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Critical Review

Preserving the legacy of reirradiation: A narrative review of historical publications

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Abstract

Purpose: The purpose of this study is to illustrate the historical development of reirradiation during several decades of the 20th century, in particular between 1920 and 1960.

Methods and materials: We chose the format of a narrative review because the historical articles are heterogeneous. No systematic extraction of baseline data, treatment details, or follow-up care was possible in many cases.

Results: Both hematological malignancies and solid tumors were treated with a second course of radiation therapy, and indications included local relapse, regional nodal recurrence, and second primary tumors developing in a previously treated region. The literature consists of retrospective single-institution analyses describing treatment approaches that included external beam radiation therapy, brachytherapy, or combinations thereof. Data on toxicities and survival were often provided. Breast cancer and gynecological, head and neck, brain, and skin tumors are among the entities included in this review.

Conclusions: The leading pioneers in the field are fully aware of many of the challenges we continue to debate today. These include the process of late tissue changes and development of personalized treatment approaches and better ways to select patients who are likely to benefit from a second course of radiation therapy.

Conflicts of interest: None.

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Introduction

Recent reviews and book chapters on reirradiation have mostly focused on clinical and experimental data from the past 25 to 30 years.[1-9] This policy carries the risk of disremembering long-term developments and the lessons learned from previous experience. Considering that in the beginning of the 20th century, ionizing radiation was often used to treat benign skin conditions, asthma, and musculoskeletal disorders, which tend to recur, and that treatment was far from standardized, repeat courses of treatment were probably prescribed in the earliest years. Of course, the dosimetric and technical limitations of early equipment and regimens were also applied for the treatment of malignant conditions, a setting necessitating much higher radiation doses than benign diseases[10]; therefore, in-field and marginal relapse were common problems.[11,12] In the absence of effective alternatives, in particular a lack of systemically administered anticancer drugs and safe surgical salvage, reirradiation was sometimes prescribed for common hematological and solid primary tumors. For this overview, the methodology, outcomes, and side effects of reirradiation were extracted from historical publications between 1920 and 1960 to compare them with modern clinical practice. We chose the format of a narrative review because the historical articles were heterogeneous and differed in several aspects from today's rigorously reviewed scientific literature. No systematic extraction of baseline data, treatment details, or follow-up care was possible in many cases.

Methods

Historical articles were identified from PubMed; the electronic archives of the *British Journal of Radiology*, *British Medical Journal*, *Strahlentherapie*, *Journal of the American Medical Association*, and *California Medicine* and its predecessors; and by crosschecking the references from already included articles and textbooks. The key words "reirradiation," "re-irradiation," "repeat radiotherapy," "second radiotherapy," "radiation retreatment," and "recurrent AND radiation therapy" were entered. English and German language articles were included. Any information a study provided about dose is described in the Results section. Unfortunately, several of the included studies provided no information about median dose or exposure. Some included a detailed description only of exemplary cases that the authors found particularly instructive.

Results

Although the focus of this review was on solid tumors, Desjardins reported a case of reirradiation of mediastinal Hodgkin disease in the 1920s.[13] In the treatment of chronic myelogenous leukemia, irradiation increased the duration of "efficient life" (a rigorous definition of this endpoint was not provided) by 30% (0.8 years), based on 82 cases reported in 1931.[14] Most often, the spleen was treated, and sometimes the spleen plus long bones. Survival outcomes were comparable regardless of treated volumes. Repeated cycles of low doses of radiation produced remarkable symptomatic improvement. The effect lasted from a few months to a year.

In 1926, Lee and Tannenbaum reported their experience with more than 300 patients managed for recurrent inoperable breast cancer at Memorial Hospital, New York.[15] The term inoperable referred to vastly different scenarios, including but not limited to technically inoperable lymph node metastases and widespread distant metastases. Roentgen rays, radium, or a combination of both was used. Individualized or personalized oncology is not a new idea, as reflected in the sentence "each patient is a special problem to be handled in a special way."[15] Lee and Tannenbaum also cited references from different countries, all of which demonstrated that reirradiation could be prescribed (eg, after failure of what was called prophylactic irradiation [postoperative adjuvant radiation therapy]). There was controversy in the literature regarding the usefulness of this approach, because some authors regarded recurrent tumors as not sufficiently radiosensitive to warrant further treatment.[16] Lee and Tannenbaum did not provide separate results for reirradiated patients. According to their general conclusion, radiation therapy for recurrent breast cancer prolonged the life of their patients and may have controlled the disease for a considerable number of years. Irradiation was used during later decades as well,[17] but, unfortunately, detailed outcome data were not reported.

