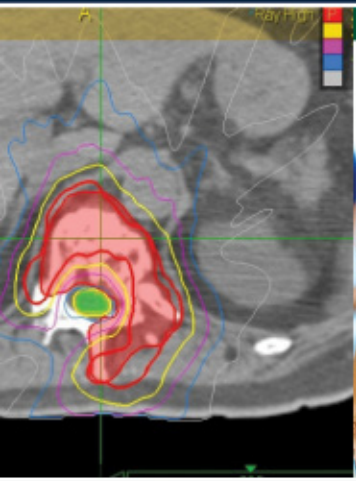
Radiation Oncology in Palliative Cancer Care

Edited by Stephen Lutz, Edward Chow and Peter Hoskin



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Edited by

Stephen Lutz, MD MS

Radiation Oncologist
Department of Radiation Oncology
Blanchard Valley Regional Cancer Center
Findlay, OH, USA

Edward Chow, MBBS MSc PhD FRCPC

Professor, Department of Radiation Oncology
University of Toronto;
Senior Scientist, Sunnybrook Research Institute
Chair, Rapid Response Radiotherapy Program and Bone Metastases Site Group
Sunnybrook Health Sciences Centre
Toronto, ON, Canada

Peter Hoskin, MD FRCP FRCR

Professor in Clinical Oncology, University College London;
Clinical Oncologist
Mount Vernon Hospital
Northwood, London, UK

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Contents

Contributor list

Shaun Baggarley, MSc
Chief Radiation Physicist
Department of Radiation Oncology
National University Cancer Institute
National University Health System
Republic of Singapore

Elizabeth A. Barnes, MD FRCP(C)
Assistant Professor
Department of Radiation Oncology
University of Toronto
Odette Cancer Centre
Toronto, ON, Canada

Susannah Batko-Yovino, MD
Assistant Professor
Department of Radiation Oncology, and Program of Palliative Medicine
John Hopkins University
Baltimore, MD, USA

Lawrence B. Berk, MD PhD
Chair, Radiation Oncology
Director, Radiation Oncology at Tampa General Hospital
University of South Florida
Tampa, FL, USA

Sean Bydder, BHB MBChB MBA FRANZCR
Consultant Radiation Oncologist
Department of Radiation Oncology
Sir Charles Gairdner Hospital;
Professor
School of Surgery
The University of Western Australia
Perth, Australia

Eric L. Chang, MD
Professor and Chair
Department of Radiation Oncology
Keck School of Medicine at
University of Southern California
Los Angeles, CA, USA

Samuel T. Chao, MD
Assistant Professor
Cleveland Clinic Lerner College of Medicine
Cleveland, OH, USA

Haris Charalambous, BM MRCP FRCR
Consultant in Clinical Oncology
Department of Radiation Oncology
Bank of Cyprus Oncology Centre
Nicosia, Cyprus

Caroline Chung, MD MSc FRCPC CIP
Radiation Oncologist and Clinician-Scientist
University Health Network-Princess Margaret
Assistant Professor
Department of Radiation Oncology
University of Toronto
Toronto, ON, Canada

June Corry, FRANZCR FRACP MD
Consultant Radiation Oncologist
Chair Head and Neck Service
Peter MacCallum Cancer Centre
Melbourne, Victoria, Australia

Henry Ddungu, MD
UCI Hutchinson Center Cancer Alliance
Upper Mulago Hill Road
P O Box 3935 Kampala
Kampala, Uganda

Gillian M. Duchesne, MB MD FRCR FRANZCR Gr Ct Health Econ
Professor of Radiation Oncology
Peter MacCallum Cancer Centre
University of Melbourne and Monash University
Melbourne, Victoria, Australia

Alysa Fairchild, BSc MD FRCPC
Associate Professor
Department of Radiation Oncology
Cross Cancer Institute
University of Alberta
Edmonton, AB, Canada

Frank D. Ferris, MD FAAHPM
Executive Director
Palliative Medicine Research and Education
OhioHealth
Columbus, OH, USA

Robert Glynne-Jones, MB BS FRCP FRCR
Macmillan Lead Clinician in Gastrointestinal Cancer
Mount Vernon Cancer Centre
Northwood, London, UK

