Cancers of the Colon and Rectum

A Multidisciplinary Approach to Diagnosis and Management

Al B. Benson III, MD • A. Bapsi Chakravarthy, MD
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The treatment of colorectal cancer has become increasingly complex, requiring the comprehensive review and assessment of multiple issues including genetics, radiology, surgery, molecular diagnostics, chemotherapy, and more. As a result, the collaboration among these specialties facilitated by a multidisciplinary team approach are crucial in providing the best care to patients and ensuring successful treatment. Cancers of the Colon and Rectum, written by a team of authors representing a range of disciplines, is a valuable resource for physicians, fellows, nurses, physician assistants, physical therapists, and all health care providers involved in the treatment of colorectal cancer.

Cancers of the Colon and Rectum summarizes the state-of-the-art issues related to the treatment of colorectal cancer and describes an approach for optimal multidisciplinary care for individuals who have been diagnosed with or who are at higher risk to develop colorectal cancer.

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Series Foreword

This volume of the series Current Multidisciplinary Oncology, devoted to colorectal cancer, brings me great pleasure to introduce the practicing clinician to a valuable resource that will aid in the multidisciplinary approach of these common solid tumors.

Drs. Al B. Benson III, A. Bapsi Chakravarthy, Stanley R. Hamilton, and Elin R. Sigurdson have put together a cadre of leading-edge investigators as contributors on the multidisciplinary approach to colorectal cancer.

Over the past decade, a myriad of advances in the diagnosis and treatment of colorectal cancer have occurred. Some of the advances include, but are not limited to, diagnostic molecular tools that may aid in predicting a response to certain treatment approaches and/or in providing a guide of a prognostic outcomes for certain patients.

Colorectal neoplasms comprise some of the most common malignancies in the world and hence warrant intense efforts to find a cure. In recent years, investment of resources to help further understand the nature of this malignancy have increased.

Drs. Benson, Chakravarthy, Hamilton, and Sigurdson represent the current generation of academic, forward-thinking oncologists who have committed their careers to eradicating colorectal cancer using multidisciplinary approaches. Their collective vision and ability to assemble an outstanding group of investigators in the field have provided a very high quality product that will be a useful resource to the busy clinician as well as those along various stages of the learning spectrum. I’m sure that you will enjoy this innovative and easy-to-read volume as you look for guidance in the multidisciplinary approach of your patients with colorectal cancer.

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Preface

Colorectal cancer (CRC) is the third most common cancer worldwide. Although largely preventable, this disease continues to engender significant morbidity and mortality. Advances in understanding the genetics of CRC (including inherited and sporadic cases), screening and prevention strategies, and treatment have resulted in improved outcomes even for patients with advanced cancer. This is the third book in the series Current Multidisciplinary Oncology, edited by Dr. Charles R. Thomas, Jr., with the intent to provide a comprehensive textbook that encompasses the entire spectrum of multidisciplinary management considerations and a significant body of evidence with references to support the decision strategies and recommendations.

The chapters in this book are arranged in a logical progression from screening and prevention to diagnosis, treatment and surveillance, which is similar to the other books in this series. Chapter 2 is composed of four in-depth sections that serve as a critical introduction to principles of screening with extensive discussion of inherited CRC, details of other risk factors including diet and inflammatory bowel disease, and review of advances in chemoprevention. Chapters that address polyps and precursor lesions and preoperative staging and endoscopic approaches such as endoscopic mucosal resection (EMR) and colonic stenting are included. Multimodality CRC imaging is reviewed in Chapter 5 revealing the utility of CT colonography, PET-CT, and MRI in rectal cancer. Principles of pathology including staging criteria and advances in molecular pathology are integrated in several chapters outlining the importance of MSI and K-ras mutation status as two examples.