For cervical cancer, radiation therapy had become an accepted treatment well before the Second World War. In describing their approach at the Los Angeles Tumor Institute, California, from 1930, Soiland and Costolow mentioned that "the duration of the first application is twenty-eight hours and the second application twenty-four hours, the radium being applied against the cervix and intrauterine at the same time."[18] "Following this, no further radium should be given for from six to twelve months. The patient is observed at monthly intervals, and late recurrences, appearing a year or so after the original treatment, are often treated with small doses of radium applied locally, although great care is exercised. Often, suspicious thickened areas remain for several months and finally disappear." This policy emphasizes a crucial point in decision making, namely to confirm the presence of active tumor before prescribing further treatment.

According to Healy, of 1574 patients with cervical cancer treated between 1918 and 1931 at Memorial Hospital, New York, only 11% required further radiation therapy.[19] Only 2 of these patients survived more than 3

years, leading Healy to conclude that "a lesion once fully and adequately irradiated cannot again be treated to advantage with radium or roentgen therapy. Irradiation leads to tissue changes, largely in the nature of endarteritis and fibrosis, and further irradiation of such structures results in the formation of indolent chronic ulcers and sloughs, which are painful and extremely difficult to heal." He also acknowledged tremendous interinstitutional variations in treatment approaches.

In 1956, Murphy and Schmitz from Roswell Park Memorial Institute, Buffalo, NY, reported on treatment of failures following an apparently adequate course of radiation for cervical cancer.[20] They stated that "re-irradiation is particularly justified when a curative surgical approach would entail not only an appreciable mortality risk but also a high degree of permanent disability. Tissue changes resulting from previous radiotherapy do not contraindicate re-irradiation if cure or palliation is possible." Between 1936 and 1941, 461 patients were reirradiated, typically with combined radium and roentgen rays (briefly reviewed in the article's introduction section, referred to as unpublished data). After reirradiation, 20% of the patients lived 5 or more years without clinical evidence of cancer. In the Murphy and Schmitz paper, 46 patients with squamous cell cancer treated between 1946 and 1950 were reviewed. Patients were aged 31 to 70 years. Adequate treatment for 1 course consisted of total doses of 7000 R and 4500 R to anatomical points A and B located 2 and 5 cm lateral to the center of a tandem intrauterine applicator (from roentgen rays and radium). In 4 illustrative cases, treatment details including technique and doses were provided. Nine patients (20%) were alive at the time of reporting, with a maximum follow-up of 8 years. The absolute 5-year survival with no evidence of cancer was 16%. In fatal cases, the average survival time was 13 months. The interval between the 2 courses was 4 to 89 months (median, 14). The disease status was categorized as persistent if the interval was short. Early and advanced stages were reirradiated, the latter being described as extrapelvic disease, uremia, or lower limb edema. No apparent correlation between the time interval and treatment outcome was evident. Many patients experienced subjective and objective palliation. Long-term survival was recorded only in patients in good physical condition with limited pelvic recurrence. Late complications in the 9 surviving patients included chronic cystitis, chronic proctitis and rectal bleeding, and rectovaginal fistula (2 patients). All patients were described as socially active and relatively comfortable. Seven patients received a second retreatment.

Garland and Sisson reported the results of irradiation for lip, tongue, and ear cancer between 1932 and 1948 (San Francisco, CA).[21] They observed that patients with marginal recurrence, or recurrence after inadequate dosage, may sometimes be cured by radical reirradiation. Of 105 patients with lip cancer, 3 developed marginal recurrences; these were reirradiated, and growth was arrested. Three of 71 patients with tongue cancer were treated for recurrent tumors after previous radiation therapy. Regarding ear cancer, 1 of 25 patients was treated for early relapse after previous radiation therapy, and 1 more patient was reirradiated at a later time after having been diagnosed with recurrence. No details about the doses, time intervals, efficacy, or toxicity were reported.