Charles F. von Gunten, MD PhD FAAHPM
Vice President
Medical Affairs
Hospice and Palliative Medicine
OhioHealth
Columbus, OH, USA

Mark Harrison, MB.BC PhD
Consultant Oncologist
Mount Vernon Cancer Centre
Northwood, London, UK

James A. Hayman, MD MBA
Professor
Department of Radiation Oncology
University of Michigan
Ann Arbor, MI, USA

David D. Howell, MD FACR FAAHPM
Assistant Professor
Department of Radiation Oncology
University of Toledo College of Medicine
Toledo, OH, USA

Candice A. Johnstone, MD MPH
Assistant Professor
Medical Director of the Froedtert and Medical College of Wisconsin Cancer Network
Department of Radiation Oncology
Medical College of Wisconsin
Milwaukee, WI, USA

Joshua Jones, MD MA
Fellow
Palliative Care Service
Massachusetts General Hospital
Boston, MA, USA

Andre Konski, MD MBA MA FACR
Professor and Chair
Department of Radiation Oncology
Wayne State University School of Medicine
Barbara Ann Karmanos Cancer Center
Detroit, MI, USA

Ian H. Kunkler, MA MB BCHIR FRCPE CRCR
Honorary Professor of Clinical Oncology
University of Edinburgh
Edinburgh Cancer Centre
Edinburgh, Scotland, UK

Yvette van der Linden, MD PhD
Radiation oncologist
Department of Clinical Oncology
University Medical Centre
Leiden, The Netherlands

Simon S. Lo, MD
Director
Radiosurgery Services and Neurologic Radiation Oncology;
Associate Professor
University Hospitals Seidman Cancer Center
Case Comprehensive Cancer Center
Case Western Reserve University
Cleveland, OH, USA

Jiade J. Lu, MD MBA
Head and Associate Professor
Department of Radiation Oncology
National University Cancer Institute
National University Health System
Republic of Singapore

Ernesto Maranzano, MD
Director
Radiation Oncology Centre
Santa Maria Hospital
Terni, Italy

Nina A. Mayr, MD
Professor
Radiation Oncology
Arthur G. James Cancer Hospital
The Ohio State University
Columbus, OH, USA

Erin McMenamin, MSN CRNP AOCN ACHPN
Oncology Nurse Practitioner
Department of Radiation Oncology
Hospital of the University of Pennsylvania
Philadelphia, PA, USA

Marcia Meldrum, PhD
Associate Researcher
Center for Health Services and Society
Semel Institute for Neuroscience and Human Behavior
University of California, Los Angeles
Los Angeles, CA, USA

Benjamin Movsas, MD
Chairman
Department of Radiation Oncology
Henry Ford Health System
Detroit, MI, USA

Arno J. Mundt, MD
Professor and Chair
Center for Advanced Radiotherapy Technologies (CART)
Department of Radiation Medicine and Applied Sciences
University of California, San Diego
San Diego, CA, USA

Firuza Patel, MD
Professor
Department of Radiotherapy and Oncology
Post Graduate Institute of Medical Education and Research
Chandigarh, India

Rinaa S. Punglia, MD MPH
Assistant Professor
Department of Radiation Oncology
Dana-Farber Cancer Institute and the Brigham and Women's Hospital
Harvard Medical School
Boston, MA, USA

Dirk Rades, MD PhD
Professor
Head of Department
Department of Radiotherapy
University Hospital Lübeck
Lübeck, Germany

George Rodrigues, MD MSc FRCPC
Clinician Scientist and Radiation Oncologist
Departments of Radiation Oncology and Epidemiology/Biostatistics
London Health Sciences Centre and University of Western Ontario
London, ON, Canada

Daniel E. Roos, BSc(Hons) DipEd MBBS MD FRANZCR
Senior Radiation Oncologist
Department of Radiation Oncology
Royal Adelaide Hospital;
Professor
University of Adelaide School of Medicine
Adelaide, South Australia, Australia

