

Late complications of radiation therapy for breast cancer: evolution in techniques and risk over time

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Contributions: (I) Conception and design: DE Wazer, KE Huber; (II) Administrative support: KE Huber; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Radiation therapy in combination with surgery, chemotherapy, and endocrine therapy as indicated, has led to excellent local and distant control of early stage breast cancers. With the majority of these patients surviving long term, mitigating the probability and severity of late toxicities is vital. Radiation to the breast, with or without additional fields for nodal coverage, has the potential to negatively impact long term cosmetic outcome of the treated breast as well as cause rare, but severe, complications due to incidental dosage to the heart, lungs and contralateral breast. The long-term clinical side-effects of breast radiation have been studied extensively. This review aims to discuss the risk of developing late complications following breast radiation and how modern techniques can be used to diminish these risks.

Keywords: Radiation; breast cancer; late toxicity

Submitted Sep 13, 2017. Accepted for publication Jan 22, 2018.

doi: 10.21037/gs.2018.01.05

View this article at: <http://dx.doi.org/10.21037/gs.2018.01.05>

Long-term cosmetic outcomes

The primary goal of breast cancer management is to achieve optimal oncologic outcomes, and a very close secondary goal is to preserve cosmesis when possible. Two main treatment paradigms to achieve this cosmetic goal include breast conservation therapy (BCT) as well as mastectomy followed by reconstructive surgery.

Intact breast

BCT for invasive disease typically includes a local surgery i.e., lumpectomy, surgical axillary staging (SLNB *vs.* ALND), and whole breast irradiation. Surgical techniques have improved over time as has radiotherapy planning and delivery. From 1969 until 1996 roughly 70–87% of patients have a good or excellent cosmetic outcome as reported

themselves or by physicians (1,2). Surgical factors affecting cosmesis include volume of resection, scar orientation, as well as having >20 cm² of skin resected (1). Similarly, radiotherapy factors affecting cosmesis include volume irradiated, breast and tumor bed dose, as well as dose distribution and homogeneity (1).

The EORTC 22881-10882 trial reported 10-year rates of moderate to severe fibrosis of 28.1% *vs.* 13.2% and severe fibrosis of 4.4% *vs.* 1.6% in the boost (16 Gy with electrons, tangents, or an iridium-192 implant) *vs.* no-boost arms respectively (3). An additional French boost trial utilized a 10 Gy electron boost, which is the modality and dose commonly prescribed today. There were no \geq grade 3 skin toxicities and at 5 years the rates of grade 1–2 toxicity were 12.4% *vs.* 5.9% in the boost *vs.* no boost arms respectively (4). Overall cosmetic scores were not different between the arms and good or excellent cosmesis

was reported to be 85% when physician-reported and 90% when patient-reported (4). Thus in the setting of a tumor bed boost patients benefit from optimal local control and the overwhelming majority of patients are still satisfied with their cosmetic outcomes.

Reconstructed breast

For women with locally advanced breast cancer or patients unsuitable for BCT, a mastectomy is the breast surgery offered which is often followed by reconstruction depending upon the patient's cosmetic goals. Reconstructed breasts pose added complexity when planning and delivering radiotherapy, and have unique toxicities compared to unreconstructed breasts. Jhaveri *et al.* reported an overall grade 3–4 complication rate of 25% for women treated with post-mastectomy radiation therapy (PMRT) after reconstructive surgery (33.3% for tissue expander/implant *vs.* 0% for autologous) (5). A series from MSKCC compared women *s/p* mastectomy and tissue expander/implant reconstruction treated with PMRT to a control group and found capsular contracture rates of 68% *vs.* 40% respectively, and acceptable cosmetic result rates of 80% and 88% respectively (6). Thus capsular contracture risk is present in radiation naïve patients and appears increased with the use of PMRT, however long-term cosmesis is still achieved by the majority.

Opinions regarding optimal timing and reconstruction type in the setting of PMRT vary between institutions but most favor a delayed reconstruction. Clemens reviewed the literature and found higher patient satisfaction with autologous reconstruction compared with prosthetic based reconstruction, additionally cosmetic outcome favored a delayed reconstruction rather than immediate (7). At our institution patients with tissue expander/implant reconstruction are treated with PMRT with the expander in place with implant replacement scheduled ~6–8 months following RT, similarly autologous reconstruction is sequenced following PMRT.

