Brachytherapy
Marie Curie visits the Standard Chemical Company in Canonsburg, PA (1921) (photograph courtesy of the National Institute of Standards and Technology).
Brachytherapy

Applications and Techniques

Second Edition

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In loving memory

Phil Devlin
1917–2009
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Foreword

It is a privilege to write this Foreword to the second edition of *Brachytherapy: Applications and Techniques*, edited by Dr. Phillip Devlin with the most able assistance of Drs. Alexandra Stewart, Robert Cormack, and Caroline Holloway.

In many ways brachytherapy can be considered the ultimate form of conformal radiation therapy as it is unparalleled in its ability to direct a large dose of radiation to the tumor while minimizing exposure to surrounding sensitive normal structures. Brachytherapy has a long and storied history in the treatment of neoplastic disease. The first successful applications of radioisotopes to treat cancer were reported shortly after the discovery of radium in 1898. Over the next century and more, the evolution of brachytherapy into a valued component of the radiotherapy of many malignancies became firmly established. Notwithstanding this remarkable legacy of success, there is a disturbing trend in the United States whereby the use of brachytherapy is in serious decline. The many profoundly negative consequences of decreasing brachytherapy utilization include greater cancer care expenditures, less patient choice, more treatment-related morbidity, and, most alarmingly, an increase in cancer-specific mortality.

Cancer patients deserve state-of-the-art evidence-based care including the delivery of high quality, high value brachytherapy. As education is essential to advance awareness of and proficiency in the full spectrum of brachytherapy applications, the appearance of the second edition of this highly regarded text is both a timely and most welcome event. The distinguished list of contributors to this work reads like a veritable “Who’s Who” of international brachytherapy expertise making this an indispensable resource for students and practitioners of this complex and challenging modality. As with the first edition, Dr. Devlin and colleagues present a sophisticated yet highly readable text that is directed to the practicing clinician. The second edition of this book maintains the exceptionally high bar set by its predecessor in that it is painstakingly detailed, comprehensive, and thoroughly up-to-date. It fully describes the rapid evolution in the many techniques, technologies, and clinical data that underpin contemporary brachytherapy as an essential element in the multidisciplinary management of cancer. A particularly welcome feature is the clinical vignettes at the close of every chapter that bring seemingly remote concepts to life in real world practical applications.
Most notably, in my view, is that this book is infused with the infectious enthusiasm of Dr. Devlin himself. It has been one of the true pleasures of my professional career to witness the joy, passion, and energy he brings to the care of his patients, the education of his students and peers, and the advancement of our field. Reflective of his deep respect for the reader, he brings those same qualities to bear in crafting this remarkable work.

With the second edition of *Brachytherapy: Applications and Techniques*, Dr. Devlin and colleagues give us a text that instills a profound appreciation for the critical value of this essential modality. This book makes it clear that brachytherapy not only works, it is an irreplaceable component of contemporary cancer care.

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Preface to the Second Edition

It gives me great personal and professional satisfaction to present this second edition of *Brachytherapy: Applications and Techniques*. Brachytherapy, although underutilized, is at the very heart of cancer care; and, even in the era of advanced proton and IGRT treatment algorithms, it still is arguably the most conformal radiation therapy. Brachytherapy defines (mostly) the use of radioactive isotopes to provide a highly conformal, image-guided curative radiation doses to complex targets either deep or superficial. It takes advantage of the availability of many isotopes with different energies and half-lives so as to provide for a host of complex clinical scenarios where the therapeutic ratio (ultimately the good done for the harm avoided) is greatly aided by the steep dose falloff characteristics of these various isotopes. One hundred and seventeen years have passed since Marie Curie produced the first therapeutic isotope radium. This era quickly saw the first use of radium for therapeutic and anticancer therapies. At this writing, brachytherapy is a full and equal component of modern cancer care as well as the management of noncancerous proliferative diseases. Brachytherapy’s early ascent as the first radiation therapy was eclipsed by the arrival of X-ray therapy. Over the years, radiation therapy has fully matured to include not only megavoltage radiations but also heavy particles such as protons. All radiation therapy has been greatly lifted by advanced image guidance for treatment planning and monitoring of its delivery. Radiation therapy has also grown hand in hand with improvements in surgical techniques as well as chemotherapy, immunotherapy, and molecular targeting therapy. Brachytherapy has grown just as external beam has. These following chapters will give a comprehensive update from our first edition 7 years ago, so that practitioners, residents, students, and other interested parties will have a sure guide along the way.

As I said in the first edition, the context for writing both editions is that of an extremely busy and comprehensive brachytherapy environment in a large Harvard teaching hospital in Boston. The Brigham and Women’s Hospital and the Dana Farber Cancer Institute’s multidisciplinary clinics have been a superb location and community in which not only to grow a large volume high-quality brachytherapy practice but also in which to explore and teach the full extent of brachytherapy’s capability and power. The chapter authors and associate editors are drawn from my own group, the group that did fellowships with us, and leaders in the other great brachytherapy centers both in the United States and abroad. This also has provided unparalleled access to essentially every conceivable clinical scenario, from which our authors can best teach you.
Any medical resource such as this textbook must, at its very core, contain and
draw from the excellence of its authorship in three interwoven areas—in the clinic, in
education, and in research. To these must also be added organizational excellence so as
to create a sustainable high-quality practice focused on patient safety. These chapters are
the latest and finest distillation of the literature, techniques, and clinical examples
with many updates on the latest developments in brachytherapy across the disease sites. Ultimately, the book, in order to continue to succeed, must clearly state why and
how to do high-quality brachytherapy.

New in this edition to lead off is a lovely view of the history of brachytherapy by
looking at the evolution of prostate brachytherapy by redounded world leader in
brachytherapy history, Jesse Aronowitz from the University of Massachusetts. This
chapter is a pure delight to read and comprehensively traces the story from Marie Curie
to the modern day. His encyclopedic knowledge not just of the technical developments
but also of the significance of these to the lives of the individuals involved is so enriching
and inspiring.

Two supportive chapters follow on Radiobiologic Concepts for Brachytherapy and
Technical Aspects of Brachytherapy. The former was again written with the deft hand of
Associate Editor Dr. Alexandra J. Stewart, a former fellow and clinical lead for oncology
of the Royal Surrey County Hospital in England, in conjunction with Robert Cormack
and Harvard’s Kathy Held. These three collaborated to give the necessary and sufficient
components for practice and illustrated the points with worked clinical vignettes. The
chapter is more streamlined than before for best access to what is needed. We all should
leave a bookmark in this chapter as we continue to refine equivalent dose paradigms for
various diseases, stages, and clinical needs (eg, recurrent disease).

The third chapter on the Technical Aspects of Brachytherapy, is an in-house production
written in collaboration with essentially all our physicists in the brachytherapy space.
Associate Editor Robert Cormack gently coordinated a wonderful review of what is
really important and necessary for a safe and high-quality practice. Starting with the
isotopes themselves, it courses over permanent and temporary, manual, and image
guided and through low, high, and pulsed dose rates. The major areas of gynecologic
and prostate are augmented with a careful look at custom surface devices. They cover
dosimetry, heterogeneity, as well as issues of transit dose and backscatter. They lead us
to look at the future with advanced planning algorithms and robotic brachytherapy, as
well as advanced enhancements to optimize workflow including all meaningful quality
end points. They explain electronically generated low-energy sources and importantly
contrast it to the more common definition of isotope-based therapy.

Genitourinary brachytherapy is commonly practiced for both early and intermittent
high-risk stages of disease with or without external beam radiation therapy, with very
low dose rate or high dose rate (HDR) with a variety of techniques across centers.
Our in-house dynamic team led by Paul Nguyen has produced a most useful update here.

They systematically approach the very low dose rate (VLDR) implants through epidemiology, relevant literature, guidelines, contraindications, from low-favorable-risk
to intermediate- and high-risk groups. They systematically cover toxicities, radiation
safety, ultrasound techniques, volume, geometry seed, and seed carrier choice. Common
treatment planning and dosimetry techniques lead into dose evaluation, operation room
(OR) procedures, and the subtleties of pre versus live in OR planning. They point to the
future deployment of SAVE and HELP techniques. With a similar approach, they have
updated HDR applications and techniques including fiducial markers and computer
dynamic dose optimization schemes.

The late breaking trial showing such significant biological control for the use of a seed
boost in the locally advanced cases may well change the management of this stage of
disease, in which there would likely be a resurgence of seed boost for this stage.

In a minor way, I also collaborated in this chapter to draw together the smaller
experience with penile brachytherapy, for which I am so grateful for the assistance
of Dr. Juanita Crook from the British Columbia Cancer Agency. A former American
Brachytherapy Society president, she is the undoubted global leader in drawing attention to the possibility of organ and functional preservation for penile cancer.

Gynecologic brachytherapy is such a bedrock of our specialty with much excellent literature that I was so happy that under the wonderful direction of my close colleagues and friends, Akila N. Viswanathan, Larissa L. Lee, and Antonio Damato have produced such a superb update to the first edition. The intervening years have yielded so much new, clinically significant data, that modern gynecologic brachytherapy is image based, not reference point based and is blessed with extremely strong internationally agreed on guidelines. This chapter covers the locally advanced cervix approaches including patient evaluation, choice for modality of care, and the subtleties of low, pulsed, and high dose rate therapy. In a similar manner, postoperative endometrial, medically inoperable and vaginal vault recurrences, and primary vaginal cancers are reviewed. Complications and follow-up care provide important practical guidance for what to expect and what to do.

The physics considerations by Antonio Damato comprehensively cover contouring, digitization, and the evolution of international guidelines. Treatment planning considerations lead us to the growing practice of expressing a common nomenclature for a host of doses and fractionation schemes with different external beam dose contributions, in terms of equivalent 2 Gy dose. This has already been proven to be incredibly useful to have better understanding of composite dose to the clinical targets as well as to the organs at risk for toxicity. Quality management for these complex cases and regulatory parameters is thoroughly discussed.

Breast brachytherapy has undergone much change and maturation in the last 7 years with new applicators and techniques as well as excellent prospective data and even more trials ongoing. To head up this revision, Atif Khan, a former fellow and dear friend and Simona Shaitelman gathered a star-studded writing group to include Frank Vicini and Doug Arthur, all four world leaders in brachytherapy and principal investigators on highly significant practice changing studies. This chapter succinctly covers the rationale, patient selection, and adroitly uses tables for easy comparisons of the already-reported as well as the ongoing trials. There is an excellent review of every applicator, from single through multilumen, to interstitial and noninvasive techniques. They discuss comparative benefits and risks, quality of life, cost of care, and considerations for the future of breast brachytherapy. Clinical vignettes top off this super revision.

Thoracic brachytherapy was also very worthy of an update in view of exciting new trials. Subhakar Mutyala until recently at Scott & White in Austin, TX, with his in-house group led the superb reworking of this chapter. For thematic simplicity, we chose to move esophagus brachytherapy to the gastrointestinal (GI) chapter. Great hope was placed on the ACASOG trial and robotic approaches for early-stage disease. The modern use of the planar and volume seeding technique is well reviewed. The locally advanced clinical scenario is comprehensively reviewed and includes the variety of isotopes as well as the context of the relationship to modern external beam techniques. The opportunity to advance the use of HDR afterloading, and intraoperative radiation therapy (IORT) in the context of dose escalation and the treatment of recurrent disease is very important for comprehensive practice. Here again the choices for dose rates, clinical planning, and review of the risk of significant complications are well reviewed. The surgical scenario is so important to understand along with its own inherent risk of complications so as to give a realistic view of what additional risk and benefit come with these brachytherapy techniques. Here again, Dr. Mutyala’s team offers lucid practical clinical advice to guide practitioners. Importantly, also the role of endobronchial brachytherapy both in the definitive and palliative settings are carefully explored for technique and also for literature-based dose and fractionation scheme. I find this a super useful review of the actual pragmatics of these important procedures that is Dr. Mutyala’s hallmark. Combination therapy including laser, stents, and photodynamic therapy (PDT) is finally explored in the important real-life contexts of tumor recurrence, reirradiation, replete with images, tables, and useful references.
The need for a good chapter on skin and superficial targets was one of the significant driving forces for this new edition. There are many unique aspects and even paradoxes here. The most practiced brachytherapy in the United States is done with the least amount of prospective literature and is done mainly by dermatologists not radiation oncologists! That being said, this superb team led by the MD Anderson’s Anna Likhacheva and Harvard’s Ivan Buzurovic has produced an honest, concise, and really useful chapter. Starting with some brief history, it courses over the most common histologies in the context of modern dermatologic practice to find a reasonable set of selection criteria including histology, physical location, cosmetic impact, and potential alternatives. They review a host of different techniques that links very well to the broad range of applications for cutaneous targets. This includes a solid review of the use of electronically generated low-energy radiation therapy sometimes called electronic brachytherapy—a phrase itself that generates controversy. While reviewing the retrospective papers and the few prospective papers, they include really useful, detailed commentary so as to guide what meaning can be taken. The sheer lack of a tradition of prospective data, as we see elsewhere in this book, is a call to start this process with patterns of care analysis, and so on. The chapter would have been sufficient, but the addition of the generalized work flow for surface application technique section by Ivan Buzurovic is comprehensive, hugely useful, and is full of process, advice, and explanation. Six clinical vignettes with image and dose conclude this stellar innovation to the book.

