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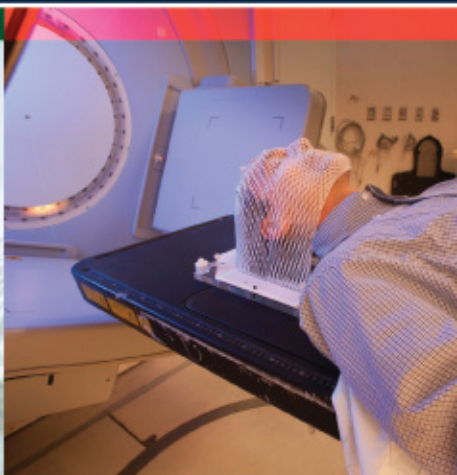
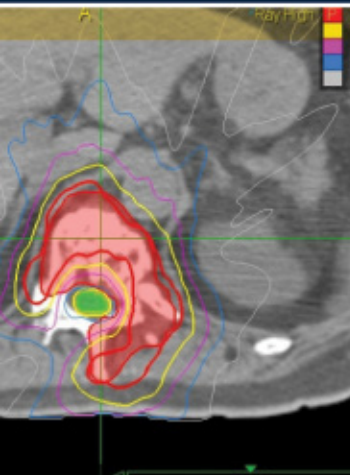
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Radiation Oncology in Palliative Cancer Care



Edited by Stephen Lutz,
Edward Chow and Peter Hoskin

PI



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**Radiation
Oncology in
Palliative
Cancer Care**

Radiation Oncology in Palliative Cancer Care

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Contents

Contributor list, xv

Foreword, xix

Part 1: General principles of radiation oncology, 1

1 A brief history of palliative radiation oncology, 3

Joshua Jones

Introduction, 3

The early years, 3

Fractionation, 6

Advances in radiotherapy technique: the 1950s and 1960s, 7

Fractionation revisited: explicit palliation, 10

Stereotactic radiotherapy, 11

Prognostication and tailoring palliative radiotherapy to anticipated survival, 11

Conclusion, 12

References, 13

2 The radiobiology of palliative radiation oncology, 15

Candice A. Johnstone

Introduction, 15

Radiation effect on cells, 15

Cell cycle characteristics, 18

Interaction of cell cycle and radiotherapy fractionation, 18

Radiotherapy fractionation characteristics, 19

Conclusion, 20

References, 20

3 The physics of radiation oncology, 22

Shaun Baggarley, Jiade J. Lu

Introduction, 22

The development of radiation therapy technology, 24

Process of radiation therapy, 27

Special considerations in developing countries, 28

Conclusion, 29

References, 29

4 Curative intent versus palliative intent radiation oncology, 31

Vassilios Vassiliou, Haris Charalambous

Introduction, 31

The determination of cure plus palliation intent versus pure palliative intent, 33