Zuppinger reported the University of Zurich data with protracted fractionated radiation therapy between 1931 and 1936 in 107 patients with head and neck tumors.[22] Of these, 13 (12%) were reirradiated (in 7 cases, after more than 5 years; minimum interval, 5 months). Four patients (31%) did not complete reirradiation. The reason for treatment was local progression, nodal relapse, or a second primary head and neck tumor. The same total dose as in first line was administered; however, overall treatment time was longer for the second course. Toxicity included need for tracheostomy and severe swallowing dysfunction in a minority of patients. Nevertheless, Zuppinger concluded that reirradiation is safe and promising unless the patient suffers from an ulcerated laryngeal tumor. Two years later, he published a larger series of 64 patients with recurrent head and neck or thyroid cancer.[23] Reirradiation was given with 170 and 180 kV roentgen rays once or twice daily over 5 to 6 weeks. The interval between the series ranged from 3 months to 7 years. In some cases, patients were followed for more than 5 years after reirradiation. The aim of treatment was symptom palliation in 9/64 patients (14%). Reirradiation was not completed as prescribed in 11/64 patients (17%). Seven patients (11%) died during treatment or within the first month. Unsatisfactory outcome was seen in patients with oral cavity and hypopharynx tumors. These data suggest that patient selection is challenging; however, reirradiation was often feasible and sometimes successful in salvaging these patients. Zöllner (Jena, Germany) performed a comprehensive study of radiation-induced complications after treatment of laryngeal cancer, which included 3 patients who developed fatal complications after reirradiation.[24] In 1 case, soft-tissue necrosis and chondronecrosis resulted in a fatal outcome after 6 courses of radiation therapy (1 high dose, 5 low-moderate dose), which were administered between 1931 and 1934. Another patient died as a result of pneumonia caused by laryngeal dysfunction after 3 courses of radiation therapy (1935-1937). The third patient died from soft-tissue necrosis, chondronecrosis, and osteomyelitis after 5 courses of radiation therapy (1933-1935).

Between 1940 and 1950, selected patients with nasopharyngeal malignancy were reirradiated at the University of California School of Medicine, San Francisco.[25] Details regarding this early experience were reported by Fu et al.[26] Their analysis of 42 patients with different

histological tumor types covered 1940 through 1974, emphasizing that only few patients were eligible for this approach. The time to reirradiation was in the range of 4 months to 9.5 years. External beam radiation therapy, brachytherapy, or combination therapy was prescribed. In contrast to earlier publications on head and neck tumors,[22,23] actuarial 5-year survival was reported (41%). Survival was better when the disease-free interval between first diagnosis and recurrence was longer. Six patients (14%) developed soft-tissue necrosis, and 3 (7%) developed osteoradionecrosis (all minimally symptomatic). The authors' preferred approach in patients with local and/or nodal recurrence was surgery followed by intracavitary radium therapy. For bulky, invasive lesions, external beam radiation therapy was administered first (3000 R in 3 weeks).

Articles about reirradiation of the cranium and central nervous system date back more than 80 years. For example, Beclere and Levy included a few illustrative cases treated before 1925 in their book chapter from 1931.[27] Brain tumors of different locations were reirradiated, twice in selected cases. One of these patients initially received subtotal resection for a cerebellar glioma followed by mixed roentgen and radium therapy and was treated with repeat radium therapy 6 years later. A different patient received 3 courses of radiation therapy between 1923 and 1926.[28] She suffered from a symptomatic brainstem tumor diagnosed by ventriculography; her pressure-related symptoms improved in 1923 and 1925, but not after the last treatment attempt in 1926. She died shortly after, and autopsy showed psammoma. Her tumor most likely belonged to the group of meningeal neoplasms, but details were not reported. The same holds true for radiation doses; it was only mentioned that the doses were identical for each of the courses. A different textbook mentioned 16 patients, mainly with glioma, 2 of whom were reirradiated after intervals of 6 and 12 months, respectively.[29] Neither histology nor treatment details were communicated for these 2 patients; however, the author acknowledged the challenges of establishing correct radiologic and tissue diagnoses and the possibility of erroneous diagnoses, especially if autopsy was not performed after the patients' demise.