A veritable who’s who of head and neck brachytherapy was assembled by Nick Lukens to give a world-class concise review of applications and techniques across the many anatomic disease sites within head and neck. Nick and Ken Hu (and I) had trained with Lou Harrison in the Memorial Sloan-Kettering Cancer Center (MSKCC) tradition. Bringing Peter Levendag and David Teguh helped us to better feature the European traditions in contrast to those of the United States. Paul Busse, my colleague here at Harvard, filled this international perspective out with “Boston’s style.” Most useful is the repetitive structure of the chapter that courses over the literature and reviews the interaction with surgery and external beam therapies in the primary, locally advanced, and recurrent settings. All dose rates, all manner of applicator and catheter techniques, and all characterizations of dose are in a matrix with this repetitive pattern. A delightful addition here is suggested important elements of each implant with regard to informed consent. The details with which each operative technique section is written are a pleasure to behold and will be most useful in our larger goal to maintain and preserve these operative skills for the next generation.

Our home team of Nils Arvold and his then central nervous system (CNS) fellow extraordinaire Abigail Stockham, have given us a most comprehensive and systematic review of brachytherapy of the CNS including the spinal cord. Each section organizes and provides detailed commentaries on what the meanings of the various studies are and where the particular data and applications belong either in ongoing new research or in ongoing clinical practice. The primary glioma section takes us through the radiobiological and physics considerations and fully reviews the level 1 data that were negative. Additional literature from Boston and San Francisco importantly teaches the strong need to balance the efficacy of a therapy with the various toxicities and need for reoperation. This section finishes by reaching to the future with modern molecular approaches and a potential new role for brachytherapy. Glioma recurrences, low-grade tumors, and atypical meningioma each gets an equally thorough exposure and with realistic evaluations of the gaps in data, as well as the complex use here of stereotactic radiosurgery and radiotherapy. The most active area of clinical research in CNS is in the deployment of Cs-131 in post-cavity resection for metastases. In addition to the excellent description of the growing literature and technique, there is a most thoughtful cost analysis review.

As we included in the first edition, the role of dural plaque and paraspinal seed therapy is nicely updated particularly demonstrating the greater potential here for both seed and catheter-based research with advanced and evolving image technology. Four of our own cases demonstrate clinical situations, indications, techniques, and dosimetric...
outcomes across two atypical meningiomas and two metastases in four different brain sites.

There is no chapter that covers so comprehensively such a large and different set of organ sites as that of the Gastrointestinal Brachytherapy chapter. And, there is no better person for such a global task than Alex Stewart of the Royal Surrey Hospital in England. Alex completed two fellowship years among us, and although she now directs her hospital’s cancer program, she has never really left us. She is the “energizer bunny” of my brachytherapy life and I have never met a harder worker. To increase the load, we moved esophagus from the thoracic chapter for greater usability and included Nitika Thawani here as she wrote much of that part. The international group hails from England, Greece, Canada, India (and Texas), as well as Burma. Their international perspective resounds throughout in the literature review and analysis, as well as in their comprehensive review of indications and techniques.

In the esophagus section, there is a deftly woven review of indications and techniques with trial data and guidelines. Discussed in the review is the potential confounding situation of a solid randomized trial being contrasted with an RTOG phase II study’s excessive toxicity that disallowed a confirmatory phase III trial and that may have changed much about how esophagus brachytherapy is performed. Palliative care is similarly reviewed importantly in the context of many other existing and future therapeutic interventions to find its optimal role. Pancreas is thoughtfully reviewed for inclusiveness with a good perspective on the lack of data and variability of presentation and other treatment philosophies.

More importantly, bile duct adjuvant therapy with external beam radiotherapy (EBRT) is advocated in selected R1 resection settings with reasonable case series. Despite a solid literature to support it, this is one of the areas where I believe we should champion new study. The fact that so many partial hepatectomies leave positive margins, should, if for no better reason than quality assurance (QA), be challenged as the “definitive” therapy and more integrative alternative, possibly including brachytherapy in selected cases could be entertained anew.

From southeast Asia, we get the larger perspective on primary liver tumors. A broad array of liver-directed therapy is reviewed and includes seeds, catheters, all dose rates, stereotactic therapy, as well as radioembolization therapy. Metastatic liver disease mostly of colorectal origin and including breast and lung disease gets a super synopsis of the literature and of ongoing trials in the context of modern systemic chemotherpay.

Our rectal cancer section steps out of the box to redefine contact orthovoltage (formerly called “Papillon”) as “brachytherapy”—a definition that used to belong purely to isotope-based energy sources. There are proponents and protagonists in many disease sites here. I am just thrilled that the conversation can also be played out in these pages. For the practitioner and patient, I would strongly advocate for inclusion to make sure all options are available as widely as possible. Another theme is the potential for extreme hypofractionation. The techniques and the case vignette are so elegantly presented by Sunny Myint, who is the undoubted world advocate. His contribution extends to causing an international cooperative study group to do prospective trial.

HDR rectal brachytherapy in the Montreal technique of Te Vuong is fully described with the various indications, techniques for preop, non-op, dose escalation, and palliative settings. Emerging literature may lead to the greater study of nonoperative approaches in which brachytherapy would play an important part.

Another “Papillon” technique is interstitial anal brachytherapy. Michele Albert, who was my very first brachytherapy fellow, and with whom I share this practice, locally inspires this final section of the chapter. Her excellent review of literature, applications, and techniques opens up the possibility that this organ sparing technique would be an increasing and really useful part of definitive care—yet another organ to preserve!

Five super vignettes for biliary, hepatic interstitial, hepatic radioembolization, rectal, and anal cases give most useful demonstrations of the great breadth and width of GI brachytherapy with so much more evidence-based work to do.
"The patient only has three things to ask you, Phillip. Save my life, save my limb and save my function." This is a direct quote from my first day in clinic with the legendary Murray Brennan at Memorial. Dr. Brennan along with Lou Harrison and Peter Pisters has championed sarcoma care with the only randomized trial of the use of brachytherapy for soft tissue sarcoma. It has given me great pleasure to have Caroline Holloway, associate editor and a former fellow, rise in this area of expertise and lead this wonderful chapter revision. Along with my surgical colleague Chan Raut they have produced a superb update with a wide review of patient selection, toxicity, results, various dose rates, and the integration with external beam approaches. The tables especially are most helpful in organizing the literature and possible approaches. Additionally, they describe special situations for retroperitoneal sites, in the setting of previous irradiation, pediatric extremity cases, as well as cutaneous applications. The technical description of placement and care of catheters, definition of clinical target volume (CTV), prescription, and treatment planning issues are given for catheters, seeds, and molds. Four cases, two with catheters and two with molds, cover sarcomas of the arm, hand, scalp, and foot.

It is important to remember, that even though the main focus of radiation oncology is cancer care, there are applications, including brachytherapy for other noncancerous proliferative life-threatening diseases. Occlusive vascular disease causes a million deaths in the United States every year. The fact that brachytherapy has played an important role in this disease and may still play an important role has kept this subject before us and makes a valid argument for its continued presence within this book. And although the first cases were treated in Venezuela, the first prospective trial was conducted at Scripps Clinic in La Jolla CA and we appropriately reach right back there for this important update on vascular brachytherapy. Peter Chin and Ray Lin share my adulation of the undisputed world leader in vascular brachytherapy, Prabhakar Tripuraneni. Prabhakar’s unbridled enthusiasm has guided me and so many of the senior brachytherapy faculty worldwide. The world of organized cardiology rapidly caused no less than seven randomized trials in coronary brachytherapy all showing significant benefit, as well as seven for peripheral vessels. The biology of coronary brachytherapy was the inspiration for the deployment of drug on a stent. The arrival of these drug-eluting stents (DES) absolutely closed down the burgeoning practice of vascular brachytherapy, practically overnight with the publication in April 2003 of two complementary trials with taxol and rapamycin showing that there was zero restenosis. “Thank you and good bye, Phillip” were the very words I heard that very day as the cath lab director jubilantly held two sets of opposable digit zeros in front of his own eyes! Alas, they were short-lived zeros and the initial response to a DES failure was the deployment of another DES within the first one. The current role of coronary artery radiation therapy (CART) is still evolving and newer studies may occur. For now, the role is in the setting of the failed stent sandwich when there is no other option than medical management. Approximately 20 centers in the United States are currently offering CART with a single strontium loaded β-emitting device model. There is still no peripheral DES on the market in the United States and there are selected cardiac DES deployed in smaller caliber vessels. The larger iliac and femoral arterial system is still an appropriate target for peripheral artery radiation therapy (PART). Treating coronary and peripheral disease similarly but separately, our authors have done such a wonderful job to present the relevant literature and definitions in a most readable way. In addition, there are most clear role definitions so that it seems like airline pilot-level instructions. The chapter covers all the delivery systems as well as the all important pullback technique so that an adequate dose can be given distally and proximally when there is a long injury length. The clinical vignette cases of a right coronary artery and a superficial femoral artery perfectly compliment this important chapter.

The final chapter, as in the first edition, covers the organization and financial foundation of a brachytherapy practice. The first edition’s final chapter was a collaboration of our own in-house administrators with our consultants. In this edition, we are delighted to have one of radiation oncology’s own national expert physicians in this area lead us with his own consultants. Jeff Demanes leads the UCLA Division of Brachytherapy, has
a wide scope practice, has a very successful brachytherapy fellowship program, and is also one of the humblest and kindest men I know.

Beginning with the first foundation of physician training and experience, this chapter courses comprehensively through planning, development, goal setting, and referring issues to full strategic planning. The roles of the necessary personnel are so well stated, and argued for. The interaction with departmental and hospital administrators is also very vital. Space, persons, time, equipment, and clinical collaborators are all so very well described. Demanes and his colleagues thoroughly explain the formulation of a business plan balancing capital equipment and staff needs against projections of income and under the assumption that the project will begin small and grow in a predictable and organized manner. Demonstrating the reality, current costs, and reimbursement figures provide such concrete numbers on which centers planning new brachytherapy services can start to plan. Business advice regarding how to navigate compliance rules, the law, and denials is the best way to help the business side flourish. The worked examples of three common cases complete this thoroughly readable final chapter.

Ultimately, the goal of this new edition of Brachytherapy: Applications and Techniques is to support the skilled deployment of a highly technical and broad-ranging modality and to enhance survival as well as organ and functional preservation. The 7 years since the release of the first edition have added so much evidence-based support for these practices, and there are significant trials in progress.

In this second edition, we have brought together disease- and modality-specific leaders and teachers to concisely share their rationale and techniques. With our new publisher, Demos Medical Publishing, we have provided the ability of greater access to the book through the availability of an e-book. Finally, as in the first edition, the combined learning of any discipline must necessarily always be a work in progress. The chapter authors, the associate editors, and I invite your creative feedback so as to continue to move this vital work ever onward and upward.

Phillip M. Devlin, MD, FACR, FASTRO, FFRRCSI(Hon)
Preface to the First Edition

Brachytherapy is the clinical use of radioactive isotopes to provide a highly conformal image-guided radiation therapy that takes advantage of the steep fall of dose characteristics and different energetic emanations to improve the therapeutic ratio. Historically, it was the first mode of radiation therapy. The last 110 years have seen the full maturing of radiation oncology. Integral to this growth of radiation oncology has been the rise and fall of various types of brachytherapy, often in a reciprocal manner to the changes in external beam radiation therapy technology. Some early methods have endured to this day, including surface applications and some forms of gynecologic care. Prostate brachytherapy was practiced very early as intraurethral radium insertions, first for benign prostatic hypertrophy and then for prostate tumors. Modern prostate brachytherapy could not be further away from this. Vascular brachytherapy has risen and fallen in a relatively short number of years, driven by huge financial pressure and eclipsed by innovative and disruptive technology, despite many randomized trials proving efficacy. Breast brachytherapy, once a part of boost therapy in the first wave of breast conservation a generation ago, is on the rise in intracavitary and interstitial forms of accelerated partial breast irradiation for early-stage breast-conserving therapy.

The context for writing this textbook is that of a dedicated division of brachytherapy in a large urban teaching hospital with three core missions: excellence in clinical care of patients, excellence in teaching, and excellence in research. This textbook addresses all three goals. It is my hope that assembling the literature, describing techniques, and illustrating these with actual clinical examples will serve to update practitioners and students on the latest developments in brachytherapy for these disease sites, be a guide to clinical care, and, in doing so, will be a valuable teaching tool. At its heart, this textbook should be a practical source to clinical teams answering two basic questions: why and how. Ten clinical disease site chapters are preceded by chapters on practical radiobiology, practical physics considerations, and followed by a final chapter on organizational practical considerations. Chapters 3 to 12 on clinical disease sites flow generally in a cephalocaudal order. These vignette descriptions will help in contextually orienting the reader.

The chapter on head and neck brachytherapy was contributed by the Beth Israel New York group, led by Peter Han and Ken Hu under the direction of my own fellowship mentor Lou Harrison. Lou’s influence on how head and neck radiation therapy is practiced is without parallel. His unstinting commitment to excellence continues to inspire. This chapter features a very nice concise history of
brachytherapy, as befits the first clinical chapter. Patient selection, techniques, and results form the backbone of the various clinical sites. Nasopharynx, lip, oral tongue, base of tongue, floor of mouth, buccal mucosa, faucial arch, tonsil, recurrences, and additional techniques are covered well. There are many useful clinical pictures, including various films of implants and applicators. The chapter finishes with some of my own clinical cases with novel applications of high dose rate (HDR) surface applicator technology for superficial head and neck targets.