Clinical diagnoses, 35

Special considerations in developing countries, 38

Conclusion, 39

References, 39

5 Side effects of palliative radiotherapy, 43

Alysa Fairchild

Introduction, 43

Issues with interpreting palliative radiotherapy toxicity data, 44

Acute side effects, 45

Late side effects, 50

Additive toxicity, 53

Clinical advice, 53

New technologies, 55

Challenges in developing countries, 55

Conclusion, 56

References, 56

Part 2: General principles of palliation and symptom control, 61

6 A history of hospice and palliative medicine, 63

Michelle Winslow, Marcia Meldrum

Introduction, 63

Before the modern movement, 63

St. Christopher's and the modern hospice, 64

Palliative care in the United States, 66

Global development of hospice and palliative care, 68

Continuing challenges, 69

References, 69

7 Radiation therapy and hospice care, 72

Charles F. von Gunten, Frank D. Ferris, and Arno J. Mundt

Introduction, 72

Hospice care around the world, 72

Hospice care in the United States, 73

Palliative radiation and hospice, 77

Conclusion, 79

References, 79

- 8** The current status of palliative care and radiotherapy, 81
Thomas Smith, Susannah Batko-Yovino
- What is palliative care?, 81
 Who can benefit from palliative care?, 81
 What are the goals of palliative care and what features of a palliative care program help to accomplish these goals?, 83
 What is the evidence regarding the benefits and risks of palliative care?
 When should palliative care be introduced to a patient?, 84
 Are there standards for palliative care? If so, what are the defining measures?, 88
 How does palliative care fit in with radiation oncology?, 90
 References, 92
- 9** Palliative care in low and middle income countries: A focus on sub-Saharan Africa, 95
Henry Ddungu, Elizabeth A. Barnes
- Introduction, 95
 The need for palliative care, 95
 Radiotherapy, 96
 Specific clinical indications for palliative radiotherapy in Africa, 97
 Challenges of palliative care delivery, 98
 Addressing challenges to adequate palliative care, 98
 Palliative care research, 100
 Delivery of palliative care, 101
 Conclusion, 102
 References, 102
- 10** Pain management, 105
Erin McMenamin
- Introduction, 105
 Pain assessment, 105
 Analgesia ladder, 106
 Primary pharmacologic interventions, 107
 Adjuvant medications, 108
 End-of-life considerations, 109
 Conclusion, 109
 References, 110
- Part 3: Locally advanced or locally recurrent diseases, 113**
- 11** Primary tumors of the central nervous system, 115
Caroline Chung, Eric L. Chang
- Introduction, 115
 Radiotherapy, 116
 Side-effect risks, 120

Radiotherapy limitations, 120
Adjuvant treatment modalities, 121
Promise of newer technologies, 121
Special considerations in developing countries, 122
Conclusion, 122
References, 122

12 The role of palliative care in head and neck cancer, 126

Albert Tiong, June Corry

Introduction, 126
Current management of head and neck squamous cell carcinomas, 126
Patient selection for palliative treatment, 127
Use of palliative radiotherapy in head and neck squamous cell carcinomas, 130
Recurrent disease, 134
The promise of emerging technologies, 135
Chemotherapy in palliative head and neck squamous cell carcinomas, 135
Non-squamous cell carcinomas histologies, 136
Specific issues in palliation of head and neck squamous cell carcinomas, 137
Special considerations in developing countries, 138
Conclusion, 138
References, 139

13 The role of palliative radiotherapy in breast cancer, 145

Ian H. Kunkler

Introduction, 145
Rates of palliative loco-regional radiotherapy, 148
Biologic considerations, 148
Definitions, clinical features, and multi-disciplinary approach, 148
Clinical scenarios, 150
Symptom control, 153
Palliative loco-regional radiotherapy for oligometastatic disease, 154
Radiotherapy dosing schedules, 154
Radiotherapy technique and the promise of newer technology, 156
Special considerations in developing countries, 158
Follow up, 158
Conclusion, 159
References, 159

14 Palliative radiotherapy in advanced lung cancer, 163

George Rodrigues, Benjamin Movsas

Introduction, 163
Radiotherapy treatment, 165

- The impact of emerging technologies, 169
 - Important circumstances, 171
 - Special considerations in developing countries, 173
 - Conclusion, 173
 - References, 174
- 15** Palliative radiotherapy for gastrointestinal and colorectal cancer, 177
Robert Glynn-Jones, Mark Harrison
- Introduction, 177
 - Treatment of dysphagia, 178
 - Gastric cancer, 180
 - Palliation of biliary obstruction, 181
 - Nodes at origin of the superior mesenteric artery, 181
 - High dose rate brachytherapy, 182
 - Locally advanced/recurrent rectal cancer, 182
 - Re-irradiation, 184
 - Anal cancer, 184
 - The promise of highly conformal therapy, 184
 - Special considerations in developing countries, 184
 - Conclusion, 185
 - References, 185
- 16** Genitourinary malignancies, 188
Gillian M. Duchesne
- Introduction, 188
 - Incidence and etiology, 188
 - Clinical behavior, 190
 - Bladder cancer, 190
 - Prostate cancer, 190
 - Renal cancer, 190
 - Palliative radiotherapy and other approaches for management of primary disease, 192
 - Specific management of metastatic disease in urologic malignancies, 194
 - The promise of highly conformal therapy, 196
 - Special considerations in developing countries, 197
 - Conclusion, 197
 - References, 197
- 17** Palliative radiotherapy in locally advanced and locally recurrent gynecologic cancer, 199
Firuz Patel
- Introduction, 199
 - Patterns of loco-regional failures for gynecologic cancers, 200

