survivorship." These innovative chapters represent a broad and in-depth review of the long-term consequences of cancer treatment with respect to specific malignancies. A chapter on "Cancer Advocacy" from the perspectives of cancer survivors is in this section.

Most of the chapters fall into sections on Solid Tumors, Hematologic Malignancies, and the Practice of Oncology. These sections cover site-specific malignances, treatment toxicities, oncologic emergencies, and supportive care. They focus on the latest multimodality approach to the patient, with an emphasis on the best-available evidence from the literature. Where available, we have asked authors to include Level 1 clinical, treatment, and management data for each site-specific chapter. In those instances where Level 1 evidence may not be available, the best clinical practices based on published clinical experience are summarized. As opposed to review articles or standard textbook chapters, the evidence-based chapters presented in this book strive to present the reader with a thorough search of the evidence, judgment of the scientific quality of the evidence, and lastly a bias-free conclusion of the evidence.

This new book offers readers a user-friendly approach to the vast amount of information in the oncology literature. It is our intention that this book will become a useful tool for the improvement of readers' clinical practices. The Editorial Board

would like to acknowledge the outstanding effort of the Springer staff for pulling this project together. In particular, we would like to thank Laura Gillan who initiated this book project, and Paula Callaghan who brought it to its completion.

Alfred E. Chang, MD
Patricia A. Ganz, MD
Daniel F. Hayes, MD
Timothy J. Kinsella, MD
Harvey I. Pass, MD
Joan H. Schiller, MD
Richard M. Stone, MD
Victor J. Strecher, PhD, MPH

Contents

Section Five Solid Tumors

Contributors

Alex A. Adjei, MD, PhD
Professor, Department of Oncology, Mayo Clinic Foundation, Rochester, MN, USA.

Manish Agrawal, MD
Staff Scientist, Department of Clinical Bioethics, Warren G. Magnuson Clinical Center and Medical Oncology Research Unit, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

Daniel M. Albert, MD, MS
Chair Emeritus, F.A. David Professor, and Lorenz E. Zimmerman Professor, Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison, Madison, WI, USA.

Mark R. Albertini, MD
Associate Professor, Department of Medicine, University of Wisconsin-Madison; Chief of Oncology, William S. Middleton Memorial Veterans Hospital, Madison, WI, USA.

Steven Alberts, MD, MPH
Associate Professor, Department of Oncology, Mayo Clinic College of Medicine, Rochester, MN, USA.

Sarah W. Alexander, MD
Assistant Professor, Department of Pediatrics, Case Western University, Division of Pediatric Hematology and Oncology, Rainbow Babies and Children's Hospital, Cleveland, OH, USA.

Asim Amin, MD, PhD
Immunotherapy Co-Director, Blumenthol Cancer Center, Carolinas Medical Center, Charlotte, NC, USA.

Scott Antonia, MD, PhD
Medical Director, Cellular Therapies Core, Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center & Research Institute, University of South Florida, Tampa, FL, USA.

Suzanne L. Aquino, MD
Assistant Professor, Department of Radiology, Harvard Medical School/ Massachusetts General Hospital, Boston, MA, USA.

Meri Armour, RN, MSN
Senior Vice President, Ireland Cancer Center/University Hospitals of Cleveland, Cleveland, OH, USA.

David A. August, MD
Associate Professor, Department of Surgery; Chief, Division of Surgical Oncology, UMDNJ/Robert Wood Johnson Medical School and the Cancer Institute of New Jersey, New Brunswick, NJ, USA.

Noreen M. Aziz, MD, PhD, MPH
Senior Program Director, Office of Cancer Survivorship, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, MD, USA.

Giuseppe Barbanti-Brodano, MD
Professor, Department of Experimental and Diagnostic Medicine, Section of Microbiology, University of Ferrara, Ferrara, Italy.

J. Carl Barrett, PhD
Director, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA.

Karen Basen-Engquist, PhD, MPH
Associate Professor, Department of Behavioral Science, The University of Texas at M. D. Anderson Cancer Center, Houston, TX, USA.