The chapter on the central nervous system (CNS) comes out of our sister hospital in Boston, the Massachusetts General Hospital (MGH). Arnab Chakravarti, with the assistance of Tom DeLaney and Jay Loeffler, has given a broad overview of the CNS and included novel approaches. The chapter reviews radiobiology and physics pertinent to temporary or permanent iodine-125 ($^{125}\text{I}$) implants, as well as colloidal $^{125}\text{I}$ for temporary intracavitary balloon implantation, $\beta$-emitting isotopes for dural plaque therapy, monoclonal tagged antibodies for gliomas, and also for surface applicator technology and permanent seed implant technology for spinal dura. I am very grateful for the additional clinical images provided by Normand Laperriere, Jim Welsh, and David Larson.

The chapter on breast brachytherapy was born out of the Virginia Commonwealth University program by Joe Kelly under the leadership of Doug Arthur and with guidance from Frank Vicini at the William Beaumont Hospital. These latter two senior doctors have changed the face of breast-conserving radiation therapy and, as leaders in the national randomized trial, are fully committed to teaching these methodologies. There is a thorough review of the history of breast conservation, the rationale for less-than-whole-breast irradiation, and the various techniques. Interstitial and intracavitary techniques are reviewed in detail, including indications, techniques, and results. Future directions are dealt with carefully and with insight. Again, in this chapter, I have added additional clinical information on novel uses of HDR surface applicator technology for postmastectomy immediate reconstruction scar boost, which I have developed to meet this specific clinical scenario.

The chapter on thoracic brachytherapy was developed in Boston. Subhakar Mutyala has shown a strong interest in learning more about this, and has enthusiastically taken these methodologies to his new practice in the Bronx at Montefiore, where he has begun to teach fellows in a cross-town collaboration with Lou Harrison. Our own program would not have been possible without the strong encouragement, support, and enthusiasm of David Sugarbaker. I am delighted that they have collaborated in the production of this chapter. Esophagus, lung and mesothelioma, and endobronchial diseases are carefully reviewed for indications, techniques, and doses, in the setting of early stage, locally advanced stage, as well as palliation. More than 50 clinically relevant references augment this chapter. Intraoperative radiation therapy and combining brachytherapy with novel techniques complete this chapter.

Brian Czito and Chris Willett, now both Duke University gastrointestinal (GI) radiation oncologists, have provided a very comprehensive core GI chapter that is augmented by recent innovations in biliary combined modality therapy and hepatic radioactive sphere therapy in collaboration with Nasir Siddiqi and Harvey Mamon from our own center. This chapter comprehensively reviews the literature, indications, and suggested treatment schemas for definitive and palliative brachytherapy for esophagus, pancreatic, biliary, colorectal, and liver metastases. More than 60 appropriate clinical references support this and further aid clinicians. It may be that the buzz previously seen about coronary artery brachytherapy may return for this last subject. Novel collaborations with interventional radiology, nuclear medicine, and radiopharmacy colleagues may prove to be not only an additional radiation therapy to aid a group of liver disease patients who were previously not referred to us, but also a very satisfying opportunity to expand the horizons of our specialty.

The chapter on prostate brachytherapy was, more than any other, a complex team effort. Books have been and will continue to be written on prostate brachytherapy alone. Caroline Holloway, Michele Albert, and Warren Suh have sought to strike the...
right balance for this disease site in the context of a general brachytherapy textbook. The chapter summarizes the basic Seattle technique and then examines interesting innovations in implant technology, including MRI-guided implants, automated seed loading, and HDR. Advanced inverse planning software is featured for both very low dose rate (VLRD) and HDR techniques. Inverse planning techniques for seed implants from Centre Hospitalier Universitaire de Quebec with André-Guy Martin and HDR from the University of California San Francisco (UCSF) with Joe Hsu are demonstrated. Particular thanks are due to John Blasko and his colleagues at the Seattle Prostate Institute, who also have shown a great deal of generosity in contributing material for this work.

Gynecologic brachytherapy is one of the mainstays of this subspecialty and is another huge area to be covered. I have taken great joy in this excellent collaboration between Akila Viswanathan and Dan Petereit. The chapter is a comprehensive review of the brachytherapy for cervix, endometrial vaginal, and vulvar cancers, and beautifully covers classic low dose rate (LDR) techniques and modern HDR and pulsed dose rate (PDR) adaptations. Cervix cancer is first reviewed with the anatomy, imaging, and modern adaptations to the role of imaging in the care of this disease site. Dose rate considerations specific to the cervix are reviewed, including modern PDR strategies. Practical instructions are provided for every aspect of the implant from preprocedural preparation, through anesthesia, operating room (OR) considerations, applicator selection, placement, packing, recovery, postoperative orders, treatment planning, isotope loading/HDR/PDR dose and fractionation schemes, applicator removal, quality assurance specific to cervix cancer care, potential for complications, and follow-up care. Endometrial, vaginal, and vulvar cancers are also treated in a similar detailed manner including cylinder, double tandem, and interstitial therapies. Palliative care is also addressed. Ninety-five references and more than 50 figures and tables aid in this excellent offering. Although books have been and will continue to be written on the subject, this offering has a unique place on your bookshelf as the most practical review that will guide your practice.

Another splendid collaboration is that between Chan Raut and Michele Albert, who have joined the dynamic influences of their training from the MGH, Memorial Sloan-Kettering Cancer Center (MSKCC), and MD Anderson Hospital Cancer Center (MDAHC;C) schools of sarcoma brachytherapy. This chapter leads off with an excellent review of contemporary management strategies and a comparison of beam versus brachytherapy approaches. Evidence-based management of extremity sarcoma with varying combinations of surgery and radiation are pertinently reviewed. A broad range of elements, including patient selection, techniques, and dose-rate considerations, leads to additional considerations for the management of recurrences, retroperitoneal sarcoma, desmoids, keloids, and low-grade disease. Quality of life and comparative considerations between external beam radiation therapy and brachytherapy are reviewed. This chapter is supported by 75 clinically important references, over 40 figures and tables and the three clinical vignettes make this a most useful adjuvant for sarcoma.

For the vascular brachytherapy chapter, we looked to Scripps Clinic in La Jolla as the American birthplace. Huan Giap and Prabhakar Tripuraneni have given us a complete review of this subject and left to the future what role may persist or return. Much was learned from this short sojourn into the world of interventional cardiology and radiology. To Radiation Oncology’s great credit, this modality was rapidly mobilized, staffs were trained, quality assurance (QA) procedures were created, and schedules were altered to cover the unpredictable cath-lab schedules. No doubt, there were mutual sighs of relief when Radiation Oncology was asked to step down in favor of the drug-eluting stent technology. Newer collaborations with the medical technology industry will continue at heightened levels as a result of this short but intense experience.

The chapter on pediatric brachytherapy was written by Tom Merchant and Matt Krasin of St. Jude Children’s Research Hospital in Memphis. Their whole approach to the use of brachytherapy for children with cancer is set in the appropriate context of an
infrequently employed modality. Nonetheless, they have given us a thorough review of the use of brachytherapy in Wilms tumor, neuroblastoma, hepatoblastoma, Ewing sarcoma, osteosarcoma, soft tissue sarcoma, rhabdomyosarcoma, retinoblastoma, and craniopharyngioma. Intraoperative radiation therapy, fractionated HDR therapy, permanent radioactive seed therapy, and eye plaque therapy are nicely reviewed. Throughout, case reports and clinical scenarios are embedded to highlight indications as well as benefits and potential risks. Fifty-eight clinically pertinent references and excellent figures support this important contribution.

The book begins with two preparatory chapters: the first on practical radiobiology and the second on practical physics considerations. The first chapter is a very lucid collaboration between a great student and a great teacher. Alex Stewart and Bleddyn Jones, who had been her mentor at the Charing Cross Hospital, have assembled a very clear concise review of the core of radiobiology as it pertains to the clinical tasks of brachytherapy. The chapter starts with a very clear explanation of the basics of this subject, through the explanation of radiobiologic equivalence, to the four Rs of radiobiology. Embedded are examples, straightforward equations, practical pearls, and an excellent integration of the important literature. Considerations of dose-rate effects and the integration of chemotherapy and other biological therapies are included. Eight worked practical examples in a problem format illustrate the need to consider not only the equivalent dose, but also to distinguish the needs and thresholds for tumor control as well as the risk of acute and late toxicities. Various practical needs that may be encountered in clinical care are reviewed: a need to replace intended external beam dose with an LDR implant, the need to replace an LDR implant with HDR fractions, how to deal with interrupted dose and a time delay, how to correct for errors of the omission of a decay factor, and the delivery of the prescribed dose. In all this, the goal to evaluate the biologically intended dose, the currently delivered dose, and the calculation of the remainder of dose to be given are elegantly demonstrated. The chapter ends with a tidy comparison of the RBEDs of three common fractionation schemes for vaginal vault brachytherapy.

The second chapter is an excellent in-house team effort led by Robert Cormack with Jorgen Hansen, Desmond O’Farrell, and Alex Stewart. The goal of this chapter is entirely practical. Starting off with the needs for personnel, imaging equipment, and treatment planning, the chapter goes on to cover the facilities and equipment, written procedures, the Quality Management Program, calibration, and emergency contingencies for both HDR and LDR brachytherapy. The chapter provides examples of clinical forms that stood the test of time as necessary and sufficient to record the various components of brachytherapy so as to minimize the risk of misunderstanding and misadministration. Floor plans for an idealized brachytherapy suite as well as the necessary physics equipment for the safe handling of radioactive sources can further assist in the development of new programs.

The final chapter of the book returns to a supportive, rather than a purely clinical subject. I am very proud of the excellent interaction between our own administrative group led by Gerard Walsh and our consultants and friends of many years Linda Lively and Jim Hugh. Their fastidious attention to detail is fabulously offset by their lucid explanations of what would otherwise be very turgid material. This chapter reviews strategic planning for brachytherapy comprehensively. The various resources, people, space, time, and equipment are reviewed in the matrix of time lines, patient care flowcharts, the population to be served, the community, and potential competition. The chapter details the elements of a successful business plan, again in the complicated matrix of time, resources, and potential reimbursement.

The final section of the chapter places the proposal for the development of a brachytherapy service squarely in the realities of 2006 reimbursement constraints in the United States. They have provided web-based resources and useful appendices. Key financial indicators commonly used in medical practices are reviewed for the evaluation of the success of a brachytherapy program. Throughout this chapter, the authors have
provided copious spreadsheets of realistic examples to further enhance this unique textbook presentation.

An ideal textbook should fulfill a need, be thorough in its review, and be able to withstand the test of time by expressing with clarity significant values of lasting worth. I invite the critical interaction of clinicians with this text. I positively hope for gracious controversy; feedback; suggestions; and the volunteering of time, talent, and new clinical material as we go forward to future editions.

Already we are approaching the realm of monoclonal antibodies, microspheres, and nanoparticles tagged with isotopes to be taken ever closer and more specifically to the heart of the ailing cancer cell, the DNA. These approaches may, one day, become the dominant paradigm for how ionizing radiation is employed. Until such a time when there will be a fluent and totally effective cure for all cancers, the oncologic specialties must continue the work to heal those currently afflicted with the disease. If this textbook assists clinicians in this task, it will have succeeded. Each contributor and the entire publishing staff join me in thanking you for participating in this dynamic process and in inviting your feedback so as to grow further together down the years, as compassionate caregivers for a suffering humanity.

Phillip M. Devlin, MD
Acknowledgments

Firstly I must express my profound gratitude to the wonderful team at Demos Medical Publishing in NYC. It was an amazing coincidence of me looking for a publisher at the same time they were looking for a new book as they grow in the Oncology Space. From my very first call with editor David D’Addona, to the practically daily interactions of these last months David, his able assistant editor Norman Graubart and managing editor Joe Stubenrauch have been superb collaborators. Their respect for the authors’ significant clinical commitments was complete. Their support of the four editors was completely fabulous. Their wonder at the subject matter warmed our hearts.

We ambitiously aimed in September 2014 to have this second edition on the shelves at the 2015 ASTRO in San Antonio and I am so excited that we have achieved this.

I also need to acknowledge the foundational contribution of the Lippincott executive editor of the first edition, Jonathan Pine. We lost Jonathan to cancer 2 years ago and I know he would have been proud that we have come to this point. Gratitude is due to Wolters Kluwer’s own successor to Jonathan, Julie Goolsby, and their managing editor Emilie Moyer. Their professionalism and grace was boundless. We simply could not have done this without them. Once again, special thanks must be given to Desmond O’Farrell and Jorgen Hansen and the entire BWH physics team who in addition to contributing their own chapter work labored countless hours to retrieve and optimize hundreds of clinical images and data so as to enhance the rest of the book. They are the “without which not” of my brachytherapy life!

I offer my deepest gratitude to so many thousands of patients who have placed their lives and trust in our hands. I am most humbled by their complete trust and generosity that has allowed effective therapy, education, and research to continue. To live a life in which one’s patients show so much trust and love is a rich life indeed.

I, of course, owe a huge thanks to chapter authors many of whom continued over from the first edition as well as the newer contributors who joined us here. Given that this is yet another example of service to the specialty, that it is unpaid volunteer work, that it needed to happen in the gaps of life on evenings and weekends, I also gratefully acknowledge all the families and the gift they continue to give us in freeing us to write. Each author epitomizes the “triple threat” of academic medical practice in excellent evidence-based practice, outstanding teaching and mentorship, and practice-changing research. I am overjoyed that so many of the new authors are in the early stages of academic careers and have a strong brachytherapy focus. Looking back over 20 years, we have come a long way. As I imagine the future, I am so encouraged by their gifts, their huge intellects, their tremendous work ethic, and their sheer dedication. Our future is bright in their hands.