Arjun Sahgal, MD
Associate Professor
Radiation Oncology
Princess Margaret Hospital and the Sunnybrook Health Sciences Center
University of Toronto,
Toronto, ON, Canada

Thomas Smith, MD FACP
Harry J. Duffey Family Professor of Palliative Medicine;
Professor of Oncology
Department of Oncology and Program of Palliative Medicine
John Hopkins University
Baltimore, MD, USA

Bin S. Teh, MD
Professor, Vice Chair and Senior Member
The Methodist Hospital, Cancer Center and Research Institute
Weill Cornell Medical College
Houston, TX, USA

Albert Tiong, MB BS M.App.Epi. FRANZCR
Consultant Radiation Oncologist
Peter MacCallum Cancer Centre
Melbourne, Victoria, Australia

Fabio Trippa, MD
Vice Chair
Radiation Oncology Centre
Santa Maria Hospital
Terni, Italy

May Tsao, MD FRCPC
Assistant Professor
Department of Radiation Oncology, University of Toronto;
Sunnybrook Odette Cancer Centre
Toronto, ON, Canada

Vassilios Vassiliou, MD PhD
Consultant in Radiation Oncology
Department of Radiation Oncology
Bank of Cyprus Oncology Centre
Nicosia, Cyprus

Tamara Vern-Gross, DO FAAP
Department of Radiation Oncology
Wake Forest Baptist Health
Comprehensive Cancer Center
Winston-Salem, NC, USA

Anushree M. Vichare, MBBS MPH
Measures Development Manager
American Society for Radiation Oncology
Fairfax, VA, USA

Deborah Watkins Bruner, RN PhD FAAN
Robert W. Woodruff Professor of Nursing
Nell Hodgson Woodruff School of Nursing
Professor of Radiation Oncology
Associate Director for Outcomes Research
Winship Cancer Institute
Emory University
Atlanta, GA, USA

Michelle Winslow, BA PhD
Research Fellow
Academic Unit of Supportive Care
University of Sheffield
Sheffield, South Yorkshire, UK

Aaron H. Wolfson, MD
Professor and Vice Chair
Department of Radiation Oncology
University of Miami Miller School of Medicine
Miami, FL, USA

Foreword

"The final causes, then, of compassion are to prevent and to relieve misery."
Joseph Butler [1692–1752]

This textbook, *Radiation Oncology in Palliative Cancer Care,* represents the full evolution of radiation therapy, and of oncology in general. This evolution in radiation oncology is in response to the changing priorities of cancer care.

More than a century ago, radiotherapy was the only treatment available for cancer, palliating the suffering from large masses and open wounds from the disease. The priority was to relieve the suffering from the disease, as the cure of cancer was rare. As medical science evolved, especially in anesthesia and surgery, the principles of cancer resection were developed. Cure of cancer became the priority, often at the accepted price of disfigurement. In the latter half of the 20th century, the development of chemotherapeutic agents dominated. Cure of cancer remained the priority, but now at the price of toxicity. Acute toxicity often limited the patient's ability to receive chemotherapy on schedule or complete the prescribed number of courses of chemotherapy. Late chemotherapeutic toxicity risked significant end-organ damage. Despite the "War on Cancer," the sacrifice of cure at any human cost was beginning to be questioned.

Quality of life, during and after cancer therapy, became a priority commensurate with cancer cure. Although often not fully recognized as such, palliative care principles were applied to improve the cancer patient's quality of life. In its broadest definition, palliative care relieves the symptoms of cancer and its treatment at any stage of disease, and maintains or restores the dignity of function. For every patient, spanning all age groups from young children to elderly adults, the palliative principles of comfort in positioning, reassurance, and beneficence, and the avoidance of treatment-related symptoms are paramount.

These principles of palliative care invoked the priority of delivering effective cancer treatment with the fewest side effects. Most notably, acute chemotherapy toxicity was significantly reduced with the development of more effective anti-emetic agents. The development of sophisticated linear accelerators, including electron beam and intensity modulated radiation, allowed improved outcomes due to the targeted delivery of higher radiation doses with fewer side effects. Previously unthinkable, advancements in radiation therapy technology also allowed multi-modality therapy, the combination of chemotherapy and radiation with function-sparing surgery for virtually every anatomic region. This exciting period both expanded the potential for cancer

cure and improved the cancer patient's quality of life because side effects of cancer therapy were more effectively controlled.

