General principles of radiation oncology
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.
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

![Image of isodose curves from 1919 and 1925 and 1980.](image)

*Figure 1.2* Isodose curves from 1919 and 1925. Reproduced from Mould [32], with permission from Taylor and Francis Publishing.
concept of fractionating radiotherapy to give three to five doses per week over
a period of 5 to 6 weeks had become a standard method for the protection of

After Coutard’s publication, studies demonstrating the efficacy of fractionated radiotherapy also suggested palliation from radiotherapy could be achieved with lower delivered doses. One specific article, published by Lenz and Freid in *Annals of Surgery* in 1931, highlighted challenges with fractionation and set forth suggestions for palliation of symptomatic metastases from breast cancer. The study explored the natural history of breast cancer metastases to the brain, spine, and bones and the effect of radiotherapy in the treatment of these metastases [12]. The study retrospectively analyzed two time periods in the course of illness: the pre-terminal period (up to one year prior to death or two-thirds of the time of illness if the patient lived less than one year) and the terminal period (the final one-third of time of illness if the patient lived less than one year). Lenz correlated the impact of grade of cancer as visualized under the microscope with the length of time of survival, finding that higher grade tumors led to shorter survival and a shorter terminal period. He also described the increased recognition of bone metastases with the use of diagnostic X-rays and indicated that diagnosis of metastases to the brain or spinal cord was still difficult to evaluate.

It was unclear to practitioners at that time if neurologic symptoms were from bone metastases causing mass effect on the central nervous system or if the metastases resided within the nervous system itself. The author subsequently evaluated the effect of radiotherapy on relief of symptoms in both the terminal and pre-terminal patients. Ten of 19 patients in the terminal stage had improvement of symptoms (primarily pain) with radiotherapy and 12 of 12 in the pre-terminal stage had improvement of symptoms, lasting a few weeks to 3 years. The dose of radiotherapy, however, did not correlate with symptomatic relief, and relief was often obtained within 24 to 48 hours after starting treatment. As Lenz described it, a treatment “series” consisted of the total amount of radiation delivered over about two months. Dose was measured according to skin erythema: less than one erythema dose was a “small” dose, one to two erythema doses was a “moderate” dose, and more than two erythema doses was a “large” dose. Treatment was certainly fractionated over the course of two months, but Lenz’s work provided an early suggestion that moderate doses of radiotherapy could produce effective palliation of metastatic disease.

**Advances in radiotherapy technique: the 1950s and 1960s**

While the field of radiotherapy experienced many advances in technology such as increases in the understanding of dose distribution and in the biologic effects of radiation through the 1930s and 1940s, the next significant clinical breakthrough in radiotherapy came in the 1950s. The first supervoltage machines capable of producing X-rays greater than 1 MeV were put into
clinical use in the early 1950s with cobalt teletherapy machines, betatrons, van de Graaf generators, and linear accelerators (Figure 1.3). These “supervoltage” machines allowed deeper penetration of the radiation beam, sparing the skin and allowing easier treatment of internal tumors. The excitement at the prospect of a cure was exemplified by the May 1958 cover of *Life* magazine which featured a new supervoltage X-ray machine. The article inside highlighted surgery and radiation as the only two possible cures for cancer and boasted “These standard approaches have now been perfected almost to their limit [13].” While expectations for curative radiotherapy had certainly increased, palliative outcomes were also being explored with the new technology.

A review of palliative radiotherapy for lung and breast cancer in the *British Medical Journal* in 1957 reported that radiotherapy was most commonly employed in palliation of symptoms of advanced cancer, but that “the question has been asked whether patients later suffer more while dying if they have had such treatment than if they had not.” [14] According to the review, the indications for palliative treatment of lung cancer symptoms, including vena cava obstruction, hemoptysis, dyspnea and cough, required a standard dose of 3000 rad as sufficient for palliation (though the fractionation was not described). The effect on life span is “difficult to assess” but prolongation is not the goal of therapy. In answering their posed question about the effectiveness of therapy, the authors responded that when radiotherapy caused more symptoms than it helped, “this suggests a failure of judgment by the radiotherapist.” The review also indicated that complication rates from palliation of breast cancer bone metastases, including fibrosis of muscle and necrosis of
bone, were diminishing. Balancing benefit with harm from palliative radiotherapy was now the task of the radiotherapist.