Very close to me are three associate editors. Robert Cormack is such a wonderful constant presence with the logic of Star trek’s Spock and the philosophic calm of Yoda.
I owe him huge thanks. Caroline Holloway of BCCA, Victoria BC has been an ever present and eager editor of all that has been put before her. She has a unique way with words that always improves meaning. Her continued presence at all our teaching and conference events more than 10 years since her fellowship is the best testament to her faithful friendship and support of the larger clinical, teaching, and research mission. She is one of the warmest hearts you will ever encounter. I owe her so, very many thanks.

Alex Stewart, one of the most active and dynamic upward bound brachytherapy leaders on the European scene has brought her considerable organizational skills and leadership to support getting the chapters and proofs in on time. Her sheer class, her best English humor and her love of travel continue to encourage so many of us to do more, to do it better and to do it on time! She finished her fellowships here over a decade ago, and it is still like she never left. She is a model of how to live life to the full.

I also wish to acknowledge the cohort of leaders across the world who participate in leadership as service to Radiation Oncology globally and Brachytherapy in particular. My sojourn on the ASTRO board showed me new levels of service and dedication exemplified by Tim Williams, Anthony Zeitman, Prabhakar Tripuraneni, Michael Steinberg, Colleen Lawton, Beth Erickson, Bruce Haffty, Bruce Minsky, David Wazer, David Beyer, Laurie Gaspar, and Brian Kavanaugh. Feran Guedea, Peter Hoskin, Michael Zelefsky, Vincenzo Valentini, Donal Hollywood (RIP), Jerome Coffey, Paul Kelly, Frank Sullivan, Chris Milross, Kari Tandrup, Richard Poetters, Janusz Skowronek, Adela Poitevin, and Beatriz Amendola inspire the brachytherapy world on the international scene. Each have touched me and encouraged me in my clinical, teaching, and research work. They have shown me that leadership is about service. Each was always there for me at the other end of the phone or email with only encouragement and possibility and never said no. Their constructive feedback and suggestions were always spot-on. It does indeed take a global village to lead our specialty, to conduct teaching and research, to write a textbook!

I repeat the acknowledgment from the first edition of the line of teachers: Dick Edlich, Gillies McKenna, Joel Goldwein, Dan D’Angio, Morton Kligerman, Louis Harrison, Larry Kun, Anthony D’Amico, Rita Linggood, Jay Harris, and Prabhakar Tripuraneni. Their unstinting belief in me, honest guidance at the important times has sustained me and grown me as a human and as an academic physician. I bow to their contribution yet again.

My clinical practice at the Brigham and Women’s and the Dana Farber Cancer Center has continued to grow, most notably in the world of skin cancers, now the most common use of brachytherapy in the United States. My dermatology colleagues, Tom Kupper, Rachael Clark, David Fisher, Andrea Ng, Marianne Tawa, Nicole LeBoeuf, Allison Goddard, John O’Malley, Jessica Fewkes, Linda Wang, and Jennifer Lin not only have taught me much, they have expanded our use of complex superficial brachytherapy with so many otherwise insoluble cutaneous situations, that has positively contributed to the expansion of the scope of practice of brachytherapy in this exciting area. As important is the fabulous basic and translational collaboration I am part of with the Kupper and Clark Lab at Harvard. This superstar couple have actively mentored me into this work on the skin resident T-cell, host immunity, and tumors. This is a practically perfect match that finds its motivation in our weekly cutaneous lymphoma multidisciplinary clinic where we live the ideal of “bench to bedside and back.”

The founding vision of Jay Harris gave me my Brigham brachytherapy start and has sustained my group as our devoted chair all these years. Perpetual thanks to him as he steps away from the chair and all success to our new wonderful Daphne Haas-Kogan who has taken it up. My inner brachytherapy physician core of Akila Viswanathan, Paul Nguyen, Larissa Lee, and Peter Orio ably partner with physicists, Robert Cormack, Jorgen Hansen, Desmond O’Farrell, Mandal Bhagwat, Antonio Damato, Ivan Buzurovic, Scott Frieden, Emily Sugar, Dan Cail and Jaime Urribarri, Kip Nissen for QA, nurses Katie Duggan, Mary Consalves, Regina Tsanotelis, Una Randall, Maureen Farrell, Alicia Offiong, Yolanda Shittu, Mittie Farmer, therapists, Marianne Weiler, Kristen Bertone, Vanessa Cedrone, Susan Finucane, Erin Randazzo, Tracy Flint,
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admins Susanna Hilfer, Andy Formosi, Diane Galiano, Adi Heller, Sharon Koogler, and Ann Semioli. We attempt to run the clinical operations at a safety level similar to that of a flight crew to safely achieve more than 2000 really complex clinical procedures per year. This is my dream team and it never fails to give me a total boost to come to work in the morning!

Many fellows have spent at least a year among us and gone on to leadership positions in brachytherapy and radiation oncology across the world. I will repeat the gold medal award sentiment of Dan D’Angio, that they are the reward; they are the gold medals hanging upon my heart. We form an international fellowship still; we share our trade with a host of residents, students, and other professionals across the world.

My own life owes everything to my parents Barney and Marcella Devlin. My dad never saw my medical career. My mom continues to brag about her son the doctor! Bernard, Sarah, Bridget, Peter, John, Patrick, and Gerard are my siblings now with their widely expanding families. It warms me to see them flourishing. My Devlin cousins are so very close, especially at the recent loss of Philip Devlin my Tyrone cousin as well as Uncle Phil. Cousin Philip Devlin of Cherry Hill is as a brother to me, as his mother Kay is my second mom. Full of love and huge hugs we hold each other close. My Hughes cousins of Quincy, Brenda Jacqui, and Dan are also completely welcoming and nurturing, in good times and bad. I am continually supported by close personal friends through life’s many changes and want to acknowledge the Steve and Liz Lewenberg of Chilmark, John and Colleen Connell of Haddonfield, and grandparents Helen and Lou Brown of Virginia. Hugh Manning, Carolina Suran, Katie Mackie, and Barbara Martin are my Boston infield support team. I give a shout out to my Yoga community at South Boston Yoga; they help me remain flexible and peaceful in heart and body. Love also to the warm and caring community of traditional Irish musicians in and around Boston, especially Kathleen Conneely, Sean Clohessy, Nancy Kleiman, and The Coynes.

An extra special acknowledgment is due to Len Gunderson and Andrea McKee for the abiding special personal solicitude and support through a unique common bond.

Three grown children give me the very greatest joy. Brendan at 24 is a fine professional athlete distance runner and coach with an encyclopedic knowledge of exercise physiology. Clare at 22 has dedicated herself to the life of the stage and technical theater and music, in which she is so very happy and dedicated. Mary is 17 and finishing high school as a serious student who is attracted to medicine. She is my most frequent recreational shopping companion and has a fine eye for style and color. Their love for each other and for their parents is so heartwarming and life giving. We always remember their brother Patrick who died suddenly 10 years ago at 9 years of age. He remains in our hearts and we tell hilarious stories of his hijinks and capers. And whereas I have resolved the acute grief, there is a perpetual ache that I accept as the price of this lost love, even in the midst of happy memories.

I have chosen to dedicate this edition to my dear departed uncle Phil Devlin. He was as the father of my grown life and a true and wonderful inspiration for us all. He lived the life of an immigrant mason in and around New York City. Though of modest means he was the most unstintingly generous person I have ever known. His love for me and my family in good times and bad was supportive, uplifting, and life saving. He took such pride in all my career ambitions and projects. We would sit for hours at the kitchen table after the little ones were put to bed and he would always say, "that ‘a boy, you can do it, and wouldn’t your father have been ever so proud.”

Phillip M. Devlin
Cambridge, Massachusetts

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Thank you colleagues all.
Karin, Kiersten, Monika,
Lilja bring such joy.

Robert A. Cormack
Boston, Massachusetts

Brachytherapy always affords new opportunities for learning. I am honored to contribute to this edition of Brachytherapy: Applications and Techniques, both as an author and now coeditor. I would like to thank my coeditors and Phillip Devlin for mentoring me in this new role and for the opportunity. Brachytherapy is truly an art and I have been blessed to count both Drs. Devlin and Akila Viswanathan as mentors and friends. I would like to thank all of those involved in the Brachytherapy fellowship program at BWH in Boston for teaching me and preparing me for an academic career in brachytherapy. I would also like to thank all of my colleagues at the BCCA Vancouver Island Centre for their ongoing support. Finally, I thank my family for being my foundation and source of unwavering counsel even in matters of grammar.

Caroline L. Holloway
Victoria, BC, Canada

Although it has been a lot of hard work, I was delighted to be asked to not only continue my role as a lead chapter author for the second edition of Brachytherapy but to also become a coeditor. My thanks go to Phillip Devlin for his careful and enthusiastic mentoring of me in the field of brachytherapy with this textbook just being the latest in a string of brachytherapy projects that we have both been involved in.

My interest in brachytherapy was sparked by working with some of the original HDR pioneers at Charing Cross and the Hammersmith Hospitals-Barbara Southcott, Roger Dale, and Bleddyn Jones. Bleddyn’s patient teaching in preparation for my Fellowship exams also encouraged a lifelong interest in radiobiology and the practical applications of it in brachytherapy. I was the only trainee to complain that the brachytherapy question had been removed from our Physics paper that year. My Fellowship in Boston was two of the most enjoyable working years of my life and I thank Phillip, Anthony D’Amico, and Akila Viswanathan for that, along with Jorgen Hansen and Robert Cormack. And of course Desmond O’Farrell, my brachytherapy buddy who continues to make physics understandable for me as a mere physician. The international brachytherapy mafia of past Fellows at the Brigham has given me a cohort of colleagues who have become close friends cementing ties as our families grow together. My thanks goes out to the hard-working brachytherapy team at St Luke’s Cancer Centre, Royal Surrey County Hospital, particularly Mel Cunningham and Carol Ewan for diligently finding ways to indulge (or curb) my enthusiasm as we develop a world-class brachytherapy service together. And to Farid Saleh who patiently supports me and learns new techniques on a regular basis to aid our development.

I could not do any of this if I did not have the support of my family. Suzy and Nick Vincent—the enthusiastic and reliable grandparent babysitters. Lauren and Callum Stewart whom I hope are proud that when Mummy is not there at bedtime she is at least off trying to cure cancer or teach others how to do so. And of course Al Stewart whose patience with me knows no bounds, particularly when I was caught up with late night editing and trans-Atlantic phone calls.

Alexandra J. Stewart
Guildford, England
A Century of Brachytherapy
(From the Prostate’s Perspective)

Jesse N. Aronowitz

Brachytherapy has played a major role in the treatment of cancer, and its history could easily fill a volume; it would be inappropriate to attempt to compress it into a single chapter. I have endeavored, instead, to chronicle the story of prostate brachytherapy, which is reflective of the history of brachytherapy as a whole.

BRACHYTHERAPY: THE PREQUEL

As the discovery of X-rays and radioactivity has been exhaustively recounted (1,2), only a brief synopsis is attempted here. Wilhelm Röntgen, professor and director of the Physical Institute at the University of Würzburg, discovered in 1885 previously undescribed rays exiting a cathode-ray tube. Within months of his discovery of the unknown (“X”) rays, they were being used for medical diagnosis and therapy.

Technically, radiotherapy preceded the discovery of X-rays. Danish physician Nils Finsen demonstrated in the 1890s that lupus vulgaris (tubercular skin lesions) could be eradicated by ultraviolet (UV) light (3) (Figure 1.1). Röntgen’s rays, a more powerful form of invisible light, were soon used in the place of Finsen’s rays. Lupus vulgaris responded, as did other dermatologic disorders; the eradication of skin cancer (rodent ulcer) by X-irradiation was reported in 1899 (4). Several radiotherapy texts were published within a decade of Röntgen’s discovery (5–7).

---

a William Crookes had invented the cathode-ray tube in the 1870s, two decades before Röntgen’s discovery.
b Tuberculosis was the most dreaded disease of the 19th century; Finsen was awarded the 1903 Nobel Prize in Medicine for discovering a new mode of treatment for it.
Antoine Henri Becquerel discovered that uranium spontaneously emitted rays similar to Röntgen rays (1896). In 1898, graduate student Marie Sklodowska Curie identified polonium and radium, two radioactive elements present in minute quantities in uranium ore. Radium seemed to emit an inexhaustible supply of energy, and engendered an entirely new frontier in physics (8). Although radium rays were soon found to have biological properties similar to those of X-rays (the first reported radium cancer cure was in 1903 [9]), its scarcity rendered it almost unobtainable by clinicians. While X-ray tubes were cheap, radium was the most precious material on Earth (10).c

The widespread practice of brachyradiumd could not become established until the element became more plentiful.

THE RADIUM INDUSTRY

The richest known deposit of uranium ore during the first two decades of the 20th century was in St. Joachimsthal (the St. Joachim Valley) in Bohemia (now Jachymov, in the Czech Republic). St. Joachimsthal’s mineral riches had been exploited for centuries; so much silver was taken from the valley that the Austro-Hungarian Empire established a mint there.c Its miners had long been known to succumb to Bergkrankheit (mountain sickness); it would be centuries before the illness was identified as lung cancer, caused by the inhalation of radioactive dust and gas (11).

