Current Clinical and Medical Education

Received 19 Mar 2024 | Revised 20 Mar 2024 | Accepted 18 May 2024 | Published Online 19 May 2024

Published By: Vision Publisher

CCME 02 (5), 195-204

ISSN 2942-0792

Radiotherapy, Radiation Boost, Dose and Fractionation, Breast Cancer: Physiological Risks of Radiation Treatment

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Abstract: Over the years, mastectomy and reconstructive techniques have been improved, enabling attractive results that are either quite similar to the natural breast shape and in symmetry with the contralateral intact breast, or even better. In a same vein, advances in radiation oncology might lessen the side effects of treatment and enhance results. Postmastectomy radiation therapy (PMRT) is linked, however, to worse cosmetic results and higher rates of problems in breast reconstruction patients. The disease stage, the chance of recurrence, the accurate delineation of the target volumes, and the treatment goals should direct radiation therapy planning. Currently, target volume delineation for breast cancer and elective nodal volumes—including after rapid reconstruction—is supported by recommendations from the European Society for Radiotherapy and Oncology (ESTRO). Reduced radiation-induced toxicity is mostly dependent on accurate target volume delineation, careful radiation planning, total dose and fractionation, dose homogeneity, and doses to organs at risk (OAR). Different groups are currently working very hard to enhance cosmetic results in breast cancer patients who are suitable for radiation therapy and mastectomy without sacrificing their medical outcomes. One of the significant late consequences of radiation therapy, radiation-induced second malignancies (RISM), affects the best course of treatment decisions. Age at radiation, dose and volume of irradiated area, kind of irradiated organ and tissue, radiation technique, and personal and family history of cancer are only a few of the many variables that lead to the development of RISM. Unknown is the precise mechanism of RISM. But now days, with more cancer survivors, it is a developing worry in oncology, and attempts are being done to avoid or reduce the prevalence of RISM

Keywords: Radiation Boost, Dose and Fractionation, Breast Cancer, Radiation Treatment, RISM.

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Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material,which is available to autho-rized users.

Introduction

A key component of cancer treatment, radiotherapy (RT) aids about 50% of instances of different kinds of cancer. The Directory of Radiotherapy Centres (DIRAC) data [1, 2] states as much. Comparing developing countries to affluent countries, the former have a larger population but fewer radiotherapy centres. Le cancer du sein. A multidisciplinary team supporting breast cancer treatment from the moment of diagnosis until the end of follow-up should provide therapy based on evidence-based guidelines. Along with perhaps improving the outcome, this strategy may also help patients feel more satisfied with their therapy and make decision-making and management easier. For better results, the multidisciplinary team comprising medical oncologists, pathologists, radiation, plastic and breast surgeons, and breast radiologists should carefully assess the treatment strategy [3, 4].

Constantly evolving surgical methods are used to enhance cosmetic outcomes. With decades of refinement, mastectomy and reconstructive techniques have produced aesthetic results that are either better than the original breast shape and in symmetry with the contralateral intact breast, or both. Moreover, this is often possible to accomplish at

the mastectomy (i.e., instant breast reconstruction, or IBR). Still, keeping oncological safety first and making it known to the patient is the most crucial idea that directs the team. The therapeutic strategy should not, therefore, cause a delay or compromise in cancer treatment. For many years, if postmastectomy radiation therapy (PMRT) was to be planned, IBR was regarded as a contraindication because of concerns about reconstruction failure and serious consequences. Patients undergoing PMRT in an IBR environment are becoming more common lately. Together with developments in radiation therapy methods, we should cooperate in this evolving reality to enhance PMRT results in the context of mastectomy and IBR [4]. Breast cancer patients can receive both internal beam radiation therapy (IBRT) and exterior beam radiation therapy (EBRT) treatment.

While IBRT is partial breast radiation with minor adverse effects, EBRT concentrates X-rays on the outside surface of the malignant body. Brachytherapy is another name for internal beam radiation treatment, in which a radioactive implant is positioned close to the tumour. Cancers in the breast and lymph node regions are treated with a dosage of between 4500 and 5000 cGy for five weeks. It is advised to add 1000–2000 Gy for a week as a boost. It is divided into numerous daily doses known as "fractions" rather than being administered in its whole at once. Usually, three to four weeks following surgery, radiation therapy begins. Typical adverse effects of radiation therapy for breast cancer include fatigue, swelling and heaviness in the breast, mild or severe skin irritation, discoloration or bruised appearance, difficulties nursing, lymphedema, acute radiation dermatitis, and the development of angiosarcoma, a very rare cancer [5].

