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Late Toxicities after Left-Sided Breast Cancer Radiotherapy in Women: Impact of Modern External Beam Radiotherapy Techniques

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Abstract

Radiotherapy is an important treatment method for breast cancer; though, women with left-sided breast cancer may at risk of late radiation-related toxicity because of the closeness of the heart, coronary arteries, and ipsilateral lung to the treatment volume. With increasing long-term survival, minimizing treatment-related morbidity while maintaining adequate target coverage has become an important objective of modern radiotherapy. This review focuses the major late toxicities related with radiotherapy for left-sided breast cancer in women and critically examines the impact of modern external beam radiotherapy techniques on normal-tissue exposure and possible late toxicity. A structured literature search was conducted addressing late toxicities and modern radiotherapy approaches in adult women with left-sided breast cancer. Evidence was critically assessed according to study design, sample size, follow-up duration, toxicity assessment, dosimetric parameters, and late effects. Cardiac and pulmonary toxicities remain important late complications following left-sided breast irradiation. Modern techniques, including three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), deep inspiration breath-hold (DIBH), image-guided radiotherapy (IGRT), surface-guided respiratory management, and proton therapy, provide increasingly effective opportunities to reduce radiation exposure to organs at risk while maintaining target coverage. DIBH lead reductions in mean heart dose (MHD) and may also reduce irradiation of the left anterior descending (LAD) coronary artery. IMRT and VMAT improve dose conformity but may increase low-dose exposure to surrounding normal tissues. Proton therapy can provide substantial dosimetric advantages in selected patients, although its long-term clinical benefit remains less well established. Modern radiotherapy techniques significantly improved the normal-tissue sparing in women with left-sided breast cancer. Longer-term studies, standardized toxicity assessment, cardiac dose-response evaluation, and patient-specific risk evaluations are required to determine the clinical significance of these technological advances.

Keywords: Left-sided breast cancer; radiotherapy; late toxicity; cardiac toxicity; DIBH.

1. Introduction

Breast cancer for women is one of the most common cancers in worldwide, and radiotherapy is a best treatment method. With improvements in treatment and management has been given to less late radiation-related toxicities, particularly cardiac, pulmonary, and breast/chest-wall. Therefore, modern breast radiotherapy aims to maintain tumour control while minimizing unnecessary radiation exposure to normal tissues [1, 2].

2. Objective of the Study

Late toxicities are adverse effects that develop or persist months to years after radiotherapy and may affect long-term health and quality of life. The objective of this study is reviewing the important late effects following breast irradiation include cardiovascular disease, pulmonary injury, breast fibrosis, pain, oedema, telangiectasia, and cosmetic changes. Because some complications, particularly cardiac effects, may have a long latency period, long-term assessment of treatment-related toxicity is important in breast cancer survivors.

Organization

This article is organized into the following sections which are as follows; Section 1 contains the introduction of left-side breast cancer and evolution of External Beam Radiotherapy, Section 2 contain the literature search methodology; contain the summary of major late toxicities, supporting evidences and impact of modern external beam radiotherapy of left-breast cancer, Section 3 contain the critical evaluation, section 4 explain the research gaps and future directions and Section 5 contain the conclusion.

Specific Concerns in Left-Sided Breast Cancer

Left-sided breast radiotherapy is very challenge because the organs at risk are very close such as heart, LAD coronary artery, and ipsilateral lung. Cardiac radiation exposure is associated with an increased long-term risk of ischaemic heart disease, while lung irradiation may contribute to radiation-induced pulmonary injury [2, 5, 6]. Therefore, major objective of

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modern treatment planning is reducing radiation exposure while maintaining acceptable target coverage.

Evolution of External Beam Radiotherapy

EBRT has progressed from conventional and 3D-CRT to more advanced techniques including IMRT, VMAT, DIBH, IGRT, and Proton therapy. These approaches can improve conformity and normal-tissue sparing, with DIBH being particularly important for reducing cardiac exposure in left-sided breast irradiation [7–9]. Proton therapy may provide further reductions in cardiac and pulmonary dose in selected patients [10, 11].