Although pitchblende ore is almost 50% uranium, radium makes up only about one part per million. Tons of uranium ore were processed (through a painstaking process of chemical reactions and fractional crystallizations) to obtain a single gram of radium.

c The price of radium peaked at $180,000 per gram in 1912.
d The term “brachyradium” (predecessor of “brachytherapy”) was proposed by Gösta Forsell in 1931 (12).

dollar originates from the coins that were minted there, Joachimsthalers, or thalers.
Several European firms (Chininfabrik Braunschweig in Germany; Armet De Lisle and the Société Centrales des Produits Chimiques in France) produced radium commercially. The cost of radium rose after the Austro-Hungarian government restricted the export of pitchblende, and the situation worsened with the outbreak of the First World War. German physicists sought a substitute in mesothorium (a mixture of $^{226}\text{Ra}$ and $^{228}\text{Ac}$), the decay product of thorium. The French discovered radium in the American West; southwestern Colorado and southeastern Utah have deposits of carnitite, a uranium/vanadium ore (13). Although comparatively radium poor (it is only about 2% uranium), carnitite was the best available source. The ore was brought by rail to Buffalo, NY for initial extraction, and the partially processed material was shipped to France for refining (14).

Large-scale American production of radium began with the Standard Chemical Company of Pittsburgh, in 1913. Brothers Joseph and James Flannery (who were originally undertakers) had become wealthy producing vanadium for strengthening steel. The Flannerys’ interest turned to radium after they were unable to obtain the substance in the United States for treatment of a cancer-stricken relative. When they learned that the carnitite that they had been mining in Colorado contained traces of radium, they shipped the ore to a reduction mill south of Pittsburgh for radium extraction. Within a few years, Standard Chemical produced more than half the world’s radium (Figure 1.2). Rich uranium deposits were discovered in the Katanga province of Belgium’s Congo colony in 1915, but were not mined until after the war. The Belgians, exploiting the Congo’s rich ore and native labor, were able to halve the cost of radium, eliminating American competition. The cost was further reduced a decade later, when rich pitchblende deposits were discovered in the Canadian Northwest Territories.

The Era of Intracavitary Radium Therapy

Prostate cancer was rarely diagnosed a century ago, but prostatitis, benign hyperplasia, and even tuberculosis of the prostate were treated by X-irradiation (15,16). Successful treatment of prostate cancer by X-rays was first reported in France in 1904 (17). Treatment of prostatic disease with radium was first reported in Paris, at a meeting of the Assoçiation Francaise d’Urologie in October 1909 (18). Ernst-Louis Desnos treated hypertrophy with a series of urethral and rectal applications (19). Henri Minet treated cancers of the prostate, bladder, and ureter with a silver tube containing 10 mg of radium, applied through a urethral catheter or a suprapubic cystotomy (20). Urologist Octave Pasteau and radium therapist Paul-Marie Degrais also began treating prostate cancer with intracavitary radium in 1909, but their first reports did not appear for several years (21). Pasteau’s rationale for preferring brachytherapy to prostatectomy was that “in cancer of the prostate the curative treatment by operation is in truth illusory; it is dangerous, and gives the most temporary results,” whereas these tumors are “particularly susceptible to the influence of radium” (22). They had used a silver capsule, containing 10 to 50 mg of radium sulfate, placed near the tip of a 17Fr coudé urinary catheter (Figure 1.3). Five treatment sessions, each lasting 2 to 3 hours, were delivered over 2 weeks. The series could be repeated periodically (annual maintenance treatments were prescribed for patients who had enjoyed a complete response). Desnos, Minet, and Degrais (who coauthored the first comprehensive radium therapy text in 1909 [23]) understood the need to filter caustic beta particles and soft gamma rays with a radiodense capsule, and that bremsstrahlung radiation (arising from the capsule) should be filtered by less dense material (rubber tubing).

1 Thorium mined in Brazil was used in the production of Weisbach mantles, the glowing filament of gaslights and lanterns. As a result, old Coleman lantern mantles are radioactive.

6 The Flannery’s vanadium was in the steel in Henry Ford’s cars and the Panama Canal locks.

8 The partially refined radium was transferred (in unshielded containers) on public passenger trolleys from their Canonsburg, PA, reduction mill to their Pittsburgh facility for further purification.

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Prostate brachytherapy was performed in Vienna in 1909 (24). Rudolf Paschkis and Wilhelm Tittinger reported the case of a 32-year-old man treated with radium at the Rothschild Hospital. The patient had been admitted for urinary retention, and digital examination suggested locally advanced, unresectable cancer of the prostate. A catheter could not be passed, so cystotomy was performed, exposing a nodular, ulcerating tumor

Figure 1.2 One of the highlights of Marie Curie’s first trip to the United States (1921) was a visit to the Standard Chemical Company’s Canonsburg facility. Curie, seen here with company officials, appears weary, perhaps due to the radium-induced aplastic anemia to which she would eventually succumb.

Source: Photograph courtesy of the National Institute of Standards and Technology.

Figure 1.3 Pasteau and Degrais’s radium-bearing urethral catheter. The catheter was slowly advanced until urine began to drip out, at which point it was withdrawn until the dripping stopped. In this way, the radium was properly positioned in the prostatic urethra.

infiltrating the bladder neck. The tumor was treated with a capsule containing 4.7 mg of radium bromide applied through the bladder fistula. Treatments lasted 20 minutes and were repeated at 2 week intervals. After 10 months of treatment, the tumor had vanished and the patient was voiding through his urethra. The case was the first to have pathologically confirmed malignancy prior to treatment, and complete clinical response following it (25).

Although Hugh Hampton Young introduced his radical prostatectomy procedure for cancer in 1904 (26), he rarely performed it, as it was uncommon for patients to be diagnosed with organ-confined disease (27). Young had attended the International Congress of Medicine in London in 1913, where he heard Pasteau and Degrais present their experience with radium therapy. He acquired 102 mg of radium and developed his own system of delivering treatment through the rectum, urethra, and bladder, as well as by applying external radium plaques (essentially “crossfiring” the tumor). A single application site was treated in a daily “seance” (treatment session) lasting 1 to 2 hours. Treatment sites were alternated and carefully mapped (Figure 1.4), so that no mucosal segment was irradiated twice; in this way, urethritis, cystitis, and proctitis were avoided (28). A typical course of treatment delivered 3,000 to 4,000 mg h of radium therapy. Results were gratifying; Young reported “amazing resorption of extensive carcinomatous involvement of prostate and seminal vesicles” resulting in the “disappearance of pain and obstruction…which is indeed remarkable” (29). He treated 500 patients with radium therapy between 1915 and 1927 (30), and his textbook of urology devoted many more pages to radium therapy than to radical prostatectomy (28).

The Era of Interstitial Radon

James Douglas, a Canadian-American mining engineer and executive, became interested in radium after losing a daughter to breast cancer. He was appalled that she had to travel to Europe to be treated with radium that had been mined in the United States. He joined with surgeon Howard Kelly (America’s leading gynecologist, one of Johns Hopkins Medical School’s “Big Four”) in lobbying Congress to nationalize American radium-bearing lands. When Congress declined to do so, Kelly and Douglas entered into a collaborative effort with the United States Bureau of Mines. They established the National Radium Institute in 1913, with Kelly and Douglas providing the capital and the Bureau supplying the mining and processing expertise. The institute leased 16 carnotite claims in Colorado’s Paradox Valley for 3 years. The ore was transported, by burro and rail, to their processing plant in Denver. Operations ceased in 1917, after 8.5 g of radium was refined. One-half gram was donated to government hospitals, and

Figure 1.4 Record of the dates and locations of rectal applications. A similar record was kept of urethral and bladder neck applications.

the remaining radium was divided between Kelly and Douglas. Douglas donated his 4 g to New York’s Memorial Hospital, with the stipulation that the hospital become dedicated to the treatment of cancer (31). j

Radium’s specific activity (ratio of activity to mass) is low, due to its long half-life (1,600 years). In practical terms, it takes at least a week to deliver a curative dose with radium needles. This would be particularly awkward for the treatment of prostate cancer, as the sources would be left in an open suprapubic or perineal wound for an extended period (32). The solution to this problem lies in radon, radium’s first daughter product (Table 1.1). As most of the therapeutic gamma rays exiting a radium tube were actually emitted by daughter product “radium C” (214Bi), radium (226Ra) itself was unnecessary for “radium therapy.” Treatment with radium C would be challenging, due to its 20 minute half-life, but radon (known as radium emanation until 1923) could serve as a reservoir for radium C. Radon has a very high specific activity, owing to its short (3.8 day) half-life; despite being a gas, 1 Ci of radon has a volume of less than 1 mm³. Because of its high specific activity, an “emanation” needle could be much thinner than a radium needle. Consequently, radium salts were kept in an aqueous solution, and the emitted radon gas was harvested for therapeutic applications.

Table 1.1 The radium-226 decay cascade

<table>
<thead>
<tr>
<th>Old Name</th>
<th>Symbol/Isotope</th>
<th>Half-Life</th>
<th>Emissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radium</td>
<td>226 Ra</td>
<td>1,600 y</td>
<td>α</td>
</tr>
<tr>
<td>Radium Emanation</td>
<td>222 Rn</td>
<td>3.8 d</td>
<td>α</td>
</tr>
<tr>
<td>Radium A</td>
<td>218 Po</td>
<td>3 min</td>
<td>α</td>
</tr>
<tr>
<td>Radium B</td>
<td>214 Pb</td>
<td>27 min</td>
<td>β (γ \text{ 0.3 MeV})</td>
</tr>
<tr>
<td>Radium C</td>
<td>214 Bi</td>
<td>20 min</td>
<td>β (γ \text{ 0.3–2.3 MeV})</td>
</tr>
<tr>
<td>Radium C'</td>
<td>214 Po</td>
<td>0.16 ms</td>
<td>α</td>
</tr>
<tr>
<td>Radium C''</td>
<td>210 Ti</td>
<td>1.3 min</td>
<td>β</td>
</tr>
<tr>
<td>Radium D</td>
<td>210 Pb</td>
<td>22 y</td>
<td>β (γ)</td>
</tr>
<tr>
<td>Radium E</td>
<td>210 Bi</td>
<td>5 d</td>
<td>β</td>
</tr>
<tr>
<td>Radium F</td>
<td>210 Po</td>
<td>138 d</td>
<td>α</td>
</tr>
<tr>
<td>Lead</td>
<td>206 Pb</td>
<td>Stable</td>
<td></td>
</tr>
</tbody>
</table>

j Kelly used his 4 g in a teleradium unit in the Howard Kelly Hospital in Baltimore (31).
Unfortunately, the collected gas was mostly composed of water vapor, hydrogen and oxygen (from electrolysis of the water), helium (from alpha particles), and chlorine (from the hydrochloric acid used to keep the radium ions in solution). Harvard biophysicist William Duane had spent 7 years as a research associate of the Curies, much of that time focusing on the purification of radon. On his return to the United States, he built a radium emanation plant at Boston’s Collis P. Huntington Hospital, which he replicated at Memorial Hospital (33,34). Memorial’s entire 4 g of radium was kept in solution (Figure 1.5), and the purified radon was encapsulated in short lengths of glass capillary tubes, 0.3 mm in diameter (Figure 1.6), which were inserted into hypodermic needles.

Figure 1.5 Memorial’s emanation plant. All of Memorial’s radium was kept in solution in the safe (bottom right). The emitted radon was captured and purified.


Figure 1.6 Capillary glass radon tubes, inserted into “serum” needles for temporary implantation.
The radon-bearing needles were used for temporary implantation (the needles’ steel filtered most beta particles and soft gamma rays).

Beginning in 1915, Memorial’s urologist, Benjamin Barringer, used these needles for outpatient treatment of prostate cancer (35). With the patient in the lithotomy position, Barringer anesthetized the perineum prior to implanting a 15 cm needle, under the guidance of a finger in the rectum, into a lateral prostate lobe. The needle, bearing 50 to 100 mCi of radon in its distal 3 cm, was left in place for 4 to 6 hours before being retracted and inserted into the other lateral lobe. The seminal vesicles were often treated through a transrectal puncture. Treatments were repeated as necessary, at intervals of several months (36). Barringer reported highly favorable tumor responses.

With abundant quantities of short half-life radon, it became appealing to perform permanent implants. At first, “bare” glass tubes were implanted into tumors, but this practice resulted in painful sloughing of necrotic tissue. Memorial’s physicist, Gioacchino Failla, recognized the offender to be unfiltered caustic beta particles. He remedied the problem by encasing the radon in a 0.3 mm thick envelope of gold (Figure 1.7) that filtered out 99% of beta particles while allowing more than 80% of therapeutic gamma rays to pass (37). Barringer implanted up to 20 seeds, each containing 1.5 to 2.0 mCi of radon, into the prostate, typically delivering 4,000 mCi h of treatment (38). Barringer’s techniques were adopted at other institutions (39,40), and a “gold” radon seed industry was established that persisted in the United States for decades (Figure 1.8) (41).k

Introduction of Man-Made Radionuclides

The large majority of prostate cancer patients undergoing radium or radon brachytherapy developed recurrence (38). This is not surprising, as most men diagnosed in that era had advanced disease that could not be cured by any means. The use of prostate brachytherapy waned after Charles Huggins (1901–1997) discovered that prostate cancer responds to androgen deprivation (1941) (42), but interest revived on recognition that castration was only temporarily effective.