Late cardiac toxicity

Realization of the potential late effects of breast radiation on the heart began as early radiation trials began to accrue longer follow-up data. A meta-analysis of 8 pre-1975 trials by Cuzick *et al.* found a non-significant increased rate in all-cause mortality for irradiated patients. This observation seemed to be driven by a significant increase in cardiac-

related deaths and was strongly impacted by survivors of the earlier trials (8). A similar finding was also made by Rutqvist *et al.* who, in a review of 960 patients with 16-year follow-up, found a significant increased risk of ischemic heart disease in a cohort of patients treated with greater than 60 Gy to the left breast with a HR of 3.2. This difference began within 5 years and increased with longer follow-up (9). With the observation of increased risk in the treatment of left breast cancers and the known higher heart radiation exposure with this treatment, studies were conducted comparing toxicities of left *vs.* right breast treatment. Paszat *et al.* reviewed over 25,000 patients in the Ontario Cancer Registry treated from 1982 to 1987 and found after 10 years median follow-up, a significant increased risk of fatal myocardial infarction for left compared to right breast treatment with a RR of 2.1 (10). It should be noted that all of the early studies demonstrating significant cardiac toxicity were conducted on patients that were treated with outdated techniques using 2D setups with much higher mean heart doses.

A landmark study was conducted by Darby *et al.*, in which they conducted a case-controlled study reviewing ischemic heart disease with radiation exposure in over 2,000 women treated between 1958 and 2001. They found a direct correlation between mean dose to the whole heart and major coronary events with no apparent threshold dose. The baseline risk of cardiac death was increased linearly by 7.4% per 1 Gy of mean heart dose and started within 5 years of treatment and continued for at least 20 years. They found no correlation with pre-existing cardiac risk factors (11). This data was further established by Little *et al.* that correlated their findings of very low cardiac risk with low dose radiation exposure and previous findings of increased risk in pediatric cancer survivors with high dose exposure (12). Data published this year by Taylor *et al.* with the Early Breast Cancer Trialists' Collaborative Group mirrors these results in patients treated more recently. In a systematic review of 75 trials from 2010–2015 with more than 40,000 patients, they found a significantly increased risk for cardiac mortality after 10 years median follow up with an increased risk of 0.04% per Gy. These trials had a mean heart dose of 4.4 Gy (13). In a 2013 SEER review, Henson *et al.* analyzed patients treated from 1973 to 2008. The cohort treated from 1973–1982 had significantly increased cardiac mortality for left-sided treatment that increased with each 5-year increment. The 1983–1992 had significant increase in lung cancer risk but not cardiac death, and the

most recent cohort had very few adverse events to review at this point (14). Similarly, Sardar *et al.* found a significant increased risk for CV mortality after 10 years follow up (15). These studies suggest a potential for increasing incidence of clinically apparent cardiac toxicity between 15 and 20 years post-treatment and that studies need sufficient follow up time before conclusions can be made.

There is mixed data regarding the importance of pre-existing cardiac risk factors in determining risk for radiation-induced heart disease. Multiple studies including the Darby study have looked into this and not found any significant correlation. However, the Taylor EBCTCG study did show a significant increase in cardiac mortality risk with smoking (13) and the Harris *et al.* trial showed higher rates of CAD with hypertension (16). Gutt *et al.* analyzed the risk of patients with pre-existing cardiac disease and found an increased incidence of cardiac deaths with left-sided treatment compared to right (17).

Advancements in cardiac imaging have allowed for earlier detection of potential cardiac effects before clinical presentation and have allowed the pathophysiology of radiation-induced ischemic heart disease to be clarified. Marks *et al.* at Duke followed 114 left breast cancers treated with RT with SPECT-CT imaging and found a volume-dependent perfusion deficit in 40% of patients within 2 years of treatment that corresponded with anterior wall motion abnormalities (18). Correa *et al.* had similar findings in reviewing a subset of patients with left *vs.* right sided radiation that revealed a significant difference in cardiac stress test findings. Seventy percent of findings were in the LAD with that majority only with LAD disease (19). Erven *et al.* completed a prospective study using echocardiography with novel strain rate imaging comparing left and right breast treatments with mean heart dose of 9 Gy for left and 4 Gy to right. They found immediate decrease in heart strain for left sided treatments that persisted for 14 months compared with no change in right sided treatments. The strain reduction was solely in the anterior wall and no findings were detected on routine echo (20). This data suggests the potential for earlier post-radiation changes in cardiac vasculature and/or myocardium that potentially does not have clinical significance for 15–20 years.

The potential risks of radiation-induced cardiac toxicity are amplified by the known risks of concurrent chemotherapy drugs that many patients with breast cancer are receiving. Bian *et al.* monitored changes in LVEF of patients treated with both trastuzumab and radiation from 2008 to 2015. Mean heart dose for right and left-sided

treatment was 1.1 and 3.63 Gy, respectively. There was a 3% decrease in LVEF overall with significant correlation with receiving doxorubicin but no correlation to radiation laterality of dose (21). This would suggest that lower doses of radiation do not significantly amplify cardiotoxic effect of chemotherapy.