While most of the focus in cancer treatment over the latter half of the 20th century was, very understandably, on these multi-modality developments, a smaller, but concerted, effort was formally launched for patients with incurable disease. Hospice care was exported from the groundbreaking work of Dame Cicely Saunders in Great Britain. Meanwhile, the contributing role and significant impact of radiotherapy in palliative care was often relegated to "service work" within academic centers. Palliative radiotherapy was neither the topic of scientific research, nor acknowledged as a valuable sub-specialty within the field.

Palliative radiotherapy finally began to be recognized as an integral aspect of radiation oncology through the convergence of multiple factors. First and foremost were advocacy efforts to improve cancer patients' quality of life. The expanding role of medical ethics within health-care systems also reinforced the responsibility to relieve suffering. Meanwhile, clinical research documented improved rates of survival among incurable cancer patients with effective symptom control.

The second factor was the continued development of systemic agents used for palliation. Expanding beyond supportive care that reduced the side effects of cancer treatment, drug development then prioritized the treatment of metastatic disease. This was exemplified most prominently by the clinical trials of bisphosphonates for bone metastases. Radiation oncology recognized the scope of palliative care within its practices as the number of patients who received bisphosphonates, instead of palliative radiation, increased. It was then determined that palliative care, even at tertiary care cancer centers, accounted for more than one-third of the requests for radiotherapeutic consultation, and represented an untapped research potential.

The third factor involved both the economics of health care, and the limited health-care resources faced in all nations. In the United States, last-year-of-life expenditures constituted 26% of the entire Medicare budget [1]. Many governments have dealt with spiraling health-care costs by developing guidelines for care that incorporate comparative effectiveness research. The potential impact and main priority for comparative effectiveness research is based on prevalence, disease burden, variability in outcomes, and costs of care. The most efficient means of delivering effective cancer treatment is an economic priority for all nations. Additionally, access to care with limited health-care resources is especially prevalent in middle and low-income nations. These economic and resource issues in health care prompted international clinical trials that evaluated the most efficient radiotherapeutic fractionation for the treatment of bone metastases. Clinical trials that address economics as well as outcomes, like that of the international palliative bone metastases trial, will not only influence palliative treatment approaches, but every aspect of cancer therapy in the future.

This textbook is an acknowledgment that palliative radiotherapy is now a sub-specialty of radiation oncology. This formally makes palliative radiotherapy a priority within patient care, academic research, quality assurance, and medical education. However, the principles of palliation were the first precepts of cancer treatment, and were first applied by radiation oncologists. The priorities of the past have now evolved to the priorities of the future.

Nora Janjan, MD MPSA MBA
National Center for Policy Analysis, Dallas, TX, USA

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PART 1

General principles of radiation oncology

CHAPTER 1

A brief history of palliative radiation oncology

Joshua Jones
Palliative Care Service, Massachusetts General Hospital, Boston, MA, USA

Introduction

A simple chronology of scientific and technologic developments belies the complexity of the history of palliative radiotherapy. The diversity of palliative radiation treatments utilized today reflects a dichotomy evident in the earliest days of therapeutic radiation, namely that radiation can be utilized to extend survival or to address anticipated or current symptoms. However, the line between "curative" and "palliative" treatments is not always obvious. Furthermore, even "palliative" radiotherapy has an impact on local tumor control, potentially improving survival and complicating the balance between effective and durable palliation with possible short- or long-term side effects of therapy. This introduction provides a basic overview of developments in the history of radiation therapy that continue to inform the complex thinking on how best to palliate symptoms of advanced cancer with radiation therapy.