Wendie A. Berg, MD, PhD
Breast Imaging Consultant, Study Chair, American College of Radiology Imaging Network, Lutherville, MD, USA.

Smita Bhatia, MD, MPH
Director, Epidemiology and Outcomes Research, Department of Pediatric Oncology, City of Hope Cancer Center, Duarte, CA, USA.

Rina M. Bloch, MD
Assistant Professor, Department of Rehabilitation Medicine, Tufts-New England Medical Center, Boston, MA, USA.

David A. Bluemke, MD, PhD
Associate Professor, The Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins Hospital, Baltimore, MD, USA.

Diane C. Bodurka, MD
Associate Professor, Department of Gynecological Oncology, The University of Texas at M. D. Anderson Cancer Center, Houston, TX, USA.

Michael Boeckh, MD
Assistant Member, Program in Infectious Diseases, Fred Hutchinson Cancer Research Center; Assistant Professor of Medicine, University of Washington School of Medicine, Seattle, WA, USA.

Jeffrey P. Bond, PhD
Research Associate Professor, Department of Microbiology and Molecular Genetics, University of Vermont, Burlington, VT, USA.

Melissa L. Bondy, PhD
Professor, Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA.

Louise J. Bordeleau, MD, FRCP(C), MSc
Attending, Department of Medical Oncology, Mount Sinai Hospital, Toronto, Ontario, Canada.

Kristin Bradley, MD
Assistant Professor of Human Oncology, University of Wisconsin, Madison, WI, USA.

Paul D. Brown, MD
Assistant Professor, Division of Radiation Oncology, Department of Oncology, Mayo Clinic College of Medicine, Rochester, MN, USA.

John Bryant, PhD
Professor, Associate Director, Departments of Biostatistics, National Surgical Adjuvant Breast and Bowel Project Biostatistical Center, Pittsburgh, PA, USA.

Julia W. Buchanan, BS
Associate in Research, Russell H. Morgan Department of Radiology and Radiological Science, Division of Nuclear Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Jan C. Buckner, MD
Chair, Division of Medical Oncology, Professor of Oncology, Mayo Clinic College of Medicine, Rochester, MN, USA.

Susan V. Bukata, MD
Assistant Professor, Department of Orthopedics, University of Rochester Medical Center/Strong Memorial Hospital, Rochester, NY, USA.

Alan K. Burnett, MD, FRCPath, FRCP(Glasgow), FRCP(Edinburgh), FRCP(London), FMSci
Professor, Department of Haematology, University of Wales College of Medicine, Cardiff, Wales, UK.

John C. Byrd, MD
Associate Professor, Department of Internal Medicine, Division of Hematology and Oncology, The Ohio State University, The Arthur James Comprehensive Cancer Center, Columbus, OH, USA.

Michele Carbone, MD, PhD
Associate Professor, Department of Pathology, Cardinal Bernardin Cancer Center, Loyola University Chicago, Maywood, IL, USA.

Daniel B. Carr, MD, DABPM, FFPMANZCA(Hon)
Saltonstall Professor of Pain Research, Department of Anesthesia; Medical Director, Pain Management Program, Tufts-New England Medical Center, Boston, MA, USA.

Shamus R. Carr, MD
Surgical Resident, Department of Surgery, Thomas Jefferson University, Philadelphia, PA, USA.

Jacqueline Casillas, MD, MSHS
Assistant Professor, Department of Pediatrics, Division of Hematology/Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.

Barrie Cassileth, PhD
Chief, Integrative Medicine Service; Laurance S. Rockefeller Chair in Integrative Medicine, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

Mark S. Chambers, DMD
Associate Professor, Head & Neck Surgery; Deputy Chief, Section of Oncologic Dentistry and Prosthodontics, M. D. Anderson Cancer Center, Houston, TX, USA.

Alfred E. Chang, MD
Hugh Cabot Professor of Surgery; Chief, Division of Surgery Oncology; Department of Surgery, University of Michigan, Ann Arbor, MI, USA.