Early reports of the palliative treatment of brain metastases, confirmed with lumbar puncture, encephalogram, and angiography, revealed symptomatic relief in many patients, even though the earliest report (1954) still used orthovoltage X-rays (Figure 1.4) [15]. In 1961, Chu provided an update on the first study to evaluate whole brain radiotherapy. Patients presented with headache, dizziness, nausea, vomiting, incontinence, visual changes, and changes in mentation; many suffered from hemiparesis or hemiplegia at the start of radiotherapy. The report detailed treatment of 218 patients with opposed orthovoltage X-ray fields to a median dose of 3000 rad over 3 weeks, starting with low daily doses and increasing to higher daily doses to avoid acute side effects of treatment. Therapy was well-tolerated with improvement in symptoms in 77.8% (123 of 158) of evaluable patients who received the prescribed dose [16].

One final episode from the early years of supervoltage therapy deserves mention. In preparation for experiments to understand the role of oxygenation on high dose irradiation, the radiotherapy group at Columbia treated 63 patients with advanced metastatic cancer with once weekly radiation treatments using a 22.5 MeV betatron with doses ranging from 800 rad to 1250 rad to total doses of 1250 to 4000 rad over 4 weeks [17]. Degree of response was complicated by short survival and many symptoms, but the authors described subjective responses in 37 of 63 patients and objective responses in 29 of 63 patients. Treatment was generally well-tolerated with mild nausea being the most common. Serious complications included edema in head and neck cancer in patients who had previously had radical surgery; radiation fibrosis of the lung in two patients previously irradiated to the lung; myelitis in one patient; and esophageal perforation in one patient who received 4000 rad in

---

**Table 3**

OVER-ALL RESULTS OF RADIATION THERAPY FOR BRAIN METASTASES

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>85</td>
<td>64</td>
<td>35</td>
<td>9</td>
</tr>
<tr>
<td>Lung</td>
<td>74</td>
<td>54</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Bone &amp; soft tis. sarcoma</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>28</td>
<td>19</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>218</strong></td>
<td><strong>158</strong></td>
<td><strong>123</strong></td>
<td><strong>35</strong></td>
</tr>
</tbody>
</table>

**Figure 1.4** Early results of palliative whole brain radiotherapy. Reproduced from [16], with permission from Wiley.
4 weeks and who exhibited no evidence of cancer at autopsy. The authors concluded that massive dose irradiation in one week interval doses is both feasible and justified in order to provide rapid relief with minimal inconvenience to the patient. The risk of severe radiation injury, the authors reported, limits total dose (they suggested 3000 rad as the maximum permissible dose) and selection of patients who might be candidates for high dose palliative radiotherapy.

In 1964, Robert Parker, of the University of Washington, published a clinical management guideline in *JAMA* describing the role of palliative radiotherapy in the management of patients with advanced cancer. He described the importance of determining whether radiation is palliative up front:

> When the initial objective of radiation therapy is palliation, new ground rules must be applied. Possible serious complications or even slowly self-limiting side effects are no longer acceptable. Overall treatment time must be short. Cost must be minimized. Convenience of treatment must be considered [18].

While the “ground rules” for palliative radiotherapy could be accepted by most, the line between purely palliative and definitively curative has continued to be an evolving target.

**Fractionation revisited: explicit palliation**

In 1969, the newly formed Radiation Therapy Oncology Group organized its first clinical trials in the use of radiotherapy in the treatment of cancer. The combined publication of two early studies (RTOG 6901 and RTOG 7361) evaluated patients with brain metastases treated with either short (one or two fractions) or long (1 to 4 weeks) courses of radiotherapy [19]. The studies demonstrated similar outcomes among the short- and long-course treatment arms with comparable rates of improvement in neurologic function, treatment morbidities, and overall survival rates, but with decreased durability of palliation in the short course arms. The authors recommended more fractionated courses with higher radiation doses for palliation of patients with brain metastases due to the durability of palliation. Subsequent trials on brain metastases sought to improve the therapeutic ratio through the addition of radiation sensitizers.

Several studies by the RTOG and other groups similarly evaluated different dose-fractionation schemes for painful bone metastases. Early studies including RTOG 7402 evaluated various dose/fractionation schemes ranging from five to fifteen fractions for solitary or multiple bony metastases. Overall improvement in pain and complete pain relief were not statistically different between regimens [20]. Further studies have evaluated single- versus multi-fraction regimens with the overall response rates being similar with a single fraction of 8Gy (800 rad) in comparison with more protracted
dose-fractionation schedules with slightly higher retreatment rates in the single treatment groups, but without significant increase in late toxicity [21,22].