The early years

Within a few short months of Wilhelm Roentgen's publication of his monumental discovery in January 1896, several early pioneers around the world began treating patients with the newly discovered X-rays [1]. Early reports detailed treatments of various conditions of the hair, skin (lupus and "rodent ulcers") and "epitheliomata," primarily cancers of the skin, breast, and head and neck [2] (Figure 1.1). Other early reports, as championed by Emile Grubbe in a 1902 review, touted both the cure of malignancy as well as "remarkable results" in "incurable cases" including relief of pain, cessation of hemorrhage or discharge and prolongation of life without suffering [3]. Optimism was high that X-rays would soon be able to transform many of the "incurable cases" to curable.

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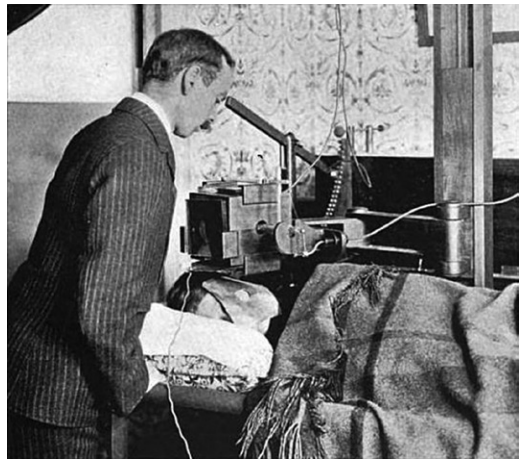

Figure 1.1 An early radiotherapy machine delivering low energy X-rays with shielding of the face by a thin layer of lead. Reproduced from Williams [4].

In his 1902 textbook, Francis Williams, one of the early pioneers from Boston, described his optimism that radiation therapy would eliminate growths on the skin: "The best way of avoiding the larger forms of external growths is by prevention; that is, by submitting all early new growths, whether they seem of a dangerous nature or not, to the X-rays. No harm can follow their use in proper hands and much good will result from this course [4]." He went on to state that, while "internal new growths" could not yet be treated with X-ray therapy, he was optimistic that such treatments would be possible in the future. In this setting, he put forward an early treatment algorithm for cancer that divided tumors into those treatable with X-ray therapy, those treatable with surgery and X-ray therapy post-operatively, and those amenable to palliation with X-ray therapy. He further described that the specific treatment varied from patient to patient but could be standardized between patients based on exposure time and skin erythema.

Other early radiology textbooks took a more measured approach to X-ray therapy. Leopold Freund's 1904 textbook described in great detail the physics of X-rays and again summarized the early clinical outcomes. In his description of X-ray therapy, he highlighted the risks of side effects, including ulceration, with prolonged exposures to X-rays without sufficient breaks. He noted that the mechanism of action of radiation was still not understood, with theories at the time focusing on the electrical effects of radiation, the production of ozone, or perhaps direct effects of the X-rays themselves. Freund highlighted early attempts at measuring the dose of radiation delivered, emphasizing the necessity of future standardization of dosing and research into the physiologic effects of X-ray therapy [2]. As foreshadowed in the textbooks of Williams and Freund, early research in radiation therapy focused on clinical descriptions of

the effectiveness of X-rays contrasted with side effects of X-rays, the determination of what disease could be effectively treated with radiotherapy, the standardization of equipment and measurement of dose, and attempts to understand the physiologic effects of X-ray therapy.

The history of radium therapy in many ways parallels developments in the history of Roentgen ray therapy. After the discovery of radium by the Curies in 1898, the effects of radium on the skin were described by Walkoff and Giesel in early 1901. This description was offered prior to the famed "Becquerel burn" in which Henri Becquerel noticed a skin burn after leaving a piece of radium in a pocket of his waistcoat [5]. Radium quickly found many formulations of use: as a poultice on the skin, as an "emanation" that could be inhaled, consumed in water, or absorbed via a bath, or in needles that could be implanted deep into the body [6]. The reports of the effectiveness of radium therapy appeared more slowly than those of X-ray therapy, however, owing to its cost and rarity.