Shine Chang, PhD
Associate Director, Office of Preventive Oncology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

Daniel N. Chatzifotiadis, MD
Post Doctoral Research Fellow, Department of Radiology, Division of Nuclear Medicine, The Johns Hopkins Medical Institute, Baltimore, MD, USA.

Caroline Chiles, MD
Professor, Department of Radiology, Wake Forest University School of Medicine, Winston-Salem, NC, USA.

Hak Choy, MD
Nancy B. and Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research, Professor and Chairman, Department of Radiation Oncology, Moncrief Radiation Oncology Center, University of Texas, Southwestern Medical Branch, Dallas, TX, USA.

Sue Chua, MBBS, FRACP
Senior Clinical Research Fellow, Breast Unit, Department of Medicine, Royal Marsden Hospital, Chelsea, London, UK.

Joseph I. Clark, MD
Associate Professor, Department of Medicine, Loyola University Chicago, Maywood, IL, USA.

Ezra E.W. Cohen, MD
Assistant Professor, Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL, USA.

Anne Coscarelli, PhD
Research Psychologist, Department of Public Health; Director, Ted Mann Family Resource Center, UCLA/David Geffen School of Medicine, Los Angeles, CA, USA.

Christopher J. Crnich, MD, MS
Research Fellow, Section of Infectious Diseases, Department of Medicine, University of Wisconsin, Madison, WI, USA.

Alvin A. Dahl, MD, PhD
Professor, Department of Clinical Cancer Research, National Hospital-Radium Hospital, Oslo, Norway.

Mary B. Daly, MD, PhD
Director, Cancer Prevention and Control Program, Department of Population Science, Fox Chase Cancer Center, Philadelphia, PA, USA.

Suzanne C. Danhauer, PhD
Assistant Professor and Associate Director, Psychosocial Oncology & Cancer Patient Support Programs, Department of Internal Medicine, Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA.

Sarah Dash, MPH
Cancer Research Training Fellow, Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD, USA.

Daniel J. De Angelo, MD, PhD
Assistant Professor, Department of Medicine, Harvard Medical School; Adult Leukemia Program, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, MA, USA.

James A. DeCaprio, MD
Associate Professor, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA.

Joachim Deeg, MD
Member, Clinical Research Division, Fred Hutchinson Cancer Research Center; Professor of Medicine, University of Washington School of Medicine, Seattle, WA, USA.

George D. Demetri, MD
Clinical Director, Sarcoma Program, Dana-Farber Cancer Institute; Associate Professor, Department of Medicine, Harvard Medical School, Boston, MA, USA.

Sophie Dessureault, MD, PhD
Staff, Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center & Research Institute, University of South Florida, Tampa, FL, USA.

Emily DeVoto, PhD, MSPH
Health Science Policy Analyst, Office of Medical Applications of Research, National Institutes of Health, Bethesda, MD, USA.

Kathleen M. Diehl, MD
Assistant Professor, Division of Surgical Oncology, Department of Surgery, University of Michigan, Ann Arbor, MI, USA.

James J. Dignam, PhD
Assistant Professor, Department of Health Studies, University of Chicago and University of Chicago Cancer Research Center, Chicago, IL, USA.

Gerard M. Doherty, MD
Norman W. Thompson Professor; Section Head, General Surgery; Chief, Division of Endocrine Surgery; Director, Department of Surgery, University of Michigan Health System, Ann Arbor, MI, USA.

Jessica S. Donington, MD
Assistant Professor, Department of Cardiothoracic Surgery, Stanford University School of Medicine, Stanford, CA, USA.

John H. Donohue, MD
Consultant in Surgery, Department of General Surgery, Mayo Clinic; Professor of Surgery, Mayo Graduate School of Medicine, Rochester, MN, USA.

Kristine A. Donovan, PhD, MBA
Assistant Professor, Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida, Tampa, FL, USA.

Afshin Dowlati, MD
Assistant Professor, Department of Medicine, Case Western Reserve University, University Hospitals of Cleveland, Cleveland, OH, USA.

