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Toxicity of Adjuvant Radiotherapy in Patients with Breast Cancer: A Review Study

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Abstract

Conservative treatment in early-stage breast cancer is considered a standard approach. Breast preserving surgery with adjuvant radiotherapy is as effective as mastectomy in the early stages of breast cancer to control local disease and distant metastasis and maintain the overall survival rate. Minimally invasive surgery for the treatment of axillary spread and new techniques of breast preservation surgery will probably lead to a reduction in mastectomy-related complications. However, the complications of adjuvant radiotherapy remain a challenge. Cutaneous, cardiac, and pulmonary toxicity are the main complications of adjuvant breast irradiation. The multidisciplinary features (systemic treatment, endocrine therapy, and surgery), patient profile (history of underlying diseases, age, and habits), and irradiation-associated parameters are the factors affecting safe adjuvant radiotherapy. Advances in irradiation techniques and facilities related to the preservation of organs at risk (such as IGRT, tracing and tracking systems, and respiratory gating) are modern tools for reducing the risk of toxicity. Reported data from clinical trials or retrospective surveys greatly help physicians in consulting the patients on the efficacy and potential side effects of treatment and leads to the improvement of the decision making process.

Keywords: Breast Cancer, Toxicity, Adjuvant Radiotherapy, Breast-Conserving Surgery

1. Context

The conservative treatment for breast cancer (BC) is a standard approach for the treatment of the early disease. Randomized trials have shown that breast-conserving surgery followed by adjuvant whole breast radiotherapy is as effective as total mastectomy in the local control of the disease and improvement of survival in patients with early-stage breast cancer (i.e., tumor size of fewer than five centimeters and lymph nodes without tumoral involvement) (1-3). However, it has been shown that the effect of breast-conserving surgery on quality of life (QoL) and the overall survival rate is superior to radical surgery. Less aggressive methods for dealing with the auxiliary region along with breast reconstruction techniques will probably further reduce the complications associated with mastectomy (4, 5).

The reported benefits of the whole breast and locoregional lymph nodes irradiation on survival have increased the potential indications of nodal radiotherapy (even in case of metastatic involvement in a small number of axillary lymph nodes). Therefore, the unwanted side effects of radiotherapy remain a challenge for BCS patients (6, 7).

Accordingly, this review article was designed to investigate evidence-based data published regarding toxicities of adjuvant radiotherapy on the heart, pulmonary system, and skin of patients with breast cancer.

2. Cardiac Toxicity

2.1. Side Effects Associated with Irradiation

Adjuvant radiotherapy, particularly for cancer of the left breast, potentially increases the risk of cardiac disease. Darby et al. showed that the dose applied to the cardiac region has a relationship with radiation-induced cardiac toxicities. The number of capillaries decreases following microvascular damages as a sub-acute injury, which is associated with low collateral circulation and vascular reserve, probably resulting in ischemia. In addition, coronary artery disease (CAD) can occur due to age-related atherosclerosis enhanced by macrovascular damages (8).

The risk of CAD increases linearly as the cardiac dose increases, although due to variations in the position of cardiac structures, no specific relationship with the amount of cardiac tissue being irradiated has been yet determined, and no definite cutoff dose has been introduced (9). The high mortality rates in patients treated with old radiotherapy methods have been attributed to myocardial infarction (10, 11).

Two-dimensional radiotherapy has been regarded as insufficient to avoid cardiac complications in breast cancer treatment, and thus has been replaced by 3-dimensional methods. Proper contouring of the cardiac and coronary arteries is strongly recommended although contouring of different parts of the heart is still challenging. Therefore, it is suggested that reproducible guidelines from the existing atlases be used (12). The mean cardiac radiation exposure recommended on the left and right sides is about 2 - 7 Gy and 1.5 Gy, respectively (13). Despite an obvious decrease in the mean cardiac dose in the past decades, in the assessment of patients undergoing low-dose irradiation, there were indications of increased risk of cardiac toxicity, even at limited doses (14).

According to Danish Breast Cancer Cooperative Group national guidelines, one of the most important priorities in radiotherapy is the preservation of organs at risk (OAR) as much as possible.