Ramsay reported that, from 1955 to 1958, 100 patients with metastatic carcinoma of the breast were treated by implantation of the pituitary, an endocrine manipulation in an era when effective drugs for this purpose were lacking.[30] Gold was used in 54 cases and yttrium in 36. The remaining 10 patients had first 1 and later the other isotope implanted. Of greater relevance is the publication by Chu and Hilaris from Memorial Hospital, New York, about brain metastases, which covers 1954 to 1958.[31] The typical dose prescription was 3000 R in 3 weeks. Selected patients (n = 17) received repeat whole-brain radiation therapy. Twelve (71%) were categorized as favorable responders and survived for 8 months on average. Patients who failed to respond survived for 1.4 months on average. No clinical evidence of damage to normal brain tissue was seen. Three patients received 3 courses. In a comparable retrospective study by Shehata et al, 81 patients with lung, breast, and other primary tumors treated with whole-brain radiation therapy were included.[32] Of these, 35 (43%) were retreated, 12 were retreated twice, and 3 patients received 4 courses. In 68%, a single dose of 10 Gy was given; other patients received a short course of less than a week (2-5 fractions). Time interval, fractionation details, and cumulative doses were not reported. A patient with non-small cell lung cancer who received 4 courses over a 20-month period (total dose, 74 Gy) experienced a clinical response each time and survived for more than 2 years. A clinical benefit was reported after the first, second, and third courses in 69%, 68%, and 50% of the patients, respectively. Mean duration of improvement was 1.8, 2.6, and 1.5 months, respectively.

In a textbook from 1965, Kramer provided a summary of the knowledge about reirradiation, including persistent, recurrent, and new primary tumor scenarios.[33] Factors to consider during decision making included the natural history of the tumor, its extent, the condition of the normal tissues, the details of the previous treatment, and the objective of the proposed reirradiation. He recommended that "an attempt must be made to determine whether the initial course of therapy has failed because of inadequate doses, geographical miss, or radioresistance of the tumor. Previously irradiated tissues are compromised a priori to some extent, whether this is clinically obvious or not." He advocated radium needle implants as the first choice in certain accessible sites. In his practice at Jefferson Medical College Hospital, Philadelphia, PA, 63 patients were reirradiated between 1956 and 1960. Of these, 8 (13%) were treated with curative intent, including 6 with head and neck squamous cell cancer. The median interval was 3 years (18 months-12 years). Six patients were treated by cobalt beam and 2 by implants. The cumulative total doses were not reported. Two patients failed locally. Another 2 patients developed necrosis. He considered reirradiation worthwhile in 7 patients. Fifty-five patients (87%) received palliative reirradiation. The largest subgroups had cervix, uterus, and head and neck cancers; other sites included lung, breast, large bowel, and brain. In 27 cases (49%), reirradiation was given within 1 year. Most patients received a minimum tumor dose of 3500 R in 2 to 3 weeks. In 24 patients (44%), reirradiation was worthwhile, in 11 doubtful (20%), and in 20 useless (36%). The results were better when the interval exceeded 1 year. In 8 patients, a major degree of necrosis appeared (5 vesicovaginal or rectovaginal fistula), in 1 case causing a fatal hemorrhage. He concluded that "there is a definite place for re-irradiation, but patients

must be selected most carefully if useless therapy is to be avoided."

