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VASCULAR BRACHYTHERAPY

Second Edition

Edited by

Ron Waksman, MD

近距离血管治疗学

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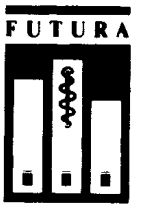

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Dedication

To my Parents
Bela and Mordechai,
my wife Tali,
and my Children
Ori, Yarden, Yonatan, and Daniel

Foreword

Since the advent of balloon angioplasty in 1977, the elusive search for a definitive treatment for restenosis has escaped basic scientists and clinical investigators. Over two decades, restenosis has remained a daunting challenge, threatening to limit clinical applications utilizing catheter-based interventional procedures. Restenosis presents mechanistic imponderables, remains a major health care cost burden (over $1 billion per year in the United States alone), and has direct personal impact on patients—often rendering a successful interventional procedure nondefinitive. In the past, attempts to importantly reduce restenosis have not been successfully addressed with adjunctive, systemic or local pharmacological agents. The use of endovascular prosthetic devices (stents) has had an important impact on both angiographic and clinical restenosis recurrence, by achieving a predictable larger initial treatment site lumen, which further provides a lower follow-up diameter stenosis. However, the basic processes of restenosis (neointimal hyperplasia and remodeling) are only partially aborted with use of mechanical scaffolds. Moreover, the iatrogenic process of diffuse instent restenosis has become an even more "malignant offender," with limited treatment options and striking recurrence rates.

Over the past several years, there has been a growing body of knowledge suggesting that vascular brachytherapy has a fundamental impact on the biology of restenosis. Certainly, there is provocative animal data that consistently demonstrate reduced neointimal growth after the balloon, mechanical, or stent barotrauma, and there are early human clinical trials that appear very encouraging. The hunger for a final "cure for restenosis" has effectively spawned a new industry encircling the field of radiation vascular therapy. Lest we too hastily jump on the radiation "bandwagon," this new subspecialty in interventional vascular therapy deserves deliberate and thoughtful consideration. Immediate patient risks, health care environmental concerns, and long-term pathobiological responses require intense evaluation.

It is in the spirit of excitement tempered by good basic and clinical science that the current edition is presented. A remarkable effort has been made to painstakingly outline mechanistic issues, vascular biology and pathology concerns, radiation physics and dosimetry problems, and preclinical animal investigations. Specific clinical applications for radiation vascular therapy (coronary, extracardiac, and others) are discussed and the integration of radiation with associated devices, such as stents, are treated in careful detail. Importantly, dozens of new clinical radiation studies are ongoing around the world, and attempts are made to summarize the early clinical data and trial designs. Finally, industry is given an opportunity to describe the technical subtleties of each vas-

cular brachytherapy system from the standpoint of design, radioisotope of choice, hardware, and delivery systems.

This definitive textbook on vascular brachytherapy clearly breaks ground and should be the forerunner of multiple future editions, which will help to put this vital new subspecialty within interventional vascular therapy in proper context. As we approach the next millennium, many of us who have dedicated our professional careers to an improved understanding and enhanced clinical application of interventional techniques, look forward to a true "cure for restenosis": radiation vascular therapy appears to be the next logical step in that quest.

Martin B. Leon, MD

Preface

Vascular brachytherapy is a young field in medicine, conceived to resolve the leading complication of vascular intervention, called restenosis. For years investigators have been trying to resolve restenosis by testing a wide variety of pharmaceutical agents and new devices. For the first time, it seems that there is a light at the end of the tunnel: namely vascular brachytherapy. Experts and investigators from widely disparate fields in medicine have joined together to contribute and to establish a new therapy for the prevention of restenosis. Thus within 6 years, a new field of medicine has evolved—a field that contains specific vascular radiation biology and radiation physics aspects, new devices and platforms to deliver the radiation intraluminally, an new safety, regulatory, and milieu issues, all related to vascular brachytherapy.

The progress in the field is meteoric; within a short period of time we have found ourselves in the midst of the clinical investigation for the effectiveness and safety of this modality. In addition, we are conducting an intensive investigation to better understand the mechanism by which this therapy works, to explore new isotopes and new systems of delivery, to reduce the radiation exposure to the patient and the personnel, and to find the clinical application for this mode of therapy.

The spectacular initial clinical success of vascular brachytherapy suggests that this technology will remain as an adjunct therapy of revascularization, at the very least, for an indication of in-stent restenosis, and probably will expand for other indications once the clinical trials are completed. It has been less than 2 years since the first edition of this book was published and here we are with the second edition of the book. This edition is a testimonial document to the progress of this field. Enormous advances in the field in just 2 years have required extensive changes and revisions of the text.

In the new edition of this book you will find 48 of 52 chapters that are new or revised. A special attempt was made to maintain the balance and the depth of the content within the variety of the multidisciplinary components of the field. The book provides to clinicians, scientists, and other individuals from each discipline, in depth information on subjects within their expertise and exposure to the basics of the other aspects of this field, as well. As in the first edition, the contributors to this book—scientists, cardiologists, radiation oncologists, radiobiologists, pathologists, vascular surgeons, radiation safety officers, regulators, engineers, and technicians—all experts and world renowned in the field, are presenting the latest available data from a multidisciplinary perspective. For those who follow the fields of vascular intervention and radiation therapy, it is evident that vascular brachytherapy has been moving rapidly from ideas and preclinical observations to clinical practice.