To comply with these priorities, the indication of the therapeutic dose to the tumor bed and the preservation of LADCA, heart, and lungs are required (15). It has been recommended a limitation of the dose applied on LADCA and heart to 20 Gy (V20) < 10% and V40 < 5%, respectively, using the fractionation standard. Hypofraction is recommended as an accepted method for total breast radiotherapy; with regard to the standard plan, it is increasingly being used (16).

There is no evidence that the cardiac side effects of hypo-fraction are higher and some authors have suggested that hypo-fraction radiotherapy may be a more likely approach for cardiac preservation (17).

2.2. Patient-Related Factors and Systematic Treatment

Some authors have tried to compare the risk of cardiovascular disease (CVD) in patients with left breast cancer who had undergone radiotherapy and those who had not. In a study conducted by Roychoudhuri et al., a middle age BC woman who survived by old age was estimated to have 22% risk of CVD mortality without radiotherapy and 30% definitive cumulative risk with radiotherapy (18). According to a report by Darby et al., the mortality risk from ischemic cardiac disease was estimated to increase from 1.9% to 2.4% prior to 80 years of age in a 50-year-old woman receiving a 3-Gy cardiac dose without underlying CVD (8).

New methods for delivering higher doses per fraction of irradiation in a shorter time such as accelerated partial breast irradiation (APBI) may decrease the dose received by the heart or even coronary arteries. The cardiac dose can be decreased by using a prone position setup (19, 20). Data regarding the role of intensity-modulated radiotherapy (IMRT) in the improvement of the toxicity profile of breast irradiation are conflicting and more research is required to conduct on IMRT and new techniques (21).

In adjuvant radiotherapy of BC, several patient and treatment-related factors affecting cardiac toxicity must be considered. Women with coronary heart disease have a 6.67 higher risk of major coronary accidents compared to healthy women. In addition, in diabetic and COPD patients, hearty smokers, and those with high BMI, the risk is higher (8).

The effect of concurrent use of cardiotoxic systematic drugs must be taken into account. The cardio-toxic effects of anthracycline-containing chemotherapy regimens are well-established (22). Therefore, it is not recommended to prescribe them simultaneously with RT. The safety of taking Trastuzumab along with standard adjuvant therapy for HER-2 plus BCs has widely been shown (23). There was no significant difference between the two drugs being used simultaneously with RT with respect to acute cutaneous complications, pneumonitis, dyspnea, coughing, and neutropenia (24, 25).

3. Pulmonary Toxicity

3.1. Irradiation-Related Side Effects

Irradiation-related lung injury occurs in up to 15% of BC patients who receive radiotherapy. These toxic effects are either as acute pneumonitis or as late fibrosis. Radiation pneumonitis usually occurs within six months after the completion of the radiotherapy course and may be subclinical or present with symptoms such as dyspnea, coughing, and occasional mild-to-severe fever. Radiographic findings, especially on computed tomography imaging, are often variable and not helpful. Clinical symptoms often respond to steroid treatment. In patients without an appropriate response, tumoral invasion and lymphangitis may be expected. Fibrosis due to irradiation is typically described as progressive chronic dyspnea that corresponds to a pulmonary scar at the site of treatment and occurs between a few months to several years after treatment. Treatment includes relieving symptoms by antifibrotic and anti-inflammatory drugs such as steroids, as well as oxygen therapy in many cases (26).

During a subclinical period, several genetic and molecular disorders can be observed successively due to irradiation. Several cytokines and growth factors (such as TNFα,

PDGF, and TGFβ), cells (Macrophage, Epithelial, Pneumocystis, and Fibroblast), and gene products are involved in this process (27-29). Post-RT hypoxia appears to prolong pulmonary damage through the generation of several active oxygen species (30). SPECT perfusion and ventilation probably has higher sensitivity than planer perfusion/ventilation in detecting RT-caused pulmonary damage (31).

In addition, irradiation-induced damage has been reported using pulmonary function tests. Diffusing capacity of the lungs for carbon monoxide (DLCO) is affected and FEV1/FVC may decrease, which is an indicator of the restrictive process (32, 33). Bronchiolitis obliterans organizing pneumonia is a rare but recognized event that usually occurs six to 12 months after radiotherapy (34).