x Contents

Management, 201
Treatment of recurrent carcinoma of the cervix, 206
Recurrence after definitive radiation, 206
Recurrence after definitive surgery, 207
The promise of newer technologies, 207
Special considerations in developing countries, 207
Conclusion, 208
References, 209

18 Hematologic malignancies and associated conditions, 210

David D. Howell

Introduction, 210
Diagnoses, 210
Specific clinical circumstances, 213
Locally advanced and recurrent disease, 216
Future directions, 216
Special considerations in developing countries, 217
Conclusion, 217
References, 217

19 Pediatric palliative radiation oncology, 220

Tamara Vern-Gross

Introduction, 220
Delivery of radiation treatment, 221
Differences between pediatric and adult populations, 222
Background, 222
Clinical indications for palliative radiotherapy, 224
Caring for the pediatric patient, 232
Barriers to the use of palliative radiotherapy, 233
Special considerations in developing countries, 233
Conclusion, 234
References, 234

Part 4: Metastatic disease, 239

20 Bone metastases, 241

Yvette van der Linden, Dirk Rades

Introduction, 241
Clinical implications and treatment modalities, 241
Clinical symptoms, 242
Technical considerations, 250

- Prognosis and choice for treatment, 250
 - Proactive approach, 251
 - Special considerations in developing countries, 251
 - Conclusion, 251
 - References, 253
- 21** Spinal cord compression, 257
Ernesto Maranzano, Fabio Trippa
- Introduction, 257
 - Treatment, 259
 - Promise of newer technologies, 264
 - Re-irradiation, 265
 - Special considerations in developing countries, 265
 - Conclusion, 266
 - References, 267
- 22** Brain metastases, 270
May Tsao
- Introduction, 270
 - Radiotherapy treatment, 271
 - Radiotherapy limitations, 277
 - Promise of newer technologies and areas of ongoing research, 277
 - International patterns of care and special considerations in developing countries, 278
 - Conclusion, 278
 - References, 279
- 23** Liver metastases, 283
Sean Bydder
- Introduction, 283
 - Radiotherapy treatment, 284
 - Whole-liver radiation therapy, 286
 - Conformal radiation therapy, 288
 - Brachytherapy, 289
 - Selective internal radiation therapy, 289
 - Surgery for liver metastases, 290
 - Radiofrequency ablation, 290
 - Promising new radiotherapy techniques, 290
 - Practice variation among different countries, 293
 - Conclusion, 294
 - Acknowledgments, 294
 - References, 294

- 24** Palliative radiotherapy for malignant neuropathic pain, adrenal, choroidal, and skin metastases, 299
Daniel E. Roos, Aaron H. Wolfson

Malignant neuropathic pain, 299
Adrenal metastases, 302
Choroidal metastases, 308
Skin metastases (A.H. Wolfson), 312
Conclusion, 314
References, 314

Part 5: Integration of radiation oncology and palliative care, 317

- 25** Design challenges in palliative radiation oncology clinical trials, 319
Deborah Watkins Bruner, Lawrence B. Berk

Introduction, 319
Challenges with the validation of palliative metrics, 319
Evolution of palliative care clinical trials: the Radiation Therapy Oncology Group experience, 320
International research efforts, 325
Conclusion, 326
References, 326

- 26** Radiation oncology cost-effectiveness, 329
Andre Konski

Introduction, 329
Cost-effectiveness, 330
Newer technologies, 332
Conclusion, 333
References, 333

