BIOLOGY AND TREATMENT OF
COLORECTAL CANCER METASTASIS
DEVELOPMENTS IN ONCOLOGY

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The proceedings of the final National Large Bowel Cancer Project workshop are dedicated to all the individuals, including the many grantees of the project, who contributed to its success, with special remembrance of the contributions of Dr. Murray M. Copeland. Throughout the history of the National Large Bowel Cancer Project, the primary goal of all the research conducted was understanding the biology of colorectal cancer, its early detection, and more efficacious therapy for improved patient care and management. This volume is written with the hope that research knowledge derived with support from the National Large Bowel Cancer Project will be of benefit to all the patients diagnosed with colorectal cancer.
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PREFACE

The theme of the current workshop was identified several years ago and was considered by the working group of the National Large Bowel Cancer Project to be an appropriate workshop topic. Although the subject was important then, it was not possible to conduct such a workshop at that time. In the interim, not only did the problems associated with colorectal metastasis still exist, but new insights on the biology and treatment of colorectal cancer metastasis emerged, making the workshop topic especially important and relevant. With input from an expert Planning Committee, a unique program was designed to provide an opportunity for information exchange between basic scientists and clinical investigators.

The published proceedings reflect the organization of the workshop which consisted of five sections:

Section I. The Biology of Colorectal Cancer Metastasis co-chaired by Drs. J. Isaiah Fidler and George Poste

Section II. Controversies in the Management of Patients with Colorectal Cancer Metastasis co-chaired by Drs. Edward M. Copeland, III and Frank Adams

Section III. The Prevention and Local Treatment of Colorectal Metastasis co-chaired by Drs. Nicholas Petrelli and Paul V. Woolley, III

Section IV. Criteria of Response co-chaired by Drs. Philip T. Lavin and Bernard Levin

Section V. Analysis of Failure co-chaired by Drs. Glenn D. Steele, Jr. and John Marsh

The chapters examine relevant questions related to the clinical management of patients with hepatic metastases from colorectal cancer and the important, but less well-defined issue, their quality of life; the better design and evaluation of clinical trials; and the biologic phenomenon associated with metastasis. In so doing, questions were posed and potential approaches were suggested for examining problems and analyzing results.

Of the 138,000 new cases of colorectal cancer in the United States in 1985, an estimated 60,000 will die and the five-year survival, which is related to the stage of disease at diagnosis, is only 44%. Although primary prevention and early detection are desirable goals, the fact is that too many patients present with more advanced disease at diagnosis. The prognosis for those patients presenting with distant metastasis at
diagnosis or with recurrent metastatic disease is not good. The chapters of this volume examine an important clinical problem and the advances being made in the clinic as well as the problems, complexities, and approaches associated with studying colorectal cancer metastasis experimentally. Despite these complexities, experimental strategies are emerging which may result in progress for the more effective therapy of this disease.

The first six chapters (Section I) examine the natural history of hepatic metastases in colorectal cancer in a retrospective study of patients with biopsy-proven, hepatic metastases that were not resected, a variety of models of metastases using three different species (the nude mouse, the marmoset, and man), careful histological and cytological differentiation and classification of colon tumors as prognostic factors, and the inherent biological properties of colorectal cancer metastases. Collectively, these chapters address a formidable problem facing clinicians and laboratory investigators, namely, tumor cell heterogeneity. Looking at the natural history of this disease process as well as using model systems and biochemical approaches, attempts are made to define what it is that endows particular colon tumor cells with the ability to metastasize selectively and at what stage in tumor progression these metastatic colon tumor cells emerge. The variety of approaches offer new avenues of practical and experimental significance.

Chapters 7 and 8 (Section II) address the complex issue involving controversies in the management of patients with colorectal cancer metastases. The focus of this section is on the issues affecting quality of life. Two themes emerged. The first is the need to develop and incorporate quality of life parameters by which to assess various treatments in clinical trials, and the second is an adequate neuropsychiatric assessment of patients with cancer with special emphasis on brain-behavior relations in oncology. Clearly, doing something simply for the sake of doing something may not always be wise. In selecting treatment options, patients should be evaluated thoroughly, spoken with compassionately, listened to, and involved in choosing the most therapeutically-effective and cost-effective approach.

The third section focuses on approaches to the prevention and treatment of colorectal metastases. Taken together, these nine chapters review recent data from studies using a variety of procedures that may offer better therapeutic response or assist in selecting more effective therapeutic approaches for patients with hepatic metastases from colorectal cancer. One such study compared the response rates and survival data
for patients treated with systemic infusion versus intra-arterial infusion therapy. Not unsurprisingly, many patients on systemic infusion developed liver disease while patients on intrahepatic therapy had extrahepatic disease progression without liver progression. This suggests the possibility of combining these two approaches to optimize control, and to maximize response rate and duration of response to hepatic and extrahepatic disease. Two studies describe the selective advantage of hepatic resection for metastases from colorectal carcinoma in carefully selected subsets of patients. These two studies call attention to the relative safety of hepatic resection as a surgical procedure, the tendency for recurrence in extrahepatic sites, the need to include matched, untreated controls in study designs, and the obvious need for more effective therapeutic agents.