Many medical areas have reported significant differences in the fractionation patterns of radiation therapy after breast-conserving surgery. Individual radiation centres have historically empirically created their own fractionation schedules, and those patterns have remained. Different fractionation regimens were also utilised in a number of important randomised trials that determined the significance of breast irradiation after breast-conserving surgery. Although few clinical trials comparing fractionation schedules have been carried out, data indicates that the widely employed schedules are probably biologically equivalent in terms of local control and toxicity [6]. Usually, reports of variation have looked at individuals who were seen at several facilities. Comparing facilities, meanwhile, could be difficult because patients are sent from various pools of recommending surgeons. Variations in radiation schedules may have some explanation in variations in local surgical patterns. Considerable delays in the delivery of radiation therapy were becoming more well known in Canada in the 1990s. Early in 1999, Ontario's breast irradiation waiting times were getting longer, thus a procedure for re-referral to other facilities was created to speed up treatment. Eligible patients were advised of lengthy wait times and given a referral to another facility, mostly in the US, at the time of appointment.

Radiation damages skin by triggering inflammatory processes and producing too much cytokines. A typical acute adverse effect, radiation dermatitis strikes more than 87% of patients and manifests itself hours to weeks after the beginning of radiation therapy [7]. Patients' therapeutic doses may be restricted by radiation dermatitis, and occasionally treatment breaks may result, jeopardising local control and survival outcomes [8]. It can also significantly affect the quality of life of the sufferers. Even with the tremendous progress in radiotherapy procedures, there are still no effective treatments for preventing acute skin reactions, and the available data cannot offer sufficient recommendations for treating this side effect. Many topical treatments have been investigated in attempts to lessen the drying effects of radiation dermatitis, including aloe vera, aqueous cream, calendula, petrolatum, and sulcrafate cream. Clinically meaningful improvements in the management of radiation dermatitis and pain associated to treatment have not been achieved, albeit [9–11]. For the treatment of radiation dermatitis, corticosteroids are perfect because of their anti-inflammatory effects and ability to reduce the expression of cytokine gene. Bolderston et al. found in a systematic review that there is little data to either favour or oppose the use of topical medications in the treatment of acute radiation dermatitis. Different institutes provide breast cancer patients different skin care guidelines. There is no universally accepted method for managing this side effect, and most of the time the choice of treatment is made by the medical practitioner without regard to scientific data. Clinical guidance frequently rests on anecdotal data [12, 13]. The current systematic review and meta-analysis aimed to evaluate the possible effectiveness of corticosteroids in the treatment of RD and its effects on pain and quality of life in patients with female breast cancer [14].

One of the most frequent adverse effects of radiation therapy, radiation dermatitis ranges in severity from mild erythema to more serious reactions including ulceration, moist desquamation, and occasionally necrosis. Mainly,

doses over 20 Gy cause wet desquamation. Numerous variables have been shown to affect the severity of RD in patients, as well as characteristics associated to the patients (such as smoking and bra size) and treatment parameters (such as beam energy, dosage, treatment methods, chemotherapy, and tamoxifen). Research is needed to confirm these tools for accurate and precise assessment, however IMRT considerably decreased the severity of RD in breast cancer patients compared to conventional treatments [15, 16]. The conclusion of this review was also selected to be grade 3 RTOG and CTCAE RD since, according to these scales, it provides the least unclear explanation of wet desquamation. The clinical scales created by authors and applied in a few of the trials in this study are especially noteworthy. As these scales were not validated nor previously published, bias may be a factor. Trials evaluating non-steroidal drugs have not shown a beneficial effect on RD. Already in use, steroids are becoming a viable substitute. Up to now, there hasn't been enough clinical data to show their advantages.