The reported risk of RT-related pulmonary damage differs widely in previous studies in the range of 4.5 to 63% (31, 35, 36). These differences may be due to several reasons: diagnostic equipment, pulmonary function tests, and toxicity damage detection scales.

Several risk factors such as patient characteristics, RT techniques, environmental characteristics, and simultaneous systemic treatment must be considered in radiation-induced pulmonary sequelae (37).

There are several reported risk factors for radiation-induced lung disease. It seems that age is the main predictive factor for RT-induced pulmonary toxicity (38). Pre-existing pulmonary function damage and smoking are the other basic risks. The association between smoking and pulmonary damage is still under debate because the results are different in the published studies (39).

Dosimetric parameters such as total prescribed dose, daily dose, and the bulk of lung being irradiated are the predictors of pulmonary radiation damage. The mean ipsilateral pulmonary dose and lung volume receiving $\geq$ 20 Gy (V20) are considered the most important parameters. In total breast radiotherapy, mean lung dose (MLD) $<$ 20 Gy and V20 $<$ 20% are considered acceptable. A strong relationship between lung volume receiving $\geq$13 Gy (V13) and radiologic changes in CT scans has been reported (38, 40). The prone position seems to be associated with less damage (19).

Recent developments in radiotherapy such as IMRT, volumetric arc therapy (VMAT), helical tomography and image-guided radiation therapy (IGRT) have provided an improvement in the dose applied to PTV and decreased the dose of the organs at risk. The published papers on IMRT indicate more uniformity in the dose applied to PTV and less acute and delayed skin complications (37).

With respect to the uncommon radiotherapy modalities, major clinical trials on hypofractionated breast RT reported no significant difference in the extent of pulmonary damage (41). The reported risk of pulmonary damage following APBI is low and depends on the technique used. The common 3-dimensional method seems to be associated with a slightly higher pulmonary dose (21).

3.2. Treatment-Related Systemic Factors

Many studies have shown that a combination of radiotherapy and hormone therapy (Tamoxifen) may be a risk factor of pulmonary fibrosis (42). Patients for whom hormone therapy is required, radiotherapy and Tamoxifen are routinely used together, but the latter must be prescribed with caution in potentially radiosensitive patients. Contrarily, using aromatase inhibitors and RT appears to be a safe combination.

Although estrogen restriction should theoretically have a negative effect on post-radiotherapy remodeling, no differences were observed in the irradiated pulmonary tissues (43).

Pulmonary damage independently can be induced by several chemotherapy agents regardless of irradiation. It is known that the concurrent prescription of taxanes such as paclitaxel and docetaxel with radiotherapy has radiosensitization effects that lead to the increased risk of pulmonary damage by the simultaneous indication of paclitaxel and radiotherapy, and thus it must be avoided (44).

Many studies on mortality due to pulmonary damage following RT have shown that more risk of damage conforms with the dose applied to the lungs. Therefore, an average dose of 7 - 18 Gy for the contra-lateral lung is recommended (45).

4. Cutaneous Toxicity

4.1. Radiation Therapy Side Effects

The quality of life and breast esthetics of BC patients can be influenced by acute and long-term skin complications from the standard radiotherapy for early-stage breast cancer.

The RT effects on esthetics are reportedly associated with short-term and long-term quality of life. A subjective/objective scale for late effects of normal tissues (LENT-SOMA scales) has been developed by the European organization for research and treatment of cancer (EORTC) and radiotherapy oncology group (RTOG) (28, 46). Current terminology criteria for adverse events comprise also a scale to assess the acute and chronic toxicity. The EORTC esthetics rating system (47) and Harvard's NSABP/RTOG scoring system (48) are the widely used scales in the cosmetic fields. There are different factors to increase the risk of skin complications resulting from RT, including individual

factors (nature, habits, associated diseases), pre and post-RT treatments (type and quality of surgery, chemotherapy, target therapy, and hormone therapy), and factors of radiation therapy (the irradiated volume, dose per fraction, total dose, and using boost and overall duration of treatment) (37).