The potential role of laser surgery in the palliative treatment of patients with colorectal cancer is described. Efforts to achieve selective therapy using pharmacokinetic data as a rationale for prolonged regional infusion are also presented. The advantages of adjuvant radiotherapy for colorectal cancer is reviewed, including approaches to minimize the irradiation of underlying organs and tissues during radiotherapy for colon cancer. Two important questions are raised relative to the use of radiotherapy for patients with rectal cancer. The first relates to the optimal dose of preoperative radiotherapy and the second to the selection criteria used in selecting rectal cancer patients to be treated with radiotherapy.

This section concludes with chapters reviewing newer, sophisticated diagnostic and staging techniques for imaging the liver, the current role of the clonogenic assay of colon tumors in predicting clinical response and in selecting therapeutic regimens, and the use of radiolabelled antibodies for diagnosis and therapy of colorectal cancer metastases. Despite advancing diagnostic technologies, at present computerized tomographic scans remain the modality of choice for diagnosis and follow-up of patients with hepatic metastases from colorectal cancer. Optimization of this modality is possible using delayed iodine imaging. Although the clonogenic assay is reproducible, methodological inadequacies, including poor tumor growth and low plating efficiency exist. At present this approach represents an experimental research tool only and currently has no place in the clinical management of patients with colorectal cancer. However, new approaches are being evaluated to improve the assay so that it may be predictive of clinical response. Finally, a balanced appraisal of the methodologies, limitations, and potential applicability of using radiolabelled antibodies for diagnosis and therapy is presented. At present, this approach is still experimental.
A recurring theme throughout the workshop was the lack of adequate definition of
terms, many of which are fundamental to interpreting and comparing data reported in
the literature. Thus, the fourth section addresses the topic of criteria of response. The
first of the four chapters in this section presents an overview of the concerns and
questions of more than theoretical interest relative to response criteria, including
deficiencies and defining categories of response. Four models and several methods of
measuring antitumor activity, each with specific application to the design and analysis of
clinical trial data are described. The use of such models permits significant sample size
reduction in the design of clinical studies. Technological advances in detecting and
measuring disease recurrence add to the problem of defining response and are addressed
in the second chapter of this section. The serial measurement of tumor markers
constitutes another complementary approach in evaluating patient response to therapy
and recurrence. The adaptation of the time-dependent covariant model to solve some of
the statistical problems associated with the analysis of marker data is presented as an
approach to assess elevated relative risk of recurrence. Data are presented suggesting
that monitoring a marker alone, such as CEA, may be as good or better than clinical
monitoring. Not only is this provocative, but it would result in cost reduction and greatly
reduced inconvenience to patients. With the availability of marker measurements at
regular time intervals, one can choose from a variety of statistical techniques to
estimate absolute risk of recurrence.

The final chapter of Section IV presents a literature review of prognostic factors for
liver metastases from colorectal cancer. The need to appreciate and report data on
prognostic variables in evaluating clinical trials is emphasized.

The last section consists of an analysis of failure in the treatment of patients with
hepatic metastases from colorectal cancer. It is essential to identify problems before
devising solutions. Critical analysis of failures in other diseases has led to successful
treatment strategies. For example, the recognition that recurrence in advanced
Hodgkin's disease following chemotherapy-induced complete remission has led to the
successful use of radiotherapy to those areas of previous macroscopic disease following
chemotherapy. In this section, not only are the clinical patterns of failure reviewed, but
the biology of treatment failure in colorectal cancer relative to drug resistance and
tumor heterogeneity is also reviewed. The clinical patterns of failure clearly point out
that there are different subsets of patients who reflect the biologic heterogeneity of
colon tumors and their metastases. Of particular note is the observation that patients
with surgically resectable, isolated hepatic metastases represent a biologically selected subset with good prognoses. It is important to note that the concept of pleiotropic drug resistance involving a number of mechanisms is applicable to the resistance noted in colon carcinomas. This is evident in the general refractoriness of colon tumors to different classes of therapeutic agents. However, this knowledge provides a biochemical rationale for the development of future strategies aimed at overcoming drug resistance in colon tumors. The theme of biological resistance of colon carcinoma to treatment is reiterated. Empirical testing of agents is not a productive approach, rather assays ought to be targeted using a spectrum of appropriate models. Clearly, the data presented suggest that the resistance of colon tumor cells is inherent and represents a multifactorial phenomenon. Despite these generally pessimistic results, the final presentation suggests some optimism for the treatment of heterogeneous cancer metastases by systemic activation of macrophages. This technique is enhanced by activating the macrophages using immunomodulators encapsulated in liposomes to achieve sustained release. Although preliminary data are encouraging, the limitations of such treatment for disseminated metastatic disease are obvious and relate both to the availability of macrophages and the tumor burden.