Congress passed the Atomic Energy Act after World War II, establishing the Atomic Energy Commission. The Oak Ridge Laboratories were transferred to civilian control and directed to provide radioisotopes for peaceful purposes, including medical applications. One of the first radionuclides made available was radiogold (Au-198); its short half-life (2.7 days) is comparable to that of radon, but is safer to handle because it does not generate megavoltage photons and has no radioactive daughter products. Microparticles of radiogold were suspended in pectin or gelatin, forming a colloid for instillation into

k Memorial’s radon plant was decommissioned in 1970. The last commercial radon seed factory in the United States closed in 1981.
pleural or peritoneal cavities (to suppress malignant effusions and ascites) (43), or injected into lymphomatous masses and solid tumors (44). The first radiogold prostate implant, at the University of Iowa in 1951, was unplanned (45). The prostate of an 80-year-old man with hormone-refractory Stage C disease was surgically exposed for radon seed implantation, but the seeds were not available. Colloidal gold was at hand, and was infiltrated into the prostate. The treatment was without apparent toxicity, the bulky tumor resolved, and follow-up biopsy was negative (46). The urologist, Rubin Flocks, began infiltrating colloidal gold into the prostate and seminal vesicles of men with Stage C disease, through suprapubic and perineal approaches. An enthusiastic report on 20 cases was published in the *Journal of Urology* the following year (47).

There were compelling reasons to consider colloidal gold as a suitable radionuclide for prostate brachytherapy. It is a beta emitter that deposits 90% of its energy within millimeters (it was assumed that the fascia investing the prostate and seminal vesicles would limit the colloid’s migration). There was evidence that gold microparticles would be phagocytosed by macrophages, which, on circulating to draining lymph nodes, would irradiate D1 metastases (48). In reality, treatment did not work as expected. Dense tumor nodules resisted infiltration; the colloid had to be injected under pressure, resulting in spattering that contaminated drapes, scrubs, and shoes (Figure 1.9). Radiation exposure to personnel was so high that surgical teams were rotated to avoid accumulation of prohibitive doses (49). Much of the injected material leaked out of the prostate, pooling in the pararectal gutters, causing severe rectal injury (50). Some of the gold microparticles entered the circulation, and autoradiographs demonstrated hepatic accumulation. Although radiogold did percolate through regional lymphatics, it did not penetrate tumor-congested nodes (50). Flocks devised several maneuvers to overcome these difficulties: Grossly abnormal lymph nodes were resected; hyaluronidase and

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**Figure 1.8** The American Association of Genitourinary Surgeons has honored Barringer by awarding the Barringer Medal for outstanding achievement in urology since 1955. Note the symbols of radioactivity, the trocar, and “seeds.” Used with permission of the American Association of Genitourinary Surgeons.
epinephrine were mixed into the colloid to improve distribution and reduce vascular uptake; and small volumes of highly concentrated suspension were used to reduce leakage from the gland (49). It became apparent that the procedure was only effective for the smallest tumors (50), and 80% of posttreatment biopsies were positive (51). Flocks eventually resorted to perineal prostatectomy, using radiogold as adjuvant therapy (infiltrating the colloid into periprostatic fascia and vascular pedicles) (46). He defended the procedure, claiming better local control (95%) for Stage C disease, compared to published prostatectomy series (70%–80%) (52). Toxicity, however, was significant: delayed healing in 80% and “persistent urethro-cutaneous fistula” in 2% (53). Use of colloidal gold continued at the University of Iowa Hospitals until its manufacture ceased in 1977; thereupon, radiogold grains were substituted.

Urologist C. Eugene Carlton (1930–) initiated a prostate brachytherapy program at Baylor Hospital in 1965. He chose to implant Au-198 grains (rather than colloid) because of ease of handling and more accurate placement. The procedure began with lymph node dissection, followed by incision of the endopelvic fascia and mobilization of the prostate, allowing implantation under direct visualization (54). Initially, a single gold grain was implanted in the tumor nodule; eventually, the procedure entailed implantation of 6 to 10 grains, distributed within the gland (55) (Figure 1.10). Cobalt (later, linac) teletherapy began 2 to 3 weeks later; the radio-opaque grains served as fiducial markers, identifying the prostate. Although the procedure was designed for Stage C disease, early results were so promising (58% negative biopsies) that it was also used to treat patients with organ-confined disease (54). Toxicity consisted mostly of thrombophlebitis and temporary extremity or genital edema (secondary to the node dissection). The incidence of proctitis was 16%, but less than 1% of patients required colostomy (56). Impotence was reported to develop in only 5% of men who were potent prior to treatment. The procedure became so popular that many private urologists at affiliated hospitals participated. But the Baylor program had serious flaws. The radiogold grains were delivered to Baylor once weekly, and their activity at time of implantation varied widely (between 2 and 9 mCi, depending on the day of implantation). Dosimetry was crude; dose was estimated by assuming that the entire implant activity was deposited at the geometrical center of the prostate, and the delivered dose was defined as the isodose that subtended a diameter equivalent to that of the gland (56). It is difficult to encompass the gland with so few sources, even if they were well placed.

Figure 1.9 Device used at the University of Iowa to inject colloidal gold under pressure. It was heavily shielded, to reduce the operator’s exposure.

later, formal dosimetric evaluation demonstrated that these implants typically delivered less than a third of the prescribed dose (57). It is not surprising that, with longer follow-up, treatment outcomes were disappointing (58,59).

Ulrich K. Henschke (1914–1980) came to New York to head Memorial’s brachytherapy service in 1955. He had spent the previous 3 years at Ohio State University, where he collaborated with William Myers in the introduction of Au-198 and Ir-192 into clinical practice (60,61). In New York, however, most of his permanent implants used radon, because the daily seed requirement was unpredictable (he was called to the operating room whenever a surgically exposed tumor was found to be unresectable) (62) and large quantities of radon seeds were produced by Memorial’s radon plant. In 1963, health physicist Donald Lawrence sought funding from Memorial for production of an I-125-impregnated suture (63). Henschke provided encouragement and modest financial support, but advised that the radionuclide be encapsulated in a seed.1 Within months, Lawrence sent him iodine seeds for animal studies, and Henschke began performing human I-125 implants for lung cancer in 1965 (64). Henschke’s protégé, Basil Hilaris (1928−), assumed leadership of the brachytherapy service upon Henschke’s departure in 1967. Brachytherapy had been used at Memorial as salvage therapy for locally recurrent prostate cancer (following failed radiation or hormonal therapy) since 1956 (65), and Hilaris proposed I-125 prostate brachytherapy as primary treatment to Memorial’s chief of urology, Willet Whitmore, Jr. (1917–1995). Whitmore was receptive; he had attempted aggressive surgical resections early in his career, but by 1963 (66), acknowledged the futility of radical prostatectomy to control locally advanced disease. He concluded that intervention for prostate cancer should consider quality of life, and “need not necessarily involve an effort at cancer cure” (67).

Memorial’s I-125 implant procedure began with the patient in a modified lithotomy position (68). A Foley catheter was inserted and an O’Connor drape (with an appendage allowing insertion of a finger into the rectum) was placed. A midline or paramedian incision extended from the umbilicus to the pubis. External, hypogastric, and obturator nodes were dissected. Fat was removed from the anterior surface of the prostate, but the puboprostatic ligaments were left intact. The endopelvic fascia was incised, mobilizing the lateral margins of the gland, but the prostate was not dissected from the rectum (69).

Figure 1.10 A Baylor implant. It is difficult to achieve adequate coverage with only six sources, even with a high energy radionuclide.


1 Henschke’s preferred radionuclide for a low-energy seed was Cs-131, and he actually performed an implant with cesium seeds in 1965. The cost of Cs-131 production was prohibitive, and the project was abandoned (63).
The radiation therapist then inserted empty 15 cm long 16-gauge steel needles into the gland, spaced approximately 1 cm apart. The needles were slowly advanced until sensed by a finger in the rectum (Figure 1.11). Gland dimensions, measured intraoperatively, were used to calculate prostate volume, which determined total implant activity. The number of seeds needed for the implant was derived by dividing the calculated total implant activity by the activity of the available seeds (the ideal seed strength was eventually determined to be 0.5 mCi). Memorial physicist Lowell Anderson developed nomograms to rapidly calculate seed requirements and spacing (70). An applicator was developed to implant the seeds (71) (Figure 1.12). Bleeding could be heavy (median blood loss was 1 L), and almost half the patients required transfusion (72). The Foley catheter was removed 1 to 3 days postoperatively, and the patient was discharged a week later. Postoperative irradiation was delivered to patients found to have lymphatic metastases or bulky tumors (73). Operative mortality was rare (0.5%). The most distressing complications (venous thrombosis, pulmonary embolism, lymphocele, lymphedema) were attributed to lymph node dissection. Impotence or incontinence occurred in fewer than 10% of cases (72).

A computer program was used to calculate dose distribution from postimplant radiographs (see the “Computer Dosimetry” section; Figure 1.13). Without accurate delineation of the target volume, however, the adequacy of an implant was difficult to determine. The dose covered by a volume equivalent to that of the prostate (calculated from intraoperative measurements) was deemed the “matched peripheral dose” (mPD; Figure 1.14) (74). This metric was misleading, as there was no indication that the target and the treated volumes coincided (75) (published radiographs suggest that they often did not [68]), and intraoperative measurement was later found to underestimate prostate volume (76). Disease control was monitored by digital examination, acid and alkaline phosphatase levels, and bone scans. Local control (as determined by palpation) was 80% at 5 years if the mPD exceeded 10,000 rads (100 Gy) (74). Of the 40% of patients found to have nodal metastases, fewer than half survived 5 years, and were found not to have benefited from nodal dissection or irradiation; thereafter, nodal dissection was eliminated from the procedure (73).
Figure 1.12 Seed implantation using an early applicator designed by Felix Mick (when he was employed by Memorial Hospital).


Figure 1.13 Computer-generated dose distribution from an open retropubic implant.

More than a thousand patients were implanted with iodine seeds at Memorial Hospital between 1970 and 1986. It was appreciated that quality implants controlled very early disease, but few patients had presented with early disease, and few implants delivered the prescription dose. Disease-free survival curves never plateaued (77), and reports of disappointing long-term control rates (78,79) led to abandonment of the procedure.

**RETURN OF THE TRANSPERINEAL APPROACH AND INTRODUCTION OF IMAGE GUIDANCE**

The template, a simple device that directed the distribution of implanted sources, appeared by mid-century (80). It improved implant quality by maintaining source spacing and parallelism (Figure 1.15) (81).

Beginning in 1971, University of Miami radiation oncologist Komanduri Charyulu (1924–) performed “closed” implants on patients with disease too advanced for the standard “Memorial” technique (82). With the patient in the lithotomy position, he passed needles through a handheld template positioned against the perineum. The template could be angled to overcome pubic arch interference. Needles were advanced, under fluoroscopic guidance, up to the contrast-filled bladder. He could not, of course, visualize the prostate by fluoroscopy, but his object was to encompass the region of the prostate with a matrix of seeds, 4 cm wide, 4 cm high, and 5 cm deep (Figure 1.16). Charyulu’s plan utilized three strengths of radon seeds (0.15, 1.0, and 0.8 mCi) in a Paterson–Parker distribution, to achieve a relatively homogeneous dose distribution. Charyulu’s transperineal patients enjoyed superior local control, without surgical complications, compared to patients with earlier disease that he had treated with the Memorial “open” retropubic technique.
At the University of Nebraska in 1979, Pradeep Kumar began implanting I-125 seeds transperineally (83). The seed requirement (to achieve a minimal prostate dose of 160 Gy) was estimated preoperatively from a CT scan. The patient was placed in the “semi-lithotomy position” with contrast in the bladder. A guide needle, without a flange, was passed anterior to the anus and rectum, under direction of a finger in the rectum. A template was slid over this needle, and implant needles were inserted through the template in a triangular pattern (defined by the pubic arch and rectum). Needle insertion was directed by fluoroscopy. Approximately 50 I-125 seeds (0.3–0.5 mCi each) were implanted with a Mick applicator (Mick Radio-Nuclear Instruments, Mount Vernon, NY) resulting in an average minimal peripheral dose (as calculated from postoperative orthogonal films) of 154 Gy (84). A 5-year local control was reported to be
85% (85). Kumar began implanting seeds in braided absorbable sutures (obtained from the 3M Corporation, St. Paul, MN) in 1983 (86). This approach maintained seed spacing and allowed placement of extracapsular seeds without the risk of seed migration. The procedure time was reduced to 45 minutes (87), and prostate brachytherapy was offered as an outpatient service in 1987 (85).

Memorial Sloan-Kettering brachytherapists transitioned from “open” retropubic implants to transperineal implants in the 1980s. Patients underwent a planning CT scan with an obturator in the rectum (88), and total the activity of the implant was determined by a nomogram (89). A custom acrylic template, with holes drilled according to the treatment plan, was fabricated for each case (Figure 1.17) (90). Patient positioning was recapitulated in the operating theater with the rectal obturator attached to the perineal template. Needles were inserted under fluoroscopic guidance, and seeds were implanted by a Mick applicator. Transrectal ultrasonography was incorporated into the procedure by 1990 (90).

The Incorporation of Sonography

Physicists involved in the discovery of radium also uncovered the principles underlying sonography. The piezoelectric effect (the property of certain crystals to...

Figure 1.17 Custom template with obturator. The treatment plan specified needle angle, as well as perineal entry position and depth.


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develop an electric potential when mechanically stressed) was described in 1880 by Marie Curie’s future husband (Pierre, 1859–1906) and brother-in-law (Jacques, 1856–1941). The following year, Marie Curie’s thesis adviser (Jonas Gabriel Lippmann, 1845–1921) predicted that a change in electric potential would alter a crystal’s dimensions (91). These phenomena underlie the function of the ultrasound transducer: The generation and detection of sound waves. The first practical application of sonography was a device to detect German U-boats (sonar), patented in 1916 by Pierre Curie’s doctoral student (Paul Langevin, 1872–1946). Sonography was later used by industry as a nondestructive method for detecting metal flaws and fatigue (replacing X-rays and gamma rays for that purpose) (92). Ultrasound was applied by physiatrists in the 1930s to therapeutically heat subsurface tissues (93). Diagnostic applications were developed in the late 1940s; initial attempts measured the transmission of ultrasound waves through tissue (hyperphonography) (94), but detection of reflected waves was investigated by 1950 (95). Sonography for detection of cancer was described in 1957 (96).