Based on trials with an average of five-year follow-up on hypofraction radiation therapy (START A, START B, and a Canadian trial), a 40 - 45 Gy dose applied to the whole breast was safe in local control and acute toxicity profile without adverse effects on esthetics (49-51).

There is a doubt about RT-related effects on skin esthetics. However, many studies have shown a relationship between RT toxicity and further delay. RT augmentation has no significant impact on retraction and rigidity of glandular tissue but can increase telangiectasia.

According to the 22881/10882 EORT trial (no boost vs. 16 Gy boost vs. 26 Gy boost), the fibrosis level and intensity during 10 years in case groups showed significant differences (1.6, 3.3, and 4.14, respectively). Removing boost in the majority of patients aged over 60 has been reported, which may decrease the negative aesthetic effects in the future (52).

An alternative therapeutic approach for patients selected with BC is APBI that has some benefits such as shorter duration of treatment, improved esthetics because of low bulk in therapy, and low cost when compared with the standard method. Different esthetic outcomes have been observed for external APBI, such as excellent esthetic outcomes in 90% of patients (53) to 21% unacceptable outcomes (54). In accordance with the RAPID trial, 33% of the patients showed adverse esthetic outcomes and less than 35% for the bulk of breast receiving the dose of 95%. They expressed that this rate can be doubled for some patients (55). These poor results might be affected by high volume receiving 50% of the prescribed dose, or by more biological effects due to twice-daily dose in the study (39).

4.2. Patient Factors and Other Treatment-Related Items

Age, size of the breast, obesity, previous history of vascular disorders, and lifestyle habits such as active or passive cigarette smoking or alcoholism are the features that have been studied the most. Older age and postmenopausal situation seem to be related to esthetic results (52). Its pathological cause may be due to the higher percentage content of adipose tissue in the glands or partially because of the resection of a greater bulk of tissue in surgery. Data regarding the theory of increased cutaneous complications related to the concomitant use of RT and hormone therapy are controversial. These treatments are basically indicated simultaneously with no obvious effect on esthetics (56).

Acute and delayed cutaneous toxicity of irradiation has been proven that are related to systemic adjuvant chemotherapy regimens (i.e., the use of Taxane and Anthracycline) (56-59). Thus, the concurrent use of RT and anthracycline or Taxan is generally not recommended. In contrast, the old CME regimen plan did not seem to be toxic in accompaniment with RT (48). The surgical approach determines the esthetic results. The amount of tissue resected is considered the characteristic mostly related to aesthetics. Regarding the rapid extension of oncoplastic techniques, post-RT esthetics and cutaneous results probably depend on the severity, timing, and technique of the surgery. The tolerance and esthetic results of breast preservation in BC patients in the areas being irradiated pre or post-surgery distinctively depend on the type of surgery method. However, further investigations are required to scrutinize the contradictory results obtained from the best succession of reconstruction and RT, the period between these two interventions, and the RT technique (60, 61).

5. Conclusions

Cutaneous, cardiac, and pulmonary complications are the most important side effects of adjuvant radiotherapy in BC. Quantitative analyses of normal tissue effects in the clinic (QUANTEC) has been developed in 2010 after great efforts by Emami et al. on a better understanding of radiation-related normal tissue toxicities.

The analysis of data from multiple studies is difficult due to primary suboptimal analysis, inadequate reporting, and variation in the analyzed models and predictors. The clinical limitation of the current data on the safety of RT is strongly related to the multidisciplinary approach to each case (systemic treatment, hormone therapy, and surgical complications), patient characteristics (such as age, associated diseases, and habits), and different aspects of irradiation.

The use of irradiation techniques (such as IMRT and VMAT) and equipment related to the preservation of organs at risk (like IGRT, tracking systems, and respiratory gating) provide new approaches for oncologists because they have demonstrated a reduction in irradiation-related toxicity. The findings reported in the published articles are helpful for physicians in consulting patients on the effectiveness and side effects of RT and optimizing the decision-making process.

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Footnotes

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