Secondary malignancies

Lung cancer

Due to the proximity of the lung beneath the breast tissue, this organ receives the highest incidental dose in women receiving radiation for breast cancer treatment. The mean total lung dose has been reported as 5.7 Gy using modern 3D-conformal techniques (13). A meta-analysis looked at over 40,000 patients in trials where they were assigned to radiotherapy versus no radiotherapy. This analysis included trials using 2D techniques, with a resulting higher mean total lung dose of 10 Gy. This study showed incidence of lung cancer ≥ 10 years after breast radiotherapy had a rate ratio of 2.10 (95% CI, 1.48 to 2.98, $P < 0.001$) while incidence of lung cancer < 10 years after radiation had a rate ratio of 1.08 (95% CI, 0.76 to 1.53, $P = 0.66$) (13). This demonstrates a latency period of 10 years to the development of subsequent lung neoplasm.

Patients who remain active smokers during radiotherapy have a higher absolute risk of developing radiation induced lung cancer. Patients who undergo radiation at age 50 and continue smoking have a lung cancer risk of 13.8% by age 80 compared to 3.9% for those who either never smoked or stopped by prior to starting radiation (13). This illustrates the importance of encouraging patients beginning radiation therapy to make efforts to quit smoking to significantly reduce their risk for subsequent malignancy.

Breast cancer

The contralateral breast is also an important organ at risk to consider given its exposure to scattered radiation. One study looked at patients who were treated with opposed tangential fields from 1985 to 1999 with an average dose to the contralateral breast of 1.3 Gy (22). It was determined that younger women aged < 40 were at increased risk, with those who received > 1 Gy dose to their contralateral breast having a 2.5-fold increased risk of developing a second primary. For women over the age of 40 there was no excess risk observed. Another case control study by Boice *et al.*

which looked at patients treated between 1935 and 1982 also showed an increase in contralateral breast cancer risk was 2.7% vs. 11.1% for women who were under 45 years old (23).

In addition to looking at lung cancer risk following breast radiation, the meta-analysis published by Taylor *et al.* showed a contralateral breast cancer rate ratio of 1.20 compared to those who did not receive breast radiation (13). This number was higher for women who had received orthovoltage radiotherapy (an older technology), which increases the amount of scattered radiation to surrounding tissues, (rate ratio =1.57). The absolute radiation induced risk of contralateral breast cancer in the non-orthovoltage trials was reported to be 1% (13).

Esophageal cancer

There is some evidence of increased incidence of esophageal cancer particularly in patients who received regional nodal irradiation, which include radiation fields immediately adjacent to or encompassing the esophagus (13). In particular, an increased risk of squamous cell carcinoma had been observed in older trials, as it is the upper two thirds of the esophagus that was exposed in patients who received post-mastectomy radiation in the 1970s and 1980s. However, even with older techniques, the incidence was low at 9.65 at 100,000 person years of observation (24). This would be expected to be even lower today given the use of modern 3D-conformal radiation that allows for angling of fields away from the esophagus.

Hematologic malignancies

In addition to the induction of solid tumors, breast radiotherapy has been shown to be associated with the development of leukemia. This risk appears to be higher in patients who receive radiation to the internal mammary and supraclavicular regions (13). In a cohort study of women treated in Italy, there was an increased incidence of leukemia in radiation patients two or more years after treatment with a relative risk of 6.67, but this was not significant as there was an extremely small cohort of seven cases in the radiotherapy group and one in the non-radiotherapy group (25). An older study that looked at the risk of leukemia and adjusted for effects of alkylating agents found a two-fold increase in risk of leukemia after breast radiotherapy. This study observed an increasing risk with increasing dose of radiation to the bone marrow, going up

to sevenfold in patients who receive more than 9 Gy to marrow (26).

Technical advancements for late complication risk reduction

Several radiation techniques for delivering dose to the breast and regional lymphatics while sparing healthy tissue have been developed, including: 3D conformal radiotherapy and intensity modulated radiation therapy (IMRT), deep-inspiration breath hold (DIBH), prone positioning, accelerated partial breast radiation (APBI), hypofractionation and proton beam radiotherapy (PBT). We will discuss each of these techniques briefly below.

3D techniques and IMRT

One of the first major advancements in radiotherapy that resulted in reduced doses to normal tissues is the use of 3D imaging for the design of the radiation plan. Radiotherapy based on computed tomography-simulation with treatment planning software and image verification of patient setup allows for more accurate estimation of target and organ dosimetry. 3D planning allows for adjustment of the radiation beam angle and the addition of in field blocks to reduce underlying lung and heart dose. In addition to a static cardiac block, field-in-field techniques have shown the greatest reduction in cardiac dose, but both forward-planning and IMRT have both been employed (27-33). These techniques result in lower volumes of heart receiving high and low doses as well as a reduced complication rates. These techniques also minimize dose inhomogeneity that results in areas that receive higher than the prescribed dose within the breast tissue and at the surface of the breast leading to decreased acute skin toxicity.