Faith M. Durden, MD
Assistant Professor, Department of Dermatology, Case Western Reserve University, University Hospitals of Cleveland, Cleveland, OH, USA.

Grace K. Dy, MD
Fellow, Department of Oncology, Mayo Clinic College of Medicine, Rochester, MN, USA.

Douglas B. Einstein, MD, PhD
Assistant Professor, Department of Radiation Oncology, Case Western Reserve University, Cleveland, OH, USA.

Ezekiel J. Emanuel, MD, PhD
Chair, Department of Clinical Bioethics, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD, USA.

Cathy Eng, MD
Assistant Professor, Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA.

Brad J. Erickson, MD
Associate Professor, Department of Radiology, Mayo Clinic Foundation, Rochester, MN, USA.

Scott E. Evans, MD
Instructor, Department of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Mayo Clinic Foundation, Rochester, MN, USA.

Marni Feldmann, MD
Resident, Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, WI, USA.

Elliot K. Fishman, MD
Professor, The Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Gini F. Fleming, MD
Associate Professor, Department of Medicine, University of Chicago, Chicago, IL, USA.

Michele R. Forman, PhD
Senior Investigator, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Sophie D. Fosså, PhD
Professor, Department of Long-term Studies, National Hospital-Radium Hospital, University of Oslo, Oslo, Norway.

Joseph S. Friedberg, MD
Chief, Division of Thoracic Surgery, Department of Surgery, Thomas Jefferson University, Philadelphia, PA, USA.

Shirish M. Gadgeel, MD
Assistant Professor, Department of Internal Medicine, Division of Hematology & Oncology, Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA.

Evanthia Galanis, MD
Associate Professor, Division of Medical Oncology, Mayo Clinic College of Medicine, Rochester, MN, USA.

Patricia A. Ganz, MD
American Cancer Society Clinical Research Professor; Director, Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center at UCLA, Professor, Schools of Public Health and Medicine, University of California, Los Angeles, Los Angeles, CA, USA.

Adam S. Garden, MD
Professor, Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA.

Patrick J. Getty, MD
Assistant Professor, Department of Orthopaedic Surgery, Case Western Reserve University/University Hospitals of Cleveland, Cleveland, OH, USA.

Maged I. Gharib, MSc, MD, MRCP, MRCPath
Attending, Department of Haematology, Royal Manchester Children's Hospital, Manchester, UK.

Caterina Giannini, MD
Consultant, Department of Anatomic Pathology, Mayo Clinic Foundation, Rochester, MN, USA.

Paula Gill, MD
Fellow, Department of Oncology, Mayo Clinic Foundation, Rochester, MN, USA.

Montgomery Gillard, MD
Lecturer, Department of Dermatology, University of Michigan, Ann Arbor, MI, USA.

Timothy Gilligan, MD
Instructor in Medicine, Department of Medical Oncology, Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, USA.

Pamela J. Goodwin, MD, MSc, FBPC
Professor, Department of Medicine, University of Toronto; Senior Scientist, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada.

Gregory J. Gores, MD
Professor, Department of Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA.

Leonidas C. Goudas, MD, PhD
Assistant Professor, Department of Anesthesiology, Tufts-New England Medical Center, Boston, MA, USA.

Annette Grambihler, MD
Staff, First Department of Internal Medicine, University of Mainz, Mainz, Germany.

Frederic W. Grannis, Jr., MD
Assistant Professor, Department of Thoracic Surgery, City of Hope National Medical Center, Duarte, CA, USA.

F. Anthony Greco, MD
Medical Director, Sarah Cannon Cancer Center, Nashville, TN, USA.

Axel Grothey, MD
Mayo Foundation Scholar, Division of Medical Oncology, Mayo Clinic Foundation, Rochester, MN, USA.

Steven Hahn, MD
Attending, Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA, USA.

John D. Hainsworth, MD
Director of Clinical Research, Sarah Cannon Cancer Center, Nashville, TN, USA.