Meghrajani et al. found in a prior review that topical steroids reduced the incidence of moist desquamation by 2.5 times. In the meta-analysis were 383 patients. With 845 patients in our study, we showed that the risk is at least five times lower. Though it has to be mentioned that the characteristics of the trials included may have affected the result seen, this is a significant improvement [17, 18]. Analysing the studies separately and trying to interpret the findings was essential to lowering bias against steroids. Wet desquamation incidence should rise in studies using Cobalt-60 and superficial X-rays (30, 31, 33). This is because the skin sparing effect was less than in the other trials that employed at least 5 MV. Moreover, the sample sizes in the higher beam energy trials were far greater than in the earlier trials. Though they used Cobalt-60 as the radiation therapy treatment delivery method, Farhan et al. surprisingly had no event in the steroid arm and just one instance of moist desquamation in the control arm. This trial had a quite large 95% CI (0.01-7.38), suggesting some degree of ambiguity in the impact size and requiring care in interpreting the findings. When the internal validity of this experiment was evaluated, it was found that selective reporting and inadequate outcome data were present. Still, our findings support the comprehensive study conducted earlier by Salvo et al., which found that topical corticosteroid medications greatly lessen the severity of RD.

Enhancement of radiation

In the past, radiation boost was used in the context of PMRT to provide the mastectomy scar a higher radiation dose in the hopes of reducing local recurrences. When it came to breast reconstruction, researchers at Massachusetts General Hospital wanted to see if there was any correlation between a chest wall increase and problems. Participants in the research were patients whose reconstructive surgeries were postponed. Boost radiation considerably increased the risk of infection, skin necrosis, and implant exposure. There was an independent correlation between the boost's addition and increased risks of implant failure for implant-based reconstruction. Adding the boost did not improve local tumour control, even in high-risk subgroups, which is the most relevant finding. Hence, for IBR, we do not advise using boost on a regular basis.

Concentration and partitioning

Treatment protocols for breast cancer patients who have mastectomy with or without internal breast radiation (IBR) differ substantially among institutions and nations in terms of total dosage and fractionation schedule. For internal beam radiation (IBR), the typical portion sizes range from 1.8 to 2 Gy, with a total dosage of 50 to 50.4 Gy. Based on long-term data from the START A/B trials [20, 21], which showed reduced toxicity of the hypofractionation scheme compared to normo-fractionation (1.8-2 Gy per fraction to 50-50.4 Gy), some countries adopted moderate hypofractionation regimens (e.g., 40 Gy delivered in 15 fractions over 3 weeks) to the chest wall and regional nodes, even in the setting of IBR. The long-term data of hypofractionation in breast conserving therapy does not indicate that it will have inferior outcomes to conventional fractionation, even though there is limited data from clinical trials assessing hypofractionation in the context of IBR to back its use. Several such trials are currently underway.

Proton-based RT

Due to the scarcity of proton centres worldwide, proton therapy has not been extensively studied or utilised for adjuvant radiation therapy for breast cancer. It is feasible to provide optimal dose coverage of key targets and ensure low exposure to OAR due to the features of proton therapy, in comparison to photon RT. When treating breast cancer, tangential field-based planning may be more effective than volumetric based-photon planning (also known as arc-based intensity modulated radiation therapy, or vIMRT). Due to the contouring and planning considerations that were

not taken into account, a low dose "bath" is administered to vast volumes using vIMRT, which might lead to unexpected toxicity and, in the case of long-term survivors, the likelihood of subsequent malignancy [22, 23]. The Bragg peak indicates the depths of tissue where the bulk of the dose from proton therapy will be deposited, and this amount is energy dependant. What this means in reality is that (I) employing pencil-beam scanning technology, we can deliver peak energy to target volumes with irregular 3-dimensional shapes; (II) there is a quick dose fall-off when energy is deposited in the target; and (III) the integral dose to the patient is reduced. The exit dose nearly disappears within millimetres as it declines from 90% to 10%. Few small cohort studies with limited follow-up have reported the efficacy, safety, and feasibility of proton therapy. Additionally, there is a dearth of clinically controlled randomised trials that provide evidence of benefit from proton therapy, measured as either increased tumour control or fewer morbidities [24]. By reducing the dosage to the heart and lungs, proton treatment has the ability to reduce the dose to the chest wall target on regional nodes during proton radiation therapy (PMRT). There is a larger-than-expected risk of morbidities from OAR due to proton therapy, which has a radiobiologic effective dose (RBE) that is predicted to be 10% higher. Studies suggest that the relative effect may be considerably higher. While the majority of proton therapy studies in early breast cancer have been retrospective and conducted at a single institution, there have been a few well-designed trials as well. From 2011 to 2016, seventy patients in a phase II trial in Boston were administered proton therapy for loco-regional RT, which included internal mammary node irradiation. Inclusion criteria included administering conventional photon RT to the left anterior descending artery or delivering more than 20 Gy to more than 5 percent of the heart. Doses ranged from 1.8 to 2.0 Gy (RBE), with 25 to 28 portions. Radiation pneumonitis of grade 3 or above, or any toxicity of grade 4 within three months after proton therapy, was the main objective. Among those who underwent mastectomy, 83% went on to get reconstructive surgery. With just one patient experiencing grade 2 pneumonitis as the highest morbidity score, the 5-year LRR was 1.5% and the overall survival rate was 91% at the median 55-month follow-up. Two phase III randomised controlled studies are currently studying the benefits and risks of proton treatment for breast cancer patients as of 2021 [25, 26]. Participants in the RadComp study, which compares proton and photon radiation therapy for patients with breast cancer stages II–III who have a medical rationale for loco-regional radiation therapy, which includes internal mammary node irradiation (NCT 02603341), are pragmatically randomised. The principal endpoint is the decrease of major coronary events by proton therapy, with the hypothesis being that this approach can reduce the rate of major coronary events from 6.3% to 3.8% over a 10-year period, in comparison to photons. We hope to enrol 1,278 patients between 2016 and 2022 for this study. Patients who have undergone breast cancer or DCIS surgery and meet the rigorous photon treatment planning criteria for dose coverage of the breast, chest wall, and nodal volumes—including an average heart dose of 4 Gy and/or a V20lung of 37%—are eligible to participate in the DBCG Proton trial (NCT04291378), which has been open for enrollment since 2020. You can find the trial protocol on Google. We expect a 10-year drop in the risk of heart disease from 10.2% to 6.3%, and this is the main outcome. Danes over the age of 60 had a 5.8% baseline risk of cardiovascular disease during the next decade. There will be 1,502 participants in the experiment.