An inventive and mechanically inclined Danish surgical resident, Hans Henrik Holm (1931–), became interested in sonography during a radiology rotation. He visited physicist Carl Hellmuth Hertz' (1920–1990) in Lund, Sweden. Hertz had explored medical applications of sonography with cardiologist Inge Edler (“father of echocardiography,” 1911–2001) and neurosurgeon Lars Leksell (“father of radiosurgery,” 1907–1986). Holm was awarded a state grant to obtain an ultrasound unit, and duplicated Lund’s multidisciplinary methodology by collaborating with a cadre of young physicians, as well as with the Welding Institute (a state technology laboratory) to adapt and develop ultrasound apparatus for clinical use. Equipment was designed to be mobile, so that bedside procedures could be performed. The group developed techniques for interventional sonography in the 1970s, including percutaneous biopsy, drainage, pericardiocentesis, amniotic fluid sampling, and percutaneous nephrostomy.

In 1974, the Welding Institute introduced a probe with transducers for transurethral and transrectal imaging (97,98). A “fixing sledge” (stepper unit) that retracted the probe at 5 mm intervals facilitated planimetric volume determinations (98). A metal template mounted on the probe shaft directed prostate and seminal vesicle biopsy (99). By 1980, Holm was using ultrasound guidance to implant I-125 seeds (separated by chromic suture spacers) into liver metastases and pancreas tumors (100,101). The prescription dose was 160 Gy, and most patients also underwent adjuvant teletherapy. By 1982, he was implanting I-125 seeds into cancerous prostates, under the direction of axial imaging from a rectal probe mounted on a sledge-stepper (102). Preplanning and implantation were performed with the patient in the lithotomy position. A modified Memorial Hospital nomogram determined the implant activity needed to deliver 160 Gy, based on Henschke’s system of dimension averaging (103). A 3 cm thick acrylic template was attached to the probe shaft (Figure 1.18). After immobilizing the gland with an empty needle passed through the template, needles preloaded with seeds and spacers were inserted. Needles that were to be advanced most deeply (in the central gland) were placed first. After proper needle position was confirmed by transverse sonographic imaging, the seeds were deposited by stabilizing the stylet while the needle was retracted. The ultrasound probe was then retracted 5 mm, and the next deepest set of needles was placed; in this fashion, concentric circles of needles were inserted and their seeds deposited. Postimplant dosimetry was performed on orthogonal radiographs the following day (Figure 1.19).

A 1989 paper reported that 33 patients had undergone implantation followed by teletherapy (40–47.4 Gy in 20 fractions) with as little as a 2 week interval between

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* In a scandal that rocked France, Langevin became Marie Curie’s lover after Pierre’s death (104). Decades later, a Curie granddaughter (Hélène Joliot) married a Langevin grandson (Michel Langevin).
* Hertz was the son of Physics Nobel laureate Gustav Hertz and great-nephew of Heinrich Hertz, after whom the unit of wave frequency was named. Carl Hertz would later invent the inkjet printer to record ultrasound images.
* Brüel and Kjær (B&K), a Danish acoustical engineering firm, acquired the Welding Institute’s interests in sonography in 1977, and maintained the productive association with Holm.
brachytherapy and teletherapy (106). Of 25 patients undergoing postimplant biopsy and/or transurethral resection, 12 had pathological evidence of persistent disease. Forty-five percent of patients had suffered “severe” late complications (hemorrhagic proctitis, anal ulceration, rectovesical fistula, or “severe persisting radiation cystitis”). The combination of disappointing disease control and high morbidity led to abandonment of the program in 1987 (107).

By then, several centers in Europe (108–111) and the United States had adopted Holm’s technique. Stefan Loening, at the University of Iowa, visited Holm in 1984 and began performing ultrasound and fluoroscopically guided transperineal implants in October (112). His technique differed from Holm’s in that he used a Mick applicator to implant Au-198 grains under axial and sagittal ultrasound imaging (113). One hundred seventy-nine patients were implanted in Iowa within 7 years (114). Patients with bulky tumors were treated with a combination of brachytherapy and teletherapy (115). Response was monitored by digital examination, prostate shrinkage on serial sonography, and biopsy. Roughly half of the 12 month biopsies were positive, but some became negative at 24 or 36 months (115). Toxicity was modest.

After visiting Holm in 1984, Seattle urologist Haakon Ragde (1927–) proposed the institution of an ultrasound-directed brachytherapy program to radiation oncologist John Blasko (1943–). Blasko had reservations; the recently introduced prostate specific antigen (PSA) test had revealed that most patients who had undergone retropubic implantation had developed recurrence. It was unclear whether failure was due to poor seed distribution or the inability of I-125 to eradicate prostate cancer. Other concerns were regarding dose and sequencing. Blasko believed that a 160 Gy implant (without teletherapy) should be adequate to control low-grade tumors. If brachytherapy was to be combined with teletherapy (for more aggressive or bulkier disease), the implant dose should be reduced and teletherapy should be delivered first (to avoid concurrent complications).

Loening returned to his native Germany in 1992 for a sabbatical at Berlin’s Charité Hospital and was appointed their chair of urology. He participated in the hospital’s adoption of high dose rate (HDR) brachytherapy for prostate cancer. Loening was instrumental in merging the urology programs in Berlin’s medical schools after the city was reunited, a service for which he was knighted.
dosing). With these alterations in place, Ragde and Blasko performed their first implant in November of 1985.

They used Brüel and Kjær (B&K) equipment (Figure 1.20). Implantation was preceded by a volume study, acquiring axial images separated by 0.5 cm. Their target volume was several millimeters wider than the prostate. The treatment plan consisted of placing seeds 1.0 cm apart (the holes on their original template were separated by 1.0 cm) throughout the target volume (placing some seeds in extracapsular locations). The total implant activity was determined by nomogram (initially, Holm’s nomogram [117]; later a modification of the Memorial nomogram [118]), and individual seed strength calculated by dividing total implant activity by the number of seeds in the plan. Computer dosimetry checked the adequacy of the preplan. Eighty to hundred seeds, of 0.30 to 0.40 mCi, were implanted. The seeds (separated by chromic suture spacers) were preloaded into 18 gauge needles.

The procedure was performed under spinal anesthesia, with the patient in the lithotomy position. The ultrasound probe was positioned to recapitulate the volume study images. After stabilizing the gland with two empty needles, the base of the prostate was viewed on axial imaging, and the central needles (which would implant seeds at the base) were inserted first. After the central needles’ seeds were discharged, the probe was retracted 1.0 cm, and a second cohort of needles was placed. In this manner, all needles were inserted and discharged. Pubic arch interference was overcome either by freehand needle angling, or by drilling holes through the bone (118)! Postimplant dosimetry was performed on orthogonal films taken 2 weeks after implantation.

Their first patient tolerated the procedure well, but it would be several months before they would perform a second implant; thereafter, 273 men were implanted.
within 4 years (119). Ragde recruited patients to ultrasound and PSA screening clinics by advertising on air and in printed media. The procedure had become so popular that Peter Grimm (1952−) and Timothy Mate (1949−) were soon incorporated into the program. The technique and equipment evolved. Spacing between template holes was reduced to 0.5 mm. Implants were reserved for prostate volumes of less than 60 mL, and pubic arch drilling was abandoned. The order of needle insertion was changed (anterior, not central, needles were implanted first). Seed activity varied, eventually settling at 0.36 mCi. Mate was concerned about the quality of the implants, and had physicist Douglas Schumacher write a computer program to calculate dose distribution from postimplant CT scans (120). CT-based postprocedure dosimetry revealed implant deficiencies, prompting modifications in technique (such as eliminating periurethral seeds) that enhanced dose distribution.

The Seattle group reported favorable treatment outcomes at meetings and in publications (121,122). Visits from interested urologists and radiation oncologists became common; to relieve the congestion of operating room visitors, the group instituted monthly training sessions. The equipment evolved; initially, they had to cut their own chromic spacers and have their needles sharpened after every 10 cases. Their success soon attracted industry attention, and a symbiotic relationship developed. Disposable brachytherapy needles (with echogenic tips), precut spacers, stiffened Vicryl seed strands, and palladium seeds were introduced. Industry helped introduce the procedure to physicians and the public, and lobbied for physician reimbursement codes.

The initial Seattle technique was identical to the procedure performed by Holm in Denmark; why were the outcomes different? The Seattle patients had earlier disease (with more favorable prognosis) because they had been diagnosed as a result of screening. Blasko’s modified dosing and sequencing reduced the intensity of therapy, resulting in less morbidity.

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8 The local medical society objected to medical advertising, but Ragde had served for three wars (in the Norwegian resistance during World War II, as a forward artillery observer in the US Army during the Korean conflict, and as a surgeon in Vietnam) and was not easily intimidated.
The ultrasound-guided transperineal procedure was rapidly accepted in the United States, accounting for a growing percentage of patients treated for prostate cancer. Some radiation oncologists made it the focus of their practice, and introduced innovations. Urologist Nelson Stone and radiation oncologist Richard Stock correlated implant dose (123,124) and adjuvant therapy (125,126) with disease control (127,128) and urinary (129,130), rectal (131,132), and sexual toxicity (133,134). Their publications have helped establish guidelines for dosing and normal tissue constraints. They adopted intraoperative treatment planning and used a computer to monitor dose distribution as seeds were deposited, allowing real-time implant modification. Radiation oncologist Frank Critz was one of the few brachytherapists to have enjoyed success in both the retropubic (135) and transperineal (136) eras. Critz adopted ultrasound-guided implantation after taking the Seattle Prostate Institute course (1992); at its peak, his program had implanted more than 1,000 men annually. Critz was an advocate of stringent PSA criteria for disease control, adopting the urologist’s postprostatectomy standard of achieving and maintaining a PSA level less than or equal to 0.2 ng/mL (137). His excellent, durable outcomes, reported in urology journals (138,139), legitimized prostate brachytherapy as a highly effective alternative to surgery.

Afterloading, Remote Afterloading, and High Dose Rate Brachytherapy

Although delayed loading of radium into previously implanted applicators had been performed as early as the first decade of the 20th century (140,141), afterloading was not seriously pursued as a radiation safety measure until the 1950s (142,143). The implantation of inert applicators facilitates deliberate, unhurried procedures (especially important for trainees), and eliminated exposure to the brachytherapist, operating-theater personnel, recovery room nurses, and radiology technicians (as well as people in the hallways through which the implanted patients passed in transit to their hospital room). It allowed dosimetric determination of optimal source distribution prior to loading. In 1953, Ulrich Henschke, Arthur James, and William Myers (at Ohio State University) described temporary interstitial brachytherapy by afterloading Au-198 seeds into previously implanted nylon tubes (144). Henschke later introduced the use of Ir-192 seeds for this purpose (145,146).

Afterloading nylon tubing with Ir-192 became an integral part of the “Paris System” (147). Court and Chassagne described the Gustave-Roussy low dose rate (LDR) prostate technique in 1977 (148). Following lymph node and prostate dissection (and suprapubic resection of adenomatous hypertrophy), the prostate was grasped between the thumb and index finger of the left hand. Steel needles were advanced through the perineum and into the prostate by the right hand. The needles were replaced by plastic loops, through which lead wires were threaded for orthogonal films. Two or 3 days later (following dosimetric calculations), Ir-192 wires replaced the lead in the loops. Sixty to 70 Gy was delivered over 6 days. A slightly less invasive technique was described by Miller in 1979; beginning in 1972, 16 patients underwent Ir-192 LDR temporary prostate implantation at the Duke University Medical Center (149). The implant was preceded by small-field prostate irradiation delivering 20 Gy in 10 fractions using anterior and posterior megavoltage beams. The implant began with a lower abdominal incision to gain access to the pelvis; neither lymph node dissection nor mobilization of the prostate was performed. Closed-end needles were passed through the perineum under the guidance of a finger in the rectum and a hand in the pelvis, directing the tips 1.5 to 2.0 cm superior to the prostate base. The three sides of a “triangular volume implant” were defined by the ischia and rectum. Following confirmation of needle parallelism by orthogonal radiographs, the needles were fixed by anchoring buttons sewn to the perineum. Six centimeter lengths of Ir-192 wire were afterloaded into the

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*Some of Henschke’s ideas were less practical; he proposed activation of inert iridium seeds after implantation, by exposing the patient to the neutron flux of a nuclear reactor (150)!*
needles, delivering 45 to 50 Gy in 4 to 5 days. There were several unique features of this program: Although it was an “open” technique, neither lymph node dissection nor prostate mobilization was performed. The patient was supine with legs abducted. Extracapsular tumor extension was encompassed by needles inserted through the obturator foramina. Small bowel was protected from irradiation by suturing the bladder dome to the posterior surface of the pubic arch, and by maintaining partial bladder filling by means of a Y-tube.