The management of colon cancer and rectal cancer has been separated in a series of distinct chapters for each of the two disease locations since the strategies vary particularly for locally advanced disease (nonmetastatic). Neoadjuvant chemoradiation for rectal cancer and adjuvant therapy for both colon and rectal cancer are extensively reviewed. The care of patients with potentially resectable metastatic disease also is highlighted. The evolving complexity of the continuum of care for patients with advanced disease receiving systemic therapy incorporates chemotherapy regimens and the most recent evidence that guides the use of anti-VEGF and anti-EGFR agents. There are two chapters devoted to management of systemic toxicities including diarrhea, skin and neurologic toxicities, as well as a section on the use of radiation as a palliative care option for patients. In addition, Chapter 15 reviews health-related quality of life both for locally advanced and advanced disease with a discussion of the instruments to measure quality of life.

There are also unique chapters that address special topics. These include chapters with an emphasis on clinical trials encompassing phase I/II clinical trials in metastatic CRC and future directions integrating concepts of the development of targeted therapies for CRC patients, biomarker clinical trial designs, and the potential of gene profiling both as a prognostic and predictive tool. Models of care delivery, including a community practice case study and patient navigation as it supports multidisciplinary care models, are innovative chapters emphasizing some of the complexities of offering comprehensive cancer care using CRC as an example. The concluding chapters speak to the growing emphasis on health disparities, surveillance and survivorship, and patient advocacy.

This book is truly multidisciplinary in scope and is designed as a management text for the gamut of health professionals who provide care for CRC patients including medical oncologists, radiation oncologists, surgeons, gastroenterologists, radiologists, pathologists, palliative care experts, nurses and other allied health professionals, students, residents and fellows in training, as well as patients, families and advocates. The CRC thought leaders who have contributed to this volume have offered their considerable expertise to provide the most current evidence-based approach, including extensive references, to provide a valuable tool designed to enhance evaluation and management of CRC patients.

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Importance of the Multidisciplinary Approach to Colorectal Cancer

AL B. BENSON III

The concept of personalized or precision medicine by definition embraces the integration of a multidisciplinary approach for the care of an individual patient. Although many would emphasize the link between tumor biologic constructs and treatment selection (admittedly an important goal if not yet a realization), precision medicine should encompass the entire spectrum of not only an individual clinical situation but also the social, psychological, and physical factors that affect the individual patient. The colon and rectal cancer patient may routinely require the expertise of the surgeon, medical oncologist, pathologist, gastroenterologist, radiologist, radiation oncologist, and primary care physician to provide the most coherent, informed, comprehensive, and effective strategy for diagnosis, treatment, and in many cases, long-term surveillance. To truly personalize the individual patient’s experience, the comprehensive cancer care program must also offer critical services including psychiatry/psychology, social work, physical and occupational therapy, and nutrition counseling as needed. Access to additional health care personnel in surgery, other medical disciplines, nursing and genetic counseling is also critical based on symptoms, potential complications, and long-term risks both for the patient and potentially for other family members who may also be at risk for an eventual cancer diagnosis.

Over the past 2 decades, and particularly during the last 10 years, there have emerged profound advances in the treatment of colon and rectal cancer, including public recognition of the importance of colorectal cancer (CRC), and the rise of advocacy groups, which focus on education and patient support, research, and significant advances in laboratory science and treatment opportunities. The end result has been fewer patients dying from CRC, more than doubling the survivorship for those with metastatic disease, enhanced potential for a cure for those with isolated metastatic disease, particularly in the liver and lung, and increases in the numbers of individuals screened for CRC. Since CRC is a preventable disease and one that can be cured when diagnosed at early stages, the involvement of multiple health professionals and patient organizations becomes of paramount importance to educate the population and provide access to the required services.

