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Oncology

An Evidence-Based Approach

Springer

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With 346 Figures in 501 Parts

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Library of Congress Control Number: 2005926820

ISBN 10: 0-387-24291-0
ISBN 13: 978-0387-24291-0

Printed on acid-free paper.

Printed in the United States of America. (BS/MVY)

9 8 7 6 5 4 3 2 1

springeronline.com

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.

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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.

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