- 27** Quality measures and palliative radiotherapy, 335
James A. Hayman, Rinaa S. Punglia, and Anushree M. Vichare

Introduction, 335
Quality measures: characteristics, 336
Developing quality measures, 338
Desirable attributes of quality measures, 340
Uses of quality measures, 340
Current uses of quality measures in radiation oncology, 341
International quality measures in radiation oncology, 342
Conclusion, 343
References, 344

- 28** Use of technologically advanced radiation oncology techniques for palliative patients, 347
Simon S. Lo, Bin S. Teh, Samuel T. Chao, Arjun Sahgal, Nina A. Mayr, and Eric L. Chang
- Introduction, 347
 - Overview of technologically advanced radiotherapy techniques, 347
 - Clinical applications reported in the literature, 349
 - Brain metastasis, 349
 - Stereotactic radiosurgery, 349
 - Scalp-sparing whole brain radiation therapy, 351
 - Hippocampus-sparing whole brain radiation therapy, 351
 - Stereotactic radiation therapy, 351
 - Spinal metastasis, 352
 - Spinal cord compression, 352
 - Bone metastasis, 355
 - Adrenal metastasis, 355
 - Toxicities associated with palliative radiotherapy using advanced technologies, 356
 - Conclusion, 357
 - References, 357
- Index, 361

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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.

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1. Hoover DR, Crystal S, Kumar R, *et al.* Medical expenditures during the last year of life: findings from the 1992-1996 Medicare current beneficiary survey. *Health Serv Res* 2002; **37**: 1625-1642.

PART 1

General principles of radiation oncology

A brief history of palliative radiation oncology

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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.

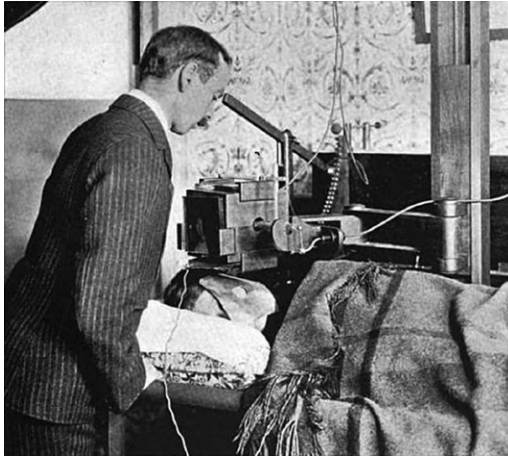


Figure 1.1 An early radiotherapy machine delivering low energy X-rays with shielding of the face by a thin layer of lead. Reproduced from Williams [4].

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

Treatment plans and isodose curves: 1919–1925 and 1980

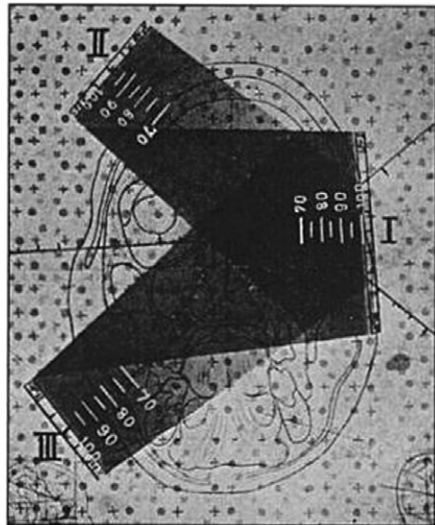
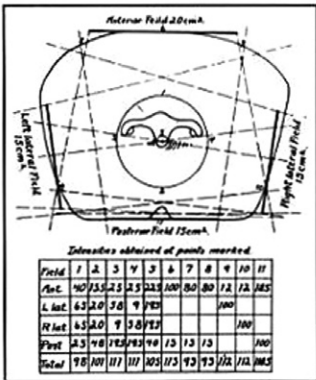


Figure 1.2 Isodose curves from 1919 and 1925. Reproduced from Mould [32], with permission from Taylor and Francis Publishing.