Discussion

In contrast to the historical 20th century reirradiation studies reviewed here, modern radiation therapy is preceded by meticulous tissue diagnosis and staging with lower probability of diagnostic error and has a very different workflow and technological basis, characterized by advanced 3- or 4-dimensional imaging, functional imaging, 3-dimensional treatment planning, image guided or stereotactic localization and verification, intensity modulated beams, and volumetric modulated arcs.[34-42] Recent developments also include new isotopes for brachytherapy, updated recommendations for dose prescription, the introduction of proton and carbon ion beams, and integration of systemic agents and hyperthermia that modify the radiation response.[43-49] In addition to retrospective analyses, many prospective studies have been performed since 1990,[50-55] including randomized phase 2 and 3 trials.[56-61] As a consequence, reirradiation has become part of clinical practice guidelines.[62,63] In addition to common indications, preliminary evidence in other areas has started to emerge (eg, esophageal cancer, soft-tissue sarcoma).[44,64] Statistical methods and toxicity scoring have evolved as well. Patient-reported outcomes have not been included in any of the historical studies. When activities of daily living and clinical symptoms were reported, these were physician-assessed. Terms such as "efficient life, socially active" or "relatively comfortable" were used to describe patients' lives. Data presentation was often incomplete, emphasizing that the process of manuscript peer review and correction has also changed. Because these limitations and the paucity of high-quality data, a narrative review format was chosen.

Reirradiation for symptom palliation was effective for hematological malignancies and breast, cervical, head and neck, brain, and lung tumors, among others. Radiation doses were not always reported; however, most authors prescribed doses in ranges that we still use today (eg, 3500 R [35 Gy] in 2-3 weeks).[33] Survival beyond 1 year was uncommon. Toxicity was not a major concern; however, occasional patients developed severe complications such as necrosis and fistula. The cumulative total doses for these patients were not systematically calculated. Because of less advanced imaging and lack of coregistration and deformable algorithms, the exact volume of overlap between 2 courses was almost impossible to quantify. Dose-effect calculations and normal tissue dose constraints emerged more recently and continue to evolve.[2,6,40,51] Animal experiments that improved our understanding of tissue recovery also were not available during the early decades.[65-67]

It was, and is still today, less common to reirradiate with curative aim (13% according to Kramer[33]). According to Zuppinger, 12% of patients with head and neck cancer were reirradiated, many with curative doses.[23] Both authors reported a certain probability of local control and 5-year survival, but also severe toxicity. This was also confirmed by Stevens et al, who used more modern technology in 100 patients treated with curative intent from 1964 to 1991.[68] This group required intact and nonulcerated mucosal surfaces and no more than minimal visible or palpable late effects from the prior irradiation. At least one-third of patients evaluated were not accepted for reirradiation. In 82 patients, external beams only were used (1.8-2 Gy per day, 5 days per week, planned dose at least 50 Gy). Thirty-two patients received cumulative external radiation doses greater than 120 Gy. Median follow-up was longer than 3 years. Actuarial 5-year survival was 17% in case of recurrent and 37% in case of new primary tumors. Nine patients (9%) developed severe late reactions, including 4 deaths from hemorrhage. In an accompanying editorial, C.C. Wang emphasized, among other points, that tumors must be small and superficial and the region must be free from excessive chronic radiation changes and fibrosis if one attempts 60 to 70 Gy reirradiation.[69] He also pointed out that "experience has shown that indiscriminate use of high dose re-irradiation often makes a bad matter worse."

Regarding cervical cancer, the absolute 5-year survival with no evidence of cancer was 16%.[20] Long-term survival was recorded only in patients with limited pelvic recurrence in good physical condition. Late complications in the 9 surviving patients included chronic cystitis, chronic proctitis and rectal bleeding, and rectovaginal fistula. In many, but not all, studies, better results were observed when the time interval between initial and reirradiation was longer; however, there was controversy in the literature regarding the usefulness of this approach because some authors

Table 1 Reasons for reirradiation

Dose required to achieve permanent local control was unknown
Dose required to achieve permanent local control could not be administered because of technical limitations and lack of radiosensitizing agents
Correct stage and target volume could not be defined because of imaging limitations
Development of second primary tumors
Need for repeated symptom palliation

regarded recurrent tumors as not sufficiently radiosensitive to warrant further treatment, whereas others stated that there is a definite place for reirradiation. Many authors acknowledged tremendous interinstitutional variations in treatment approaches, which often developed based on personal education and experience rather than scientific evidence. Table 1 summarizes some of the reasons that may have necessitated reirradiation in the early 20th century.

It is important to remember that the leading pioneers in the field were fully aware of many of the challenges that continue to be debated today. These include the process of late tissue changes (underlying mechanisms, mitigation, and treatment), development of personalized treatment approaches, and better ways to select patients who are likely to benefit.[15,19,22,33,70]

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