The second edition is divided into nine parts: Part I deals with the mechanisms of restenosis and alternative treatments for the next millennium. Part II

is concerned with the basic radiobiology of intravascular radiation, and discusses different mechanisms by which radiation prevents restenosis. In addition, this part brings the view of the pathologist on late effects of vascular radiation. Part III is dedicated to radiation physics—from basic principles to dosimetry planning for vascular brachytherapy for both beta and gamma sources, to health physics perspectives. Part IV summarizes the preclinical work that was conducted in animals; results from studies utilizing external radiation and endovascular radiation both with beta and gamma emitters are detailed. Part V deals with radiation as adjunct therapy to intracoronary stenting, from the biology, physics, animal experiments, pathology, and clinical experiments. Part VI presents the data accumulated so far from use of vascular brachytherapy in the peripheral vascular system. This chapter contains the latest update on patients who were treated with radiation to their superficial femoral artery lesions, and following intervention to arteriovenous dialysis shunts. Part VII provides the latest data from the clinical trials for coronary arteries that used both gamma and beta emitters, including those clinical trials with the radioactive stent. Part VIII describes the various systems that are currently available for testing in the clinical trials for vascular brachytherapy, and includes a detailed description of the system design and its advantages for this technology. Part IX, the final section in the book, is dedicated to regulatory and health care milieu issues. Radiation safety issues and practical implantation of this technology for use in the catheterization laboratory, the Food and Drug Administation perspective, and the economic aspects of this field are detailed.

The rapid pace at which vascular brachytherapy continues to advance made it a challenge to provide a timely picture of this field in a traditional textbook. But still, the fundamentals are submitted for those who wish to introduce themselves to this fascinating field, which may change the approach to cardiovascular intervention.

As in the first edition, we call to keep in perspective the level of enthusiasm and expectation. Given the multifactorial and mechanistic nature of restenosis, perhaps it is too naive to think that a single therapy of vascular brachytherapy will completely resolve this problem. It is the nature of every new technology to be driven by its own investigators, industry, and supporters to a high level of expectation and promises. The real challenge of a technology is measured over time, and not by the initial positive results coming from feasibility trials. The vascular interventionalists who have been introduced to vascular brachytherapy are actually in a "honeymoon phase" with this new technology. It is inevitable that we will have to deal with difficulties once the honeymoon is over. I hope that the content of this book will provide the tools of education and venues of research to handle those problems when they come. It is also important to remember that radiation may be associated with potential late toxic effects and other complications of radiation exposure, including misadministration of the dose and other unknown complications. This all should motivate us to peruse, with intensive research efforts, to improve the technology for a better vascular brachytherapy for the care of our patients.

In closing, I must acknowledge the tremendous efforts of Jacques Strauss and his dedicated staff at Futura, who did not save any effort to bring this high quality and comprehensive edition of this book to reality in a very timely manner. Their dedicated work helped to turn this book from a pivotal document in the first edition to basic comprehensive textbook of vascular brachytherapy.

Ron Waksman, MD
Washington, DC

Preface

(Adopted and modified from the first edition)

More than 20 years ago, in 1977, the first coronary balloon angioplasty by Andreas R. Gruentzig introduced a new dimension to the field of interventional cardiology. The main concept was that the atherosclerotic plaque could be physically removed or ablated from within the vessel. This has lead to an evolution of new innovations, new devices, and prosthesis technologies all delivered within the vessel to treat arterial vasculopathies. However, it was learned very early that, subsequent to the intervention, a wound-healing process known as restenosis significantly limits the success of this new treatment modality. Restenosis modified the initial enthusiasm of balloon angioplasty and challenged scientists and clinicians to find a solution for a significant medical problem. Several therapeutic approaches have been suggested, including pharmaceutical agents, physical new devices, and, recently, gene therapy has been studied, but the problem of overexuberant cell proliferation after intervention leading to restenosis, although better understood, still remains the Achilles heel of this field.

Since the discovery of radium by Madame Curie in 1898, ionizing radiation has been well known as an antiproliferative agent for benign and malignant disorders; it is also documented that proliferative cells are radiosensitive to low doses of radiation. Therefore, several investigators have suggested that local treatment with radioactive sources placed nearby the angioplasty site (brachytherapy) will inhibit restenosis. This has led to the evolution of a new field in medicine called endovascular brachytherapy.

This book was conceived to introduce the field of endovascular brachytherapy from a multidisciplinary perspective. The contributors—cardiologists, interventional radiologists, radiation oncologists, medical physicists, radiobiologists, pathologists, vascular surgeons, as well as industry representatives in this field—have shared their experience in this new, exciting field. Thus this book is meant to serve all disciplines that need to collaborate in order to bring this therapy into clinical use. The integration of these many disciplines is reflected in the chapters of the book.

A word of caution is offered in regard to the enthusiasm and the eagerness to move forward into large clinical studies. Yet there is a lot to explore about the radiobiological mechanisms of endovascular brachytherapy and how they are contributing to the fight against restenosis. It is also important to remember that very little is known about the long-term effects of this therapy in terms of safety to the patients. Thus, further work at the interface of physics, cell biology, science, and device engineering, as well as meticulous clinical work, should provide further progress and insight into the best way of treating diseases, and should help in patient care.

Ron Waksman, MD, FACC

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Part I

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