3. Related Work

A structured literature search was conducted using PubMed, Scopus, and Google Scholar to identify relevant published studies in English on late toxicities following EBRT in adult women with left-sided breast cancer. Keywords were used to search as “left-sided breast cancer”, “radiotherapy”, “late toxicity”, “cardiac and pulmonary toxicity”, “DIBH”, “IMRT”, “VMAT”, and “proton therapy”. The methodological quality and relevance of the evidence were critically assessed from the selected studies according Study type, Late toxicity, effected site, Clinical displays, risk factors, dosimetric parameters, Technique, Lung sparing, Dose conformity, Low-dose exposure and Major limitation.

i). Late Toxicities in Women with Left-Sided Breast Cancer

Late toxicities following left-sided breast radiotherapy can involve the cardiovascular, pulmonary, breast/chest-wall, and lymphatic systems. Cardiac toxicity is particularly important because radiation exposure to the heart and cardiac substructures may contribute to ischaemic heart disease, coronary artery disease, myocardial injury, and cardiac mortality, with risk influenced by cardiac dose, irradiated volume, treatment technique, and individual cardiovascular risk factors [2, 5]. Important dosimetric parameters include MHD, LAD coronary artery dose, and left-ventricular dose, which provide complementary measures of cardiac exposure [6, 8]. Pulmonary toxicity may include radiation pneumonitis, pulmonary fibrosis, and long-term pulmonary-function changes, with V5, V10, V20, and mean lung dose (MLD) commonly used to evaluate lung exposure and risk [6, 12].

Late breast and chest-wall effects include fibrosis, induration, edema, pain, telangiectasia, cosmetic changes, and, rarely, radiation-associated rib fracture, which may affect physical comfort, breast appearance, and quality of life [3, 13, 14]. Other late effects, including lymphedema, musculoskeletal changes, brachial plexopathy, and occasionally esophageal toxicity, may occur particularly when regional lymph nodes are included in the treatment field. Lymphedema is multifactorial and may be influenced by both surgical treatment and regional nodal irradiation [4]. Overall, these potential late toxicities highlight the importance of careful treatment planning and minimization of unnecessary radiation exposure to organs at risk while maintaining adequate target coverage. The Major Late Toxicities Following Radiotherapy for Left-Sided Breast Cancer in Women is tabulated in table 1 and Evidence Supporting Late Toxicities in Women with Left-Sided Breast Cancer is given in table 2.

Table 1: Major Late Toxicities Following Radiotherapy for Left-Sided Breast Cancer in Women.

Reference	Late Toxicity	Main Organ/site	Clinical Displays	Key Dosimetric Parameters	Important Risk Factors
[2]	Ischemic heart disease / coronary artery disease	Heart, coronary arteries, LAD	Myocardial infarction, angina, coronary revascularization and cardiac death	MHD, LAD dose	age, smoking, hypertension, diabetes and pre-existing cardiovascular risk
[4]	Lymphedema	Breast/ipsilateral upper limb	Arm or breast swelling, heaviness and functional discomfort	Regional nodal volume and dose	Axillary dissection, regional nodal irradiation
[8]	Radiation-induced cardiac injury	Heart, and cardiac substructures	Myocardial injury, fibrosis and cardiac dysfunction	MHD, LAD dose	Cardiac dose, treatment volume, cardiovascular risk
[13]	Breast fibrosis / induration	Breast/chest wall	Firmness, tissue thickening, reduced elasticity and altered breast shape	Breast dose, boost dose, dose homogeneity	Dose inhomogeneity, tumour size, surgery and individual tissue response
[14]	Breast pain	Breast/chest wall	Persistent breast or chest-wall pain	Breast dose and irradiated volume	Surgery, fibrosis, radiation exposure and individual tissue response
[16]	Radiation pneumonitis	Ipsilateral lung	Cough, dyspnea, fever and radiological lung changes	V_5, V_{10}, V_{20}, MLD	Lung dose/volume, regional nodal irradiation, smoking and pre-existing lung disease
[17]	Breast oedema	Breast/lymphatic tissues	Swelling, heaviness and discomfort	Breast/lymphatic treatment volume and dose	Surgery, axillary treatment and regional nodal irradiation
[18]	Brachial plexopathy	Brachial plexus	Paresthesia, sensory loss, weakness and motor dysfunction	Brachial plexus maximum dose	Supraclavicular irradiation, long follow-up

Table 2: Evidence Supporting Late Toxicities in Women with Left-Sided Breast Cancer.