The future of radium mining in the United States for use in medical treatments was pushed forward by the incorporation of the National Radium Institute in 1913, a joint venture by a Johns Hopkins physician, Howard Kelly, a philanthropist and mine executive, James Douglas, and the US Bureau of Mines. However, the notion of protecting lands for radium mining was vigorously debated in Congress in 1914 and 1915. The debate focused on therapeutic uses of radium, risks to radium workers, and the nuances of the economics, given that radium had previously been exported for processing and re-imported at much higher cost. The debate over the use of radium treatments escaped from the medical literature into the public consciousness [7]. Kelly championed the curative effects of radium therapy, but there was significant opposition to the use of radium in medicine due to a reported lack of efficacy. In 1915, Senator John Works from California made a speech before the United States Senate urging no further use of radium in the treatment of cancer:

> The claim that radium is a cure for cancer has been effectually exploded by actual experience and declared by numerous competent authorities on the subject to be ineffectual for that purpose . . . If radium is not a specific [cure] for cancer, the passage of the radium bill would be an act of inhuman cruelty. It would be taken as an indorsement [*sic*] by the Government of that remedy and would bring additional suffering, disappointment, and sorrow to sufferers from the disease, their relatives and friends, and bring no compensating results [8].

In spite of these concerns and the growth and subsequent decline of popular radium treatments including radium spas and radium baths in the 1920s and 1930s, radium therapy continued to grow and develop an evidence base for both the curative treatment of cancer and the relief of symptoms from advanced cancer.

With publicity surrounding the development of cancer and later death among radium dial workers (the first death coming in 1921), radium therapy was again under attack in the early 1920s. In 1922, in an address to the Medical Society of New York, Kelly sought to "emphasize the *palliative results*." As reported in the Medical Record, Kelly believed "If he could do nothing more than improve and relieve his patients, as he had been able to do, never curing one, it would still be worth his while to continue this work [9]." Palliative radiotherapy, with the explicit goal of palliation and not cure, had been recognized as a legitimate area of study.

Fractionation

A challenge that has persisted through the history of the treatment of cancer is how best to improve the therapeutic ratio: specifically, how best to target cancer cells while minimizing damage to surrounding normal tissue. In the earliest years of radiation therapy, minimizing toxicity to the skin was a significant challenge as the kilovoltage X-rays delivered maximum dose to the skin, creating brisk erythema, desquamation, and even ulceration (Figure 1.2). In the 1920s, Regaud conducted a series of experiments demonstrating that dividing a total dose of radiation into smaller fractions could obtain the same target effect (sterilization of a ram) while minimizing skin damage [10]. These observations were later applied by Coutard in the radiotherapy clinic to the treatment of cancer, both superficial and deep tumors. By the mid-1930s, the

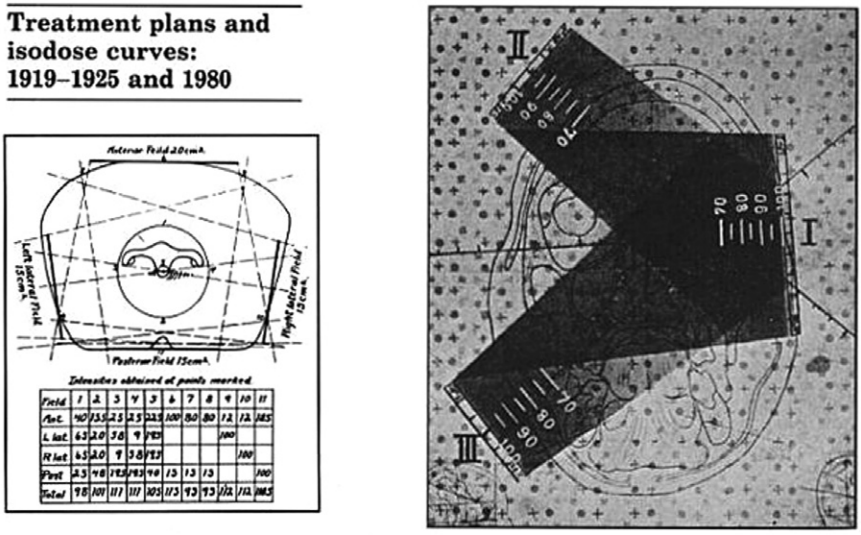

Figure 1.2 Isodose curves from 1919 and 1925. Reproduced from Mould [32], with permission from Taylor and Francis Publishing.