The unmasking of critical components of the biology of CRC, beginning with the understanding of the adenoma-to-carcinoma sequence leading to the current advances in the understanding of the molecular pathogenesis of CRC, has crystallized the importance of integrating laboratory science in the construct of the multidisciplinary team. Chapter 2 of this text, for example, highlights the identification of three major molecular pathways, which has led to refinement in genetic counseling, risk assessment, prognosis determination, and screening programs. The chromosomal instability pathway is characterized by the initial alteration of the APC gene, followed by genetic and epigenetic events, including the mutation of K-ras, the presence of global hypomethylation, and allelic deletions of other tumor suppression genes. The DNA mismatch repair pathway (mutator phenotype pathway) is characterized by the presence of microsatellite instability and contributes to approximately 15% of all CRCs. The third critical pathway includes inflammatory bowel disease resulting in increased risk for development of CRC with defined genetic and epigenetic events. In addition, there is also perhaps a fourth pathway, the serrated pathway, involving mutations including BRAF and hypermethylation of CpG islands generally evolving from hyperplastic polyps through serrated adenomas. These pathways further support the concept of tumor heterogeneity, reinforcing the observation that CRC does not represent a single disease entity but a growing assortment of subsets of tumors. Tumor heterogeneity also is a potentially confounding factor for individual patients, further complicated by observed biological differences comparing primary versus metastatic disease. The identification of the accumulation of molecular events within an individual patient will mandate novel clinical trial designs to incorporate molecular pathology, multiple pathway-driven drug development strategies, and sequential biopsies over time for patients with metastatic disease to determine a more optimal biologically driven treatment strategy.

Identifying individuals at risk for CRC is a responsibility across health care disciplines, particularly shared by the primary care physician and gastroenterologist. The
Cancers of the Colon and Rectum

Inclusion of experts in quality of life and symptom management has enhanced a multidisciplinary approach for CRC patients. Clinical trials comparing treatment vs best supportive care for patients with refractory CRC, for example, have demonstrated both a survival benefit as well as maintenance of quality of life for irinotecan, cetuximab, panitumumab, and regorafenib. Quality of life measures have been integrated into the design of randomized phase III clinical trials. With the introduction of new agents and the potential toxicity of such, health-related quality of life (HRQL) assessment is an important methodology to incorporate aspects of function (eg, mood, affect), as well as the patient’s perspective. Treatment related symptom management strategies have incorporated algorithms to more effectively manage diarrhea as an important example. The development of oxaliplatin has resulted in the recognition of prevention and control of treatment related peripheral neuropathy. The use of anti-EGFR treatments has brought dermatologists into the multidisciplinary team to better control the treatment related rash associated with agents such as cetuximab and panitumumab.

The last decade has heralded a focus on care delivery in the United States, including patient navigation in cancer care, assessment of comprehensive CRC care, and access to care in the community with development of new models for care delivery. Patient navigation is designed to eliminate barriers to care as well as to streamline care, ensuring timely diagnosis and treatment. Since multidisciplinary CRC disease teams are essential for optimal patient care, navigation programs are increasingly integrated in cancer center programs to achieve the goal of seamless multidisciplinary delivery of care. In addition, survivorship has emerged as an integral component of comprehensive cancer care, particularly as increasing numbers of CRC patients are surviving their disease. It is estimated that there are over 11 million patients with a diagnosis of CRC living in the United States. Cancer centers must increasingly address survivorship issues including access to health care and follow-up treatment, assessment of late effects of treatment, evaluation of second cancers and quality of life. The 2006 Survivorship Report from the Institute of Medicine (IOM) states that multiple disciplines must be involved in survivorship efforts, including health care providers, patient advocates as well as other stakeholders with the intent of raising the awareness of the needs of cancer survivors and embracing the four critical components of comprehensive survivorship care, including prevention, surveillance,
intervention, and coordination of care. In this text, there is also a chapter devoted to racial disparities in the care of patients with CRC, which is particularly relevant since this topic not only applies to providing access to high quality cancer care, but also reflects the importance of risk assessment. For example, the incidence and mortality rate for CRC are highest among African Americans.

The chapters in this text have been assembled to provide the current best available evidence to support the standard of care integrating multidisciplinary approaches to CRC, including prevention and screening, diagnostics, treatment, and surveillance. In addition, with an eye to the future, there is discussion of the role of phase I/II trials in metastatic CRC with an emphasis on the importance of pharmacokinetics, refinement of pharmacodynamic markers and the integration of genomics, including the identification of genetic and epigenetic changes which are potential targets for drug development. The chapter devoted to future directions discusses gene expression profiling as well as integrative genomics, clinical trials designed to validate prognostic and predictive biomarkers and surrogate endpoints, and potential biologic targets for drug development. The future continues to embrace the era of multidisciplinary CRC care and research strategies, signifying a fusion of bench to bedside strategies.