Reference	Study Type	Main Focus	Key Finding	Main Relevance
[2]	Case-control	Cardiac toxicity	Major coronary events and mean heart increased	Establishes the cardiac dose–response relationship.
[5]	Systematic review	Heart dose	Modern techniques and breathing-control reduced cardiac exposure.	Supports cardiac dose reduction with modern EBRT.
[13]	Systematic review	Fibrosis and	Treatment-related and patient-related factors	Supports assessment of breast/chest-wall

		cosmesis	influence breast fibrosis and cosmetic outcomes.	late effects.
[15]	Systematic review	Pulmonary toxicity	Lung dose-volume parameters V20 and MLD, are important indicators of pulmonary exposure.	Supports evaluation of lung dosimetry and pulmonary toxicity.
[16]	Systematic review/meta-analysis	Chronic skin toxicity	Chronic fibrosis and other skin effects.	Supports evaluation of chronic breast/skin toxicity.
[17]	Clinical review	Brachial plexopathy	Radiation-induced late complication	Highlights uncommon neurological late toxicity.
[18]	Meta-analysis	DIBH	DIBH significantly reduced heart, LAD and ipsilateral lung doses compared with free breathing.	Provides evidence for respiratory motion management and cardiac sparing.

ii). Impact of Modern External Beam Radiotherapy Techniques

The evolution of EBRT techniques has gradually improved target conformity and reduced unnecessary radiation exposure to organs at risk in women with left-sided breast cancer. Conventional radiotherapy (2D-RT) relied on simple beam arrangements and limited anatomical information, whereas 3D-CRT incorporated three-dimensional imaging to better shape the radiation fields around the target; however, some heart and ipsilateral lung exposure may remain unavoidable [2, 8]. IMRT further improves conformity and target homogeneity through modulation of beam intensity and can reduce high-dose exposure to the heart and lung in selected patients, although it may increase the volume of normal tissue receiving low-dose radiation [7]. VMAT delivers radiation during continuous gantry rotation, providing highly conformal and efficient treatment, but its effect on cardiac and pulmonary doses depends on treatment planning, field arrangement, and individual anatomy, with potential increases in low-dose exposure [7]. Among heart-sparing approaches, DIBH is particularly important for left-sided breast radiotherapy because deep inspiration expands the lungs and increases the separation between the heart and chest wall, thereby reducing MHD and potentially reducing irradiation of the LAD coronary artery while maintaining target coverage [6–8]. IGRT, together with respiratory monitoring, respiratory gating, and surface-guided radiotherapy (SGRT), can improve positioning and respiratory-motion management, although these approaches require additional equipment, training, and quality assurance [9, 10]. Proton therapy may provide further dosimetric advantages by reducing exit dose and potentially lowering heart and ipsilateral lung exposure in selected patients; however, evidence of long-term clinical superiority remains limited, and cost, availability, and sensitivity to anatomical changes remain important limitations [10, 11]. The Comparison of Modern EBRT Techniques for Left-Sided Breast Cancer in Women is given in table 3.

Table 3: Comparison of Modern External Beam Radiotherapy Techniques for Left-Sided Breast Cancer in Women.

Technique	Heart Sparing	Lung Sparing	Dose Conformity	Low-dose Exposure	Major Limitation
2D-RT	Low	Low–moderate	Low	less extensive than inverse techniques, poorer dose precision	Limited anatomical and dose-distribution accuracy
3D-CRT	Moderate	Moderate	Moderate–good	low-dose than IMRT/VMAT	Less conformal than inverse-planned techniques
IMRT	Good	Good–variable	High	May increase low-dose exposure	Planning complexity and low-dose bath
VMAT	Good–very good, depending on optimization	Good–variable	Very high	May increase low-dose bath	Greater low-dose exposure to surrounding tissues
DIBH	Excellent, particularly for heart/LAD	Good–variable	Depends on underlying technique	favorable for cardiac sparing	patient cooperation and reproducible breath-hold
IGRT/SGRT	Indirect benefit through improved reproducibility	Indirect benefit	Improves geometric accuracy	Does not inherently reduce dose	Additional equipment, training and QA
Proton therapy	Excellent potential	Excellent potential	Very high	Very low integral/exit dose	Cost, availability and sensitivity to anatomical changes