Deep-inspiration breath hold

For patients with left sided breast cancer, cardiac motion varies with the respiratory cycle. Multiple studies show that with DIBH, the heart moves away from the chest wall and the distance from the heart to the breast increases, resulting in reductions in heart and lung dose (34-39). Use of breath hold and gating techniques compared with free breathing technique are estimated to reduce cardiac mortality by 4.7% and carry a median cardiac mortality normal tissue complication probability (NTCP) of 0.1% (35). Several techniques have been described for delivering treatment

during inspiratory hold including active breathing control and surface tracking. One of the limitations of this technique is the need for patient cooperation. DIBH may be difficult for patients with poor pulmonary function who are unable to sustain inspiration.

Prone positioning

Prone treatment technique has been shown to reduce dose to the lung and heart by allowing the breast tissue to fall away from the chest wall. These results are most consistently shown in women with larger breast volumes. Prone positioning can be combined with 3D conformal, IMRT or APBI techniques (40-44). Concerns for difficulty with the reproducibility of patient setup exist, but image guidance with cone-beam CT has demonstrated improvement in reproducibility (44,45). Additionally, prone positioning of pendulous breasts decreases the total tissue thickness, which allows for better dose homogeneity within the breast. This lowers the rate of late tissue fibrosis and is correlated with high reported rates of favorable cosmesis (40-43,45).

Accelerated partial breast radiotherapy

Partial breast radiotherapy is appealing for treating early, small breast cancers, and has shown to provide equivalent local control in carefully selected patients (46). Smaller volumes of breast tissue are treated with APBI and, consequently, the incidental dose to the breasts, heart, and lung are also lower. A variety of techniques can be used including, multi-catheter, balloon-catheter and external beam techniques, with accompanying dosimetric studies demonstrating a reduction in low and high dose to the heart and lung (47-50). Heterogeneous fractionation schedules have been used across studies to treat differing volumes of breast tissue, making interpretation of current data difficult; however, a Cochrane meta-analysis of published phase 3 trials showed inferior normal tissue toxicity and local control with accelerated partial breast irradiation compared to whole breast radiotherapy (50). Care must be taken when using APBI as the inferior outcomes can occur with if too much of the breast undergoes extreme hypofractionation. In contrast, the results of the IMPORT LOW study at 5 years comparing hypofractionated whole breast radiation (40 Gy in 15 fractions) to two experimental arms, a partial breast arm (40 Gy in 15 fractions) and a reduced dose arm (36 Gy in 15 fractions) in women with

hormone-receptor positive early stage breast cancers were recently published showing non-inferior physician- and patient-reported cosmetic outcomes and non-inferior local control (51). Moderate hypofractionation may provide the ideal balance between patient convenience and long term cosmetic outcomes.

Hypofractionation

Whole breast hypofractionated radiotherapy is a shorter course of treatment given over three rather than five weeks, and it is non-inferior in comparison to conventionally fractionated treatments with regard to ipsilateral breast tumor control. With a compressed course of radiation, cosmesis is non-inferior with a possible trend towards improved when compared to conventional fractionation (52). There is no evidence that modest hypofractionation, such as used in these trials, impact either late cardiac toxicity or the risk of secondary malignancy. Therefore, the same care should be taken to reduce incidental heart and lung dose using 3D conformal planning and DIBH when feasible.

PBT

PBT is a technique that allows for reduced dose to structures beyond the clinical target based on the particle characteristics of the proton, with rapid dose fall off beyond the Bragg peak. Proton beam therapy is associated with high costs of treatment and outside of clinical trial is not routinely used. Modern techniques of PBT are being studied including intensity modulated proton therapy and post-mastectomy PBT (53-56). Conclusive results on the potential benefits of PBT for the treatment of breast cancer are still emerging.

Conclusions

Overall there is a trend towards less late toxicity with modern radiotherapy techniques. There is clearly evidence of a dose-driven risk of late cardiac toxicity with mortality risk and every effort should be taken to reduce incidental dose to normal tissues using these modern techniques without decreasing local control. As many of these women will have long-term survivability, the issue of late radiation-related complications will continue to be clinically relevant, making further exploration into improved strategies for dose reduction imperative.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Brownlee Z, Garg R, Listo M, Zavitsanos P, Wazer DE, Huber KE. Late complications of radiation therapy for breast cancer: evolution in techniques and risk over time. *Gland Surg* 2018;7(4):371-378. doi: 10.21037/gs.2018.01.05