Dima A. Hammoud, MD
Assistant Professor, Department of Diagnostic Radiology, Division of Neuroradiology, The Johns Hopkins University, Baltimore, MD, USA.

Lindsay A. Hampson, BS
Fellow, Department of Clinical Bioethics, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD, USA.

Paul M. Harari, MD
Associate Professor, Department of Human Oncology, University of Wisconsin Comprehensive Cancer Center, Madison, WI, USA.

Russell Harris, MD, MPH
Professor, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA.

Lawrence E. Harrison, MD
Associate Professor, Chief, Division of Surgical Oncology, UMDNJ-New Jersey Medical School, Newark, NJ, USA.

Daniel F. Hayes, MD
Clinical Director, Breast Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA.

Craig Hofmeister, MD
Fellow, Division of Hematology-Oncology, Loyola University Chicago, Cardinal Bernadin Cancer Center, Maywood, IL, USA.

Brent Hollenbeck, MD
Lecturer, Department of Urology, University of Michigan, Ann Arbor, MI, USA.

Steven M. Horwitz, MD
Clinical Assistant Physician, Lymphoma Services, Department of Hematology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

Thomas Huff, MD
Staff, Department of Orthopaedic Surgery, Case Western Reserve University, Cleveland, OH, USA.

Scott A. Hundahl, MD, FACS, FSSO, FAHNS
Professor, Department of Clinical Surgery, U.C. Davis; Chief of Surgery, VA Northern California Health Care System, Sacramento VA at Mather, Mather, CA, USA.

Stephen D. Hursting, PhD, MPH
Deputy Director, Office of Preventive Oncology, National Cancer Institute, Bethesda, MD, USA.

Jimmy Hwang, MD
Attending, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA.

Paul B. Jacobsen, PhD
Professor and Program Leader, Health Outcomes and Behavioral Program, Department of Psychosocial and Palliative Care Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA.

Timothy M. Johnson, MD
Professor, Departments of Dermatology, Otolaryngology, and Surgery, University of Michigan Medical School, University of Michigan, Ann Arbor, MI, USA.

Stephen R.D. Johnston, MA, PhD, FRCP
Consultant Medical Oncologist, Department of Medicine—Breast Unit, Royal Marsden Hospital, London, UK.

Stein Kaasa, MD, PhD
Professor, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, The Norwegian University of Science and Technology and the Palliative Care Unit, St. Olavs Hospital, Trondheim, Norway.

Ihab R. Kamel, MD, PhD
Assistant Professor, The Russell H. Morgan Department of Radiology and Radiological Sciences, The Johns Hopkins Hospital, Baltimore, MD, USA.

Phillip W. Kantoff, MD, PhD
Professor, Department of Medicine; Chief, Division of Solid Tumor Oncology; Director, Lank Center for Genitourinary Oncology, Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, USA.

Theodore G. Karrison, PhD
Research Associate, Associate Professor, Department of Health Studies, University of Chicago and University of Chicago Cancer Research Center, Chicago, IL, USA.

Satomi Kawamoto, MD
Assistant Professor, The Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins Hospital, Baltimore, MD, USA.

Thomas Kearney, MD, FACS
Associate Professor, Department of Surgery, UMDNJ/Robert Wood Johnson Medical School; The Cancer Institute of New Jersey, New Brunswick, NJ, USA.

Vicki Keedy, MD
Fellow, Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN, USA.

Michael L. Kendrick, MD
Assistant Professor, Department of Surgery, Mayo Clinic College of Medicine, Rochester, MN, USA.

Michael S. Kent, MD
Staff, Department of Cardiothoracic Surgery, Weill-Cornell Medical Center, New York, NY, USA.

James Khatcheressian, MD
Assistant Professor, Department of Internal Medicine, Division of Hematology/Oncology, Virginia Commonwealth University Health System, Richmond, VA, USA.

Timothy J. Kinsella, MD
Vincent K. Smith Professor and Chairman, Department of Radiation Oncology, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, OH, USA.