4. Critical Evaluation of Current Evidence

i). Strengths of Current Evidence: Modern radiotherapy has substantially improved normal-tissue protection through better dose conformity, DIBH, respiratory monitoring, image guidance, and cardiac-substructure assessment. These approaches can reduce cardiac and pulmonary exposure while maintaining target coverage [1–3].

ii). Limitations of Current Evidence: Despite these advances, much of the evidence remains based on retrospective, dosimetric, or planning studies. Differences in patient characteristics, treatment techniques, dose constraints, toxicity definitions, and follow-up make direct comparisons difficult. Long-term clinical evidence for newer approaches such as IMRT, VMAT, DIBH, and proton therapy also remains limited [2, 3].

iii). Dosimetric Evidence Versus Clinical Evidence: The key limitation is the gap between dose reduction and demonstrated clinical benefit. Modern techniques may substantially reduce MHD, LAD dose, or lung dose, but this does not automatically prove a reduction in late cardiac or pulmonary events. Thus, the evidence should be viewed as a progression from dose reduction → predicted toxicity reduction → demonstrated clinical benefit, with the final step requiring longer follow-up and stronger prospective evidence [1–3, 5]. This section includes the details about your proposed work. This section includes the details about your algorithms, flowchart,

proposed models or techniques and other proposed works [6, 7].

5. Research Gaps and Future Directions

Despite substantial advances in modern EBRT, important uncertainties remain regarding the long-term prevention of late toxicities in women with left-sided breast cancer. Although techniques such as DIBH, IMRT, VMAT, IGRT and proton therapy can reduce cardiac and pulmonary radiation exposure, long-term clinical evidence demonstrating corresponding reductions in toxicity remains limited. Further research is needed to establish dose–response relationships for individual cardiac substructures, particularly the LAD and left ventricle, and to develop patient-specific models incorporating cardiovascular risk factors and treatment characteristics. Personalized motion-management strategies and AI-based approaches for automated contouring, treatment planning and toxicity prediction also require prospective validation. In addition, better identification of patients who may derive meaningful clinical benefit from proton therapy is needed. Key research gaps and future directions are summarized in Table 4.

Table 4: Research Gaps and Future Directions.

Research Area	Current Evidence	Main Limitation	Future Requirement
Long-term clinical outcomes	Modern techniques reduce heart and lung dose.	Limited long-term follow-up for newer techniques.	Large prospective studies with long-term clinical outcomes.
Cardiac substructure protection	LAD and LV doses provide additional information beyond MHD.	Optimal dose constraints and dose–response relationships remain uncertain.	Standardized contouring and validated substructure-specific constraints.
Dose–response relationships	Cardiac risk increases with radiation exposure.	Optimal predictors and thresholds for individual structures remain unclear.	Large datasets linking dose with major cardiac events and late toxicity.
Patient-specific toxicity prediction	Toxicity depends on both radiation dose and patient characteristics.	Current constraints do not fully account for individual risk.	Models integrating age, cardiovascular risk, systemic therapy and dosimetry.
Motion management	DIBH and respiratory control reduce cardiac exposure.	Breath-hold reproducibility and patient suitability vary.	Personalized DIBH, gating and surface-guided approaches.
AI and automated planning	AI can assist with contouring, planning and toxicity prediction.	Limited external validation and clinical implementation.	Prospective validation of AI-based personalized radiotherapy.
Proton therapy selection	Proton therapy can reduce cardiac and lung dose in selected patients.	Cost, availability and limited long-term clinical evidence.	Patient-selection models identifying those most likely to benefit.

6. Conclusion

Modern EBRT has significantly improved the management of women with left-sided breast cancer by providing better target coverage and reducing unnecessary radiation exposure to critical organs. Cardiac and pulmonary toxicities remain important late effects, particularly because of the long-term survival of breast cancer patients. Techniques such as IMRT, VMAT, DIBH, IGRT, and Proton Therapy offer varying degrees of normal-tissue sparing, with DIBH showing particularly consistent cardiac dose reduction. However, dosimetric improvements do not always directly translate into confirmed reductions in long-term clinical toxicity. Therefore, treatment selection should consider individual anatomy, cardiac and pulmonary risk factors, treatment volume, and patient-specific requirements. Longer follow-up, standardized toxicity assessment, cardiac-substructure evaluation, and integration of AI-based personalized planning may further improve the safety and effectiveness of radiotherapy for women with left-sided breast cancer.

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