Possible side effects of radiation therapy for different types of cancer on the body

It is widely recognised that ionising radiation has the ability to cause cancer. Both single-strand and double-strand DNA breaks (DSBs) can be caused by ionising radiation exposure. This is because DSBs can be formed during cell replication from single strand breaks. DNA damage breaks can cause mutations in genes, which can cause the irradiated cell to convert into a cancerous state [41]. The likelihood of developing a second cancer may rise if there is a change to the DNA repair protein. One such protein is ataxia telangiectasia mutated (ATM), which detects DNA damage and sets off a chain reaction to fix it. A higher risk of cancer and radio sensitivity can result from mutations in this gene [42]. It is common practice to analyse retrospective cohort studies in order to get the dose-response relationship for the purpose of cancer risk prediction. Japanese atomic bomb survivors now have the most data accessible. Research on this group of patients has shown that secondary malignancies caused by radiation therapy tend to develop in areas where the initial radiation field dosed the patient at levels higher than 2.5 Gy. On the other hand, even a quarter of a Gy dose can harm distant organs, most notably the lungs [43, 44]. The main factors that determine the risk of radiation-induced cancer include the kind of tissue exposed, the radiation dose, the duration of exposure, and the time after exposure. Compared to atomic bomb survivors, who mostly received a single acute exposure, patients undergoing radiation therapy (RT) typically receive fractionated exposures ranging from 1 to 5 Gy per fraction and cumulative doses ranging from 15 to more than 50 Gy, resulting in decreased hazards per unit dose.

Radiation method

The risk of radiation-induced sickle cell disease (RISM) is higher when earlier radiation procedures are used [26]. More and more people are worried that RISM is linked to the rising use of intensity-modulated radiation treatment (IMRT). The increased exposure of more normal tissue to lower radiation doses in IMRT increases the possibility of a greater total dose and, by extension, the risk of radiation-induced tissue damage (RISM). To determine whether IMRT truly raises the risk of RISM, however, we need data from long-term follow-up studies. The development of image-guided radiation treatment (IGRT) is another step forward inRT technology. Normal tissues located outside of the main treatment field get approximately 5–20% of the total dosage when IGRT is used for setup verification [45]. Exposures of up to 100 mGy daily, which can be caused by routine use of portal imaging or mega-voltage (MV) cone beam computed tomography (CT), can enhance the risk of RISM in the long run [46].