**Stereotactic radiotherapy**

Beginning in the 1950s, Leksell and his neurosurgical team developed a “stereotactic” approach to the treatment of deep brain lesions including arteriovenous malformations, craniopharyngiomas and acoustic neuromas [23]. Simultaneously, advances in anatomic and functional imaging from the 1970s to the present day have contributed to earlier detection of metastatic disease with computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). When the advanced imaging was combined with computer treatment planning and the stereotactic approach of Leksell, high doses of radiation could be delivered in a conformal manner to small areas in the brain with either multiple cobalt sources (i.e. Gammaknife) or a linear accelerator. Early experience with stereotactic treatment of brain metastases that had previously been irradiated revealed minimal toxicity with significant improvement in neurologic symptoms and ability to have patients discontinue corticosteroids [24].

These stereotactic techniques were applied in the RTOG 9005 dose escalation study of stereotactic radiosurgery for the treatment of previously irradiated brain metastases or primary brain tumors [25]. Subsequently, the RTOG 9508 study combining whole brain radiotherapy with or without stereotactic radiotherapy boost demonstrated that combined stereotactic radiosurgery and whole brain radiotherapy led to an improvement in performance status at 6 months and a survival advantage for patients with a single brain metastasis [26]. Such studies that demonstrate improvement in length of life have complicated the previously purely palliative nature of radiation for brain metastases. The safety, efficacy, and possible enhancement of survival with stereotactic radiotherapy to the brain have led to questions seen earlier in history: when is highly conformal radiotherapy appropriate in the treatment of brain metastases? When is surgical resection appropriate in the treatment of brain metastases? When is whole brain radiotherapy appropriate in the treatment of brain metastases? And when is palliative care, without radiotherapy or surgical intervention, appropriate in the management of brain metastases?

**Prognostication and tailoring palliative radiotherapy to anticipated survival**

In an attempt to further characterize the results of the early trials of stereotactic radiosurgery for brain metastases, the RTOG conducted a recursive partitioning analysis (RPA) to evaluate factors predictive of survival in patients with brain metastases [27]. The RPA analyzed patients from three RTOG
studies of different dose fractionation schemes with and without sensitizers. The RPA revealed three categories of patients from 1200 eligible patients, divided into classes based on Karnofsky performance status, age, and presence or absence of extracranial metastases (see Chapter 22 for full study details). This RPA was validated [28], and new models for survival prediction (namely the diagnosis-specific Graded Prognostic Assessment or GPA) have been developed to further refine estimates of prognosis. The RPA, GPA, and other models of prognosis (for other sites of metastatic disease) may assist in developing treatment algorithms, but challenges remain in tailoring treatment to survival estimate.

As an example of the challenge with tailoring treatment to survival, Gripp and colleagues analyzed a group of 216 patients with advanced cancer admitted to the hospital for palliative radiotherapy. All patients had survival estimates completed by physicians and data were collected to help inform prognosis. Thirty-three patients died within 30 days of hospital admission and were analyzed in a pre-planned subgroup analysis to determine adequacy of treatment [29]. Physician survival estimates (characterized as less than one month, 1 to 6 months, or more than 6 months) were more likely to be greater than 6 months (21%) than less than 1 month (16%), although all patients died within 30 days of admission. Half of the patients were on treatment more than 60% of their remaining lives. In this setting, Gripp retrospectively asks the question: can we tailor treatment to anticipated survival? In an accompanying editorial, Hartsell responds by applauding the conclusion (that patients are often over-treated toward the end of life), but reaffirms previously described principles of palliative radiotherapy, namely that the treatment should be delivered in the shortest time possible with the fewest side effects possible. Incorporating the goals of providing evidence-based, convenient, palliative radiotherapy with the fewest possible side effects while being aware of long-term side effects in possible long-term survivors is a challenge; determining the role of stereotactic radiotherapy in this mix is one of the pressing tasks within the palliative radiotherapy community.

Conclusion

The prevalence of abstracts presented at the American Society for Radiation Oncology (ASTRO) Annual Meetings from 1993 to 2000 that focused on symptom control and palliative care remained steady and low, ranging from 0.9% to 2.2% of all abstracts presented during those years. In 2004, ASTRO made “palliative care” a discrete topic for submission of abstracts [30]. While the total number of abstracts on symptom control and palliative care has increased from 2001 to 2010, the majority of the increase is related to the use of stereotactic radiotherapy in the treatment of metastatic disease. Even with this increase, the proportion of abstracts related to symptom control and palliative care remains low at about 5% of all abstracts [31]. Upwards of 40% of all radiotherapy treatments have palliative intent; with the increasing
complexity of palliative radiotherapy treatment options and treatments, it is incumbent upon the fields of palliative care and radiotherapy to continue to work to implement best practices in the treatment of patients with palliative radiotherapy.

References