Nisar Syed (1949−) was a surgeon prior to training in radiation oncology at Manchester’s Christie Hospital and with Henschke at Howard University. He came to the University of Southern California in 1974, where his colleagues included gynecological oncologist Philip Di Saia and physicist David Neblett. Syed and Neblett developed site-specific acrylic templates to fix transperineal needles during treatment (151). Disappointed with the results of retropubic prostate implants (more than half of his biopsied patients were found to have persistent disease), he began using a template-guided transperineal technique to temporarily implant the prostate with Ir-192 (152). After lymph node dissection and exposure of the prostate, needles were advanced to the bladder neck under guidance of a hand in the pelvis. The templates contained concentric circles of holes; initially, each hole held a needle containing a ribbon with seven seeds of 0.4 mg Ra eq strength. After several patients developed serious complications, however, the needles were differentially loaded, with central and pararectal ribbons containing half-strength seeds (153). The implants delivered 30 Gy to the prostate over 40 hours; an additional 40 Gy was delivered by linear accelerator, beginning 10 to 14 days after the implant was removed. He treated 200 patients with this technique between 1977 and 1985; of 74 patients biopsied from 4 to 24 months after treatment, only 16% had evidence of persistent disease (153).

Although manual afterloading reduced exposure to the brachytherapist and operating theater personnel, it did not address exposure to the physician loading or unloading the implant, the staff member preparing or restoring the sources, or the nursing staff caring for the implanted patient. To eliminate all exposure to personnel, remote afterloading was introduced in 1962 at Stockholm’s Radiumhemmet (154). The single channel unit, based on the source transport system of a teleradium unit (155), remotely delivered a Cs-137 source on a flexible cable into a hollow applicator. This unit, and others that soon followed (Cervitron, Curietron), essentially reproduced standard Manchester gynecological distribution and dose rates. The GammaMed, an afterloading unit with a high activity Ir-192 source deployed through a single channel (Figure 1.21), was introduced in 1964 for stereotactic treatment of brain tumors. The same year, Henschke introduced the concept of an ingenious afterloading device that could simulate an infinite variety of source loadings by cycling a single high-activity source (Figure 1.22) (156). He suggested treating patients in minutes (rather than days), declaring, “On the basis of our limited experience with such short treatment times in the last three years, we feel that they may be used with impunity if the total dose is divided into more fractions” (157).

Few brachytherapists (or radiobiologists) shared Henschke’s confidence that fractionated high dose rate (HDR) treatments would be safe. When the Cathetron, a HDR remote afterloading unit (using capsules of Co-60 that delivered a dose more than 100 times more rapidly than standard radium sources) was introduced at London’s Charing Cross Hospital, clinicians approached its use carefully. They performed animal experiments to assess the relative potency of large fractions (158). Toxicity data from hypofractionated teletherapy regimens were considered (159). Physicist William Liversage applied his cell survival equation (a predecessor of the linear–quadratic equation) to calculate appropriate HDR fractionation schemes (160). After the applicator was placed, but prior to delivery of therapy, very low activity sources were inserted into the applicator and the dose delivered to the rectum was measured at 1 cm intervals (161). The first patients to be treated were women who were to undergo hysterectomy for endometrial or cervical cancer, because they would be treated to a lower dose, and the resected irradiated uterus would undergo pathological examination (159). When compared to patients treated with
traditional radium loading, the uteri of HDR patients showed more frequent complete responses, and the patients had fewer complications (162).

Originally, HDR units utilized Co-60 sources. Ir-192, however, has a greater specific activity, and its adoption for HDR allowed fabrication of 1 mm source capsules,
amenable to interstitial application. After visiting Holm, urologist Hagen Bertermann proposed the institution of an ultrasound-directed prostate implantation program at the Christian-Albrechts-University Hospital in Kiel, Germany. His radiotherapy colleagues agreed to collaborate, but preferred to use their HDR equipment rather than I-125 seeds. Beginning in August of 1985, they treated prostate cancer with HDR brachytherapy and external radiation (163). The prostate was targeted with 40 Gy teletherapy in 2 Gy fractions from a linear accelerator (164). Interposed with teletherapy were two fractions of HDR brachytherapy, each delivering 15 Gy to the prostate peripheral zone. The implants were preplanned; needle insertion, treatment, and needle removal were all performed in a single operation in the brachytherapy suite, while the patient was anesthetized. Initially, only two to four needles were inserted. PSA-based recurrence-free survival was 69% at 10 years (a very respectable result, considering that a third of their patients had pretreatment PSA greater than 20) (165). Grade 3 rectal and urinary complications occurred in 4% and 2% of patients, respectively (166).

Timothy Mate already had experience with HDR for gynecological malignancies and had performed ultrasound-guided prostate seed implantation when he instituted a prostate HDR program at Seattle’s Swedish Hospital (Figure 1.23) (167). Flexible cystoscopy was added to the procedure to position needle tips under bladder mucosa (168). Based on his gynecological experience, he prescribed 12 to 16 Gy, delivered in four fractions spread over 40 hours. Teletherapy, up to 50 Gy, was begun 2 weeks after brachytherapy. Acute urinary toxicity was low (compared with his experience with permanent implantation), but 8% of patients developed urinary stricture at 5 years. Recurrences were uncommon (8%) if pretreatment PSA was less than 20. He treated 104 patients between 1989 and 1995; Andy Grove, CEO of Intel, was among them. Prostate brachytherapy gained important publicity when Grove’s enthusiastic report became the cover story of Fortune Magazine (169).

Figure 1.23 Timothy Mate and an afterloaded prostate implant.  
Source: Courtesy of Timothy Mate.
Ultrasound-directed HDR brachytherapy was initiated at William Beaumont Hospital in 1991 (170). The procedure was performed on outpatients, in the brachytherapy suite, under spinal anesthesia. A computer generated the treatment plan (including needle position and source dwell times) intraoperatively. Dose distribution was recalculated during implantation to account for actual needle position. Initially, patients with intermediate- or high-risk disease were treated with three HDR applications, interdigitated with teletherapy (46 Gy). Between 1991 and 1995, the HDR fraction size rose from 5.5 to 6.5 Gy; thereafter, the number of HDR applications was reduced to 2, and fraction size gradually rose from 8.25 Gy to 11.5 Gy. It became apparent that disease control strongly correlated with HDR fraction size (171,172), resulting in a recalculation of the $\alpha/\beta$ ratio for prostate cancer (from 10 to less than 2) (173). The Beaumont Group and the California Endocurietherapy Cancer Center have published promising results using HDR monotherapy for favorable- and intermediate-risk disease (174,175).

**COMPUTER DOSIMETRY**

In the earliest days, brachytherapists relied on atlases, tables, and experience to determine source strength, distribution, and treatment time (176,177). By mid-century, two systems of source distribution were widely used: Paterson–Parker and Quimby. The Paterson–Parker system, developed at Manchester’s Holt Radium Institute, specified an inhomogeneous distribution of activity to achieve a relatively homogeneous dose distribution (178,179). The system developed by physicist Edith Quimby, at New York’s Memorial Hospital, stipulated a homogeneous distribution of sources to generate an inhomogeneous distribution of dose (180,181). In both cases, the systems were used for preplanning, to determine the strength and arrangement of sources required to deliver a specified minimum dose to the target.

Actual implants were often seriously flawed. It was difficult (even for expert brachytherapists) to reproduce the “ideal” source geometry specified by the systems, and the achieved “minimum” target dose typically fell well below the mark (182). The situation became more complicated with the introduction of I-125, as attenuation had to be incorporated into calculations (the inverse square law sufficed when calculating dose distribution from radium, radon, Au-198, or Ir-192) (183). Shortcomings were not recognized because postimplant dosimetric analysis was not typically performed. Manual calculation of dose at more than a few points was tedious, especially when many sources were to be identified and their dose distributions plotted and summated. A system was needed to identify a large number of sources, then calculate, summate, and spatially describe the distribution of dose over the entire volume of interest (not just the periphery). The system should be rapid enough so that decisions regarding source loading and removal could be made in a timely fashion.

In 1958, Richard Nelson and Mary Lou Meurk, physicists at New York’s Memorial Hospital, introduced a system for calculation of brachytherapy dose distribution using tabulating machines (184). Stereoshift radiographs of an implant localized the sources, which were assigned locations at the nearest point on a three-dimensional Cartesian coordinate lattice with 5 mm interspaces. The location of each source was transferred to a punch card, and the tabulating machine summed the contribution of all sources to plot a dose distribution. Only the inverse square law was considered in the calculations (which was adequate, as only high-energy sources were then in use). Output was represented as a matrix of points with 1 cm spacing; isodose lines were drawn by hand. By 1961, the system was programmed on FORTRAN for a time-shared IBM 7090 computer system, which was “sufficiently fast that its results have been used to modify interstitial implants before and during treatment.” It could be used for radium needles and Ir-192 ribbons in afterloading tubes; localization of individual seeds was “possible but not always practicable” (the program accommodated an “equally spaced array of seeds”) (185).
Radium needles and gold seeds were the sources of choice at Houston’s MD Anderson Hospital. “Applied mathematician” Marilyn Stovall (1931–) wrote computer code for brachytherapy dosimetry in 1960. Her program was first used to calculate postimplant dosimetry for radium needle implants. Source localization was by transverse tomography. The square of the distance to points on a 1 mm grid was computed and doses (assigned based on a table) were summated; isodose curves were manually drawn (186). It took an hour for each plane to be calculated, at which point a new set of cards would be fed into the computer. The situation was remedied when the Physics Department acquired its own, faster computer (IBM 1620), which could perform the same task in minutes. In a retrospective analysis, Stovall demonstrated that most recurrences occurred in regions of underdosage, whereas tissue necrosis occurred in regions of overdosage (187). Timely dose calculation (with rapid depiction, by plotter or cathode-ray tube) allowed compensation for less than ideal geometry, by adjusting needle removal time for interstitial implants, and selection of source strength for afterloaded implants (188).

Physicist Stephen Balter (1940–) revised the Memorial Hospital computer dosimetry system shortly after joining the physics staff in 1963. He wrote a program in FORTRAN II for Memorial’s CDC-160A computer. It could spatially display dose distribution for a large seed implant in any plane, calculate average and minimum doses, and generate dose–volume histograms (182,189). The program had to be broken into modules that ran sequentially, because the computer’s memory could not store the entire program. First, seed location was determined by a stereo-shift method, a tedious task (lung implants frequently contained more than 50 radon seeds; Figure 1.24). After the source locations were entered, dose was calculated to points on a matrix. It took 100 milliseconds to calculate dose to a single point from a single source. With dose points typically 1 cm apart, there were 1,000 dose points in a 10 × 10 × 10 cm volume. It therefore took 100 seconds to calculate the dose to all dose points from a single source, or more than an hour to calculate the sum of contributions from all sources to all (widely separated) dose points. A printout of dose to points on any plane could be generated, but isodose lines were still generated by hand (Figure 1.25). The situation improved when Memorial’s Physics Department installed a stereographic reference frame (to maintain fixed geometry for stereo-shift or orthogonal radiographs), a digitizer and program for localizing seeds, and an IBM 1800 16k computer. Although the “Memorial Implant Dosimetry Application System” (MIDAS) was freely shared, few institutions had the computing power to utilize it. Beginning in 1967, Memorial offered a computational service for outside institutions, communicating by teletype (190). By 1972, there were more than 60 participating hospitals (191).

University of Washington physics graduate student Philip Heintz (1943–) collaborated with physicist Douglas Jones to generate a radiation treatment planning system from elements of the Memorial and Anderson public domain programs. Heintz rewrote the program several times while in private practice, launching it commercially as “Prowess-2000” (running on the IBM AT) in 1988. In addition to teletherapy planning, Prowess had modules for brachytherapy (with radium, Cs-137, iridium and iodine seeds, and tantalum wire). The program transitioned to being Windows-based (“Prowess 3000”) in the early 1990s.

Physicist David Neblett introduced “ROCS,” a treatment planning program (with a brachytherapy module) written in BASIC for the PC, in 1988. William Saylor launched “Therpac,” a complete treatment planning system written in BASIC, in 1974. His son, Michael Saylor, rewrote the program in Microsoft C for the IBM PC (“Therpac-PC”), which was introduced in 1986. A transperineal ultrasound-guided implant (TUI) module was added in 1993; within a few years, it was capable

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* Computation of dose distribution typically required 10 hours on the hospital’s billing computer, to which Stovall had access only at night. She napped on a cot in the business office when not feeding punch cards into the computer.
Figure 1.24 The coordinates of dozens of implanted seeds were manually tabulated.

*Source: Courtesy of Stephen Balter.*

Figure 1.25 (A and B) Computer-calculated dose-point distributions with hand-drawn isodose lines. Although plotters were available, they were expensive and used too much computer memory.

*Source: Courtesy of Stephen Balter.*

(continued)
of importing ultrasound images for preplanning and CT images for postimplant dosimetry. “Therpac” was sold to Multimedia Medical Systems when William Saylor retired in 1996, but Michael stayed on and rewrote the TUI module for Windows (renamed MMS B3DTUI) in 1997. Two years later, the TUI module was acquired by Varian, and renamed VariSeed.

CONCLUSION

Brachytherapy has evolved over the century of its existence. Initially the province of surgeons, it is now performed by radiation oncologists in collaboration with medical physicists, dosimetrists, and allied specialists. Computers and stepping source applications have provided precision to the deposition of dose, increasing efficacy, and limiting toxicity. Radium and other high-energy sources have been replaced by safer radionuclides; together with remote afterloaders, they have greatly reduced or eliminated radiation exposure to the brachytherapist and other health personnel. Although the modern ultrasound-directed transperineal procedure is unsurpassed in its capacity to eradicate prostate cancer (192), SEER data indicate that its use has declined in the 21st century. Multiple causes have been implicated, including competition from other modalities (image-guided dose-escalated teletherapy, less invasive surgery), poor remuneration, and the promotion of conservative management. As we have seen, prostate brachytherapy has rebounded several times; it may yet enjoy another renaissance.

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