Linda S. Kinsinger, MD, MPH
Assistant Director, VA National Center for Health Promotion and Disease Prevention, Durham, NC, USA.

Clifford Y. Ko, MD
Associate Professor, Department of Surgery, UCLA School of Medicine/West Los Angeles VA Medical Center, Los Angeles, CA, USA.

Jonathan E. Kolitz, MD
Director, Leukemia Service, Department of Medicine, North Shore University Hospital, New York University School of Medicine, Manhasset, NY, USA.

Barnett S. Kramer, MD, MPH
Associate Director for Disease Prevention, Office of Disease Prevention, National Institutes of Health, Bethesda, MD, USA.

Alexander S. Krupnick, MD
Fellow, Department of Surgery, Division of Cardiothoracic Surgery, Washington University, St Louis, MO, USA.

Tracey L. Krupski, MD
Resident, Department of Urology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA.

Amit Kumar, MD
Resident, Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, WI, USA.

Dan Laheru, MD
Assistant Professor, Department of Medical Oncology, The Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins, Baltimore, MD, USA.

Wendy Landier, RN, MSN, CPNP
Pediatric Nurse Practitioner, Division of Pediatrics, City of Hope Comprehensive Cancer Center, Duarte, CA, USA.

Joseph Lau, MD
Professor, Department of Medicine, Institute for Clinical Research and Health Policy Studies, Tufts-New England Medical Center, Boston, MA, USA.

Donald P. Lawrence, MD
Assistant Professor, Division of Hematology-Oncology, Tufts-New England Medical Center, Boston, MA, USA.

Cheryl T. Lee, MD
Assistant Professor, Department of Urology, The University of Michigan, Ann Arbor, MI, USA.

Julie Lemieux, MD
Attending, Department of Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada.

Nathan Levitan, MD, MBA
Professor, Department of Medicine, Ireland Cancer Center/University Hospitals of Cleveland, Cleveland, OH, USA.

Andrew H. Limper, MD
Professor of Medicine, Biochemistry, and Molecular Biology, Department of Pulmonary & Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA.

Thomas S. Lin, MD, PhD
Assistant Professor, Department of Internal Medicine, Division of Hematology and Oncology, The Ohio State University, Columbus, OH, USA.

Andrew J. Lipman, MD
Clinical and Research Fellow, Division of Hematology-Oncology, Tufts-New England Medical Center, Boston, MA, USA.

Mark S. Litwin, MD, MPH
Professor, Department of Urology and Health Services, David Geffen School of Medicine, School of Public Health, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA, USA.

Jon Håvard Loge, MD, PhD
Professor, Department of Behavioural Sciences in Medicine, University of Oslo and the Centre for Palliative Medicine, Ulleval University Hospital, Oslo, Norway.

B. Jack Longley, MD
Professor, Department of Dermatology, University of Wisconsin-Hospital and Clinics, Madison, WI, USA.

Charles Loprinzi MD
Professor, Division of Medical Oncology, Mayo Clinic Foundation, Rochester, MN, USA.

John R. Lurain, MD
John & Ruth Brewer Professor of Gynecology and Cancer Research, Department of Obstetrics and Gynecology; Director, John I. Brewer Trophoblastic Disease Center; Northwestern University Feinberg School of Medicine, Chicago, IL, USA.

Scott D. Luria, MD
Associate Professor, Department of Medicine, University of Vermont, Burlington, VT, USA.

John S. Macdonald, MD
Professor, Department of Medicine, New York Medical College; Medical Director, St. Vincent's Comprehensive Cancer Center, New York, NY, USA.

Cormac O. Maher, MD
Chief Resident Associate, Department of Neurosurgery, Mayo Clinic College of Medicine, Rochester, MN, USA.

Dennis G. Maki, MD
Chief, Section of Infectious Diseases, Department of Medicine, University of Wisconsin Medical School, Madison, WI, USA.

Karim S. Malek, MD
Assistant Professor, Department of Medicine, Section of Hematology and Oncology, Boston University School of Medicine, Boston, MA, USA.