While definitive answers to very complex and perplexing problems may not be presented, important questions are identified and important new approaches and directions for research initiatives in the area of metastases are identified. The chapters provide an update of the state-of-the-art treatment of colorectal cancer metastases without necessarily providing a consensus as there is some disagreement in certain areas of patient management. Nevertheless, the presentations should provide a better understanding of the patterns and mechanisms of colon tumor spread, both experimentally and in the natural history of the disease. In addition, the chapters evaluate the biologic and biochemical reasons for colon tumor resistance, better define criteria of response to therapy, and hopefully will stimulate new research approaches and define important and relevant clinical questions requiring additional laboratory investigation. The latter will best be achieved through complementary interaction of basic scientists of varying disciplines with clinical investigators. Finally, for progress to be made in this area, it is suggested that a national registry for surgical treatment of hepatic metastases be established to accumulate data from hepatic resections. These data could be derived from both retrospective and prospective studies, and would be useful in designing future studies and in evaluating the most effective therapy of hepatic metastases and the best treatment of extrahepatic disease. It is hoped that the contents
of this volume will be of benefit in providing improved management of patients with hepatic metastases from colorectal cancer.

Throughout the proceedings basic science concepts have been integrated with clinically relevant questions and studies. In this way, the proceedings should be of interest, not only to clinicians treating patients with hepatic metastases from colorectal cancer, but also to laboratory investigators of diverse disciplines interested in elucidating the biology of the metastatic process. In fact, many of the concepts and approaches presented in these proceedings have more widespread applicability to sites other than large bowel cancer.

Anthony J. Mastromarino
ACKNOWLEDGMENTS

This volume, *The Biology and Treatment of Colorectal Cancer Metastasis*, represents the contributions of many individuals. The workshop itself, held at the Stouffer's Greenway Plaza Hotel, Houston, September 13-15, 1984, was the last of 18 multidisciplinary workshops sponsored by the National Large Bowel Cancer Project during its 12-year administration at the University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas. From 1972 to 1984 the headquarters of the National Large Bowel Cancer Project was supported by grant R26 CA14140 from the National Cancer Institute (NCI). During that time the National Large Bowel Cancer Project received encouragement and support from the administration of The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, especially from Dr. R. Lee Clark, Dr. Robert C. Hickey, and Dr. Charles A. LeMaistre, and was under the capable direction of Dr. Murray M. Copeland (1972-1982), Dr. Edward M. Copeland III (1982-1983), and Dr. Richard G. Martin (1983-1984). During this period, each project director was complemented by a scientific support staff which included Drs. Rulon W. Rawson, William Spears, Birger Jansson, Marvin M. Romsdahl, Michael G. Brattain and myself, a working group of outstanding, dedicated consultants and advisors from numerous institutions, and an office staff of highly skilled and technically competent individuals. In addition, the National Large Bowel Cancer Project enjoyed the constant support and assistance of the Organ Systems Program Branch at the NCI, especially from Dr. Andrew Chiarodo and Dr. Vincent Cairoli, Program Director for the National Large Bowel Cancer Project. Since I am so indebted to all of the above individuals, I wish this volume to be a tribute to all those who made the National Large Bowel Cancer Project the success that it was.

As with the proceedings of any workshop its success is predicated on the contributions of many. This conference was no different. As chairman of the conference and editor of the proceedings, I am especially indebted to those who served on the Planning Committee. Their suggestions resulted in an integrated program of basic scientists and clinical investigators, the identification of key topics to be discussed, and the selection of an outstanding program faculty. I am also gratefully indebted to those who served as Session Chairpersons, and of course, to all the speakers and workshop discussants and participants for their active role in the workshop and for their contributions to the proceedings. This workshop and its published proceedings have fulfilled one of the important objectives of the National Large Bowel Cancer Project,
that is, information transfer between clinical investigators and basic scientists from diverse disciplines.

From my perspective as editor, the most important components in the completion of this project were the relentless dedication of my executive secretary, Ms. Deborah Maloney, and the cooperation and expertise provided by the staff of the Department of Scientific Publications. Those persons, specifically, Ms. Carol Kakalec, editor, and her assistant Kathleen Robertson as well as Ms. Dorothy Kisling and Ms. Mary Deiss, were invaluable in editing and assisting Ms. Maloney in entering the manuscripts on the word processor for camera-ready copy. The product speaks for itself and attests to their competence and dedication to detail. The success of the workshop is attributable to their collective efforts, skillful planning, and organizational capabilities.

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