Radioactive material

Proton beam therapy (PBT) had a lower crude rate of second malignancies than photons (5.2% vs. 7.5%), according to research by Chung et al. [47]. The likely explanation for this is that photon dose deposition is nearly exponential, but proton dose deposition abruptly approaches its range limit, resulting in the Bragg peak. In photon beam therapy, this results in an integral dosage that is two to three times higher than that of protons. After a median follow-up of 7 years (range, 3.9 to 10.3 years) [48], no patient was diagnosed with a second malignancy in a prospective analysis of 59 medulloblastoma patients who had PBT. A case-matched series of 43 patients who were treated with photons throughout the same period was also compared to it. The photon cohort had three patients who experienced RISM, whereas the proton cohort did not [49]. Sethi et al. [50] conducted a retrospective study to determine the frequency of secondary cancers in retinoblastoma patients treated with photon (31 patients) or proton beam radiation (55 patients). Within the proton group, the median follow-up was 6.9 years (range, 1.0 to 24.4 years), while within the photon cohort, it was 13.1 years (range, 1.4 to 23.9 years). At 10 years, the photon cohort had a much higher cumulative incidence of RISM or in-field second malignancies (0 vs. 14%; $p = 0.015$).

A second malignant neoplasm screening

Childhood cancer and breast cancer following HL have received the most of the research attention regarding screening of cancer survivors. The United Kingdom (UK) [52] and the United States (US) [53] have issued national screening recommendations that suggest starting screening earlier (25–30 years, or 8 years after treatment), screening more frequently (annually), and using more modalities (MRI, ultrasound, mammography, either alone or combined) than in the general population programme. Mammography has a higher recall rate than general population screening and can detect 80-100% of tumours, according to studies [54]. Screen detection and early diagnosis are more common in breast cancers diagnosed after HL compared to the general population. Early detection may have resulted from screening's implementation, according to some evidence. There is currently no screening tool that can impact prognosis for many cancers, even though certain survivors are more likely to get them, such as those of the stomach and lung.

Prevention of SMN through intervention

An appealing objective is the development of intervention measures to decrease the incidence of SMNs. One of the primary causes of secondary cancers in HL patients is RT. Consequently, smaller involved field procedures [56] progressively supplanted the wide field'mantle' [55] and 'inverted Y' [55] strategies that constituted the backbone of HL treatment in the 1960s and 1970s. Fields such as "involved node" [57] and "involved site" [58] have only lately emerged. Strategies that do not involve radiation have also been studied. More recent studies in HL have explored response-adapted techniques, which involve adjusting treatment based on initial response. When planning or executing treatment for the initial malignancy, it is possible to take measures to lessen the likelihood of SMN. Antiestrogens like tamoxifen or interventions to temporarily postpone menarche may provide protection for young women who have undergone breast tissue radiation at an earlier age and are at a high risk of developing breast cancer. Given that the risk of breast cancer following chest radiation therapy at early ages is similar to that of people with BRCA mutations [59], it may be prudent to consider bilateral preventative mastectomy in certain individuals, particularly those with a family history of breast cancer [60]. Appropriately designed clinical studies should assess the efficacy of lifestyle

measures after therapy, such as stopping smoking, limiting alcohol intake, exercising regularly, and losing weight, in lowering the prevalence of SMNs [61].

Conclusions

The development of more effective surgical and radiation methods led to a dramatic shift in the way breast cancer was treated. The progression of the disease, the likelihood of recurrence, the accuracy of the target volumes, and the goals of treatment should all be considered while planning radiation treatments. Important factors in lowering RT toxicity include complete dose and fractionation planning, dose uniformity, and OAR doses. The goal of the interdisciplinary team should be to enhance the clinical and trial outcomes for patients undergoing mastectomy. Although radiotherapy has a proven role in the treatment of solid malignancies, it is unfortunate that it might promote cancer even after treatment has ended. This is known as the "double edged sword" of radiotherapy. The rising number of survivors makes the risk of RISM a major worry, particularly in the paediatric population. Patients with RT are disproportionately likely to acquire a second cancer because to their genetic susceptibility and lifestyle choices, which is one of the key factors. In some cases, this consideration is more crucial than radiation safety. Genetic variations, lifestyle choices, and environmental variables are all potential risk factors for second malignancies, although little is known about these factors at this time. For some high-risk survivor populations, several nations have established guidelines for monitoring for recurrent cancers, particularly breast cancer. But rather than being grounded in evidence, most guidelines are based on consensus. A deeper knowledge of the mechanisms underlying treatment-related secondary malignancies is essential for developing effective screening strategies. Research on the clinicopathological features and prognosis of cancers associated with treatment is urgently needed because there is a current dearth of information on the mechanisms via which various treatments influence the development of second malignancies. Estimating and reducing the risk of treatment-related second malignancies requires integrated research integrating clinical investigations, radiobiology, and physics.

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