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Cardiac alterations following radiation therapy in individuals with breast cancer

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Abstract
One of the most prevalent cancers in women is breast cancer, which is typically treated with radiation therapy (RT) which can lead to cardiovascular (CV) disease. The severity of these complications depends on the amount of radiation to the heart. In addition to hurting the cardiac tissue, RT also damages the blood vessels. Individuals with left breast cancer have a higher risk of developing CV disease as a result of RT than those with right breast cancer. Furthermore, women with risk factors for heart disease, such as diabetes, high cholesterol, smoking, and family history, are more likely to develop CV disease side effects from RT.

Keywords: Breast cancer, Radiation therapy, Cardiovascular diseases, Cardiac dose, Dose reduction, Electrocardiography, Echocardiography
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Introduction

Cancer is a public subject all over the world. In 2018, GLOBOCAN appraisals that approximately 18.1 million people are suffering from cancer and 9.6 million deaths by cancer (1). Among them, carcinoma of the breast is the most prevalent neoplasm and a major cause of mortality in women worldwide (2). Standard breast cancer therapy includes surgery, radiation therapy (RT), chemotherapy, hormone therapy, and targeted therapy (such as trastuzumab) (3). Of these, RT is effective in the treatment of over 50% of cancer patients (4); however, RT, like any cancer treatment method, has complications. One of the most serious side effects of RT thoracic and chest wall tumors is acute and late cardiovascular (CV) diseases (5). Recognition of CV disease caused by RT, includes; coronary artery diseases (CADs), arrhythmias, myocardial ischemia, pericardial diseases, valvular diseases, cardiomyopathy, and conduction system diseases (6). The breast cancer RT causes the most damage to the pericardium layer of the heart (7). Radiation doses of more than 30 Gy to the whole heart lead to CV damage (8). However, modern techniques and advances in RT, beam energy, and contouring modalities help to reduce heart dose and consequently reduce the risk of heart disease (2). According to a study, the chance of having a coronary incident increases by 7.4% for every 1 Gy of mean radiation supplied to the heart in breast cancer survivors (9). Other studies reported that the heart of women with left-sided breast cancer during RT receives a higher radiation dose than women with right-sided breast cancer (10). Studies have found that the most exposed coronary artery, is the left anterior descending (LAD) coronary artery during left breast irradiation (11). Studies have shown that risk factors such as age, hypertension, diabetes mellitus, total cholesterol, smoking, obesity, and chemotherapy drugs increase the risk of developing CV toxicity (2). CV diseases is indicated by electrocardiographic (ECG) and echocardiographic (ECHO) changes (12). This review's purpose is to examine the CV issues brought on by breast cancer RT and to talk about how ECG and ECHO can be conducted to detect radiation-induced CV impairments.

Electrocardiography

In 1902, the first ECG was introduced by Willem Einthoven, and obtained the Nobel Prize in Medicine in 1924 for it. An ECG is a record of electrical currents caused by heart muscle stimulation, There are three main components to an ECG, namely the P, the QRS, and the T waves (13). Heart damage caused by RT for breast cancer is detected via an ECG test (14). According to studies, between 13% and 37% of breast cancer patients experienced RT-induced ECG alterations (14). T-Wave changes are common in breast cancer RT-induced early ECG changes (14). Table 1 reveal studies of ECG changes by RT for breast cancer.

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Implication for health policy/practice/research/ medical education

The findings of this review study showed that radiation therapy in breast cancer patients can affect the cardiovascular system.

Echocardiography

Echocardiography or cardiac ultrasound is a painless method that provides moving images of the heart using non-ionizing radiation. Echocardiography has a variety of types, such as Doppler, stress, trans-thoracic or transesophageal and contrast echocardiography and speckle tracking echocardiography (STE), that can help diagnose RT-induced heart disease for instance pericardial disease, myocardial disease, CAD and valvular disease (19). One of the most significant applications of echocardiography is the evaluation of a left ventricular function, which it is usually assessed by calculating or estimating the ejection fraction (19). Frequently, heart problems caused by cancer treatment are associated with a decrease in left ventricular ejection fraction (20). The left ventricular ejection fraction has a few limitations, including the dependency on the loading conditions, as well as the requirement of high-quality image for accurate calculation (21). Global longitudinal strain (GLS), as one of the two-dimensional STE parameters is a better indicator of left ventricular ejection fraction (LVEF) to detect heart problems (22). Table 2 shows studies of echocardiography changes by RT for breast cancer.

Left anterior descending coronary artery

The entire heart was initially considered to be an organ at risk, but it was later found that the effects of radiation exposure depended on specific heart components. After RT, the LAD in patients with left breast cancer receives the highest dose of all the heart's substructures (24). The LAD during shielding of the heart of the patients with left breast cancer is more to be placed in the penumbra area of the radiation field so that it receives more radiation from the whole heart (25). A study has revealed that reducing the gap between CT slices from 5 mm to 2.5 mm leads to a better portrayal of the LAD on the computed tomography (CT). Therefore, its contouring will be easy and as a result, will receive less radiation dose during RT (24). Table 3 shows studies that have calculated dose distribution to the LAD and the whole heart.

Dose reduction

Increasing awareness of heart problems and the advancement of RT techniques have led to a decrease in heart dose and its substructures (29). The use of intensity-modulated radiotherapy, deep inspiration breath-hold techniques, and the prone positioning of the patient during breast cancer RT lead to a reduction in heart dose (30). Studies reported that the use of multileaf collimation for heart shielding has reduced the heart and the LAD doses in the left-sided breast cancer (25).

Conclusion

Although RT is the main part of breast cancer treatment,

Table 1. ECG findings on cardiotoxicity reported by several studies of breast cancer radiation therapy

Author, year	References	Patients	Summary of finding
Elme et al, 2013	(14)	414	ECG changes were reported in 13% of patients.
Tuohinen et al, 2015	(15)	49	T-wave alterations were noticed in 16 individuals.
Tuohinen et al, 2016	(16)	78	Electrocardiogram changes were seen in 31% of patients with left breast cancer. T wave variations were common.
Tuohinen et al, 2017	(17)	73	Electrocardiogram changes were reported in 25% of patients, which the most changes related to T- wave changes.
Tuohinen et al, 2017	(18)	80	Electrocardiogram changes due to RT were observed in 55% of patients. T wave variations were prevalent.

Table 2. Echocardiographic findings on cardiotoxicity reported by several studies of breast cancer radiotherapy

First Author, year	Reference	Patients	Summary of finding
Tuohinen et al, 2015	(15)	49	In 67% of the patients, the tricuspid annular plane systolic excursion (TAPSE) decreased; generally, radiation decreased the right ventricle's systolic function.
Tuohinen et al, 2016	(16)	78	After radiation, the echo density of the right ventricular free wall and the ventricular septum increases in individuals with left breast cancer. In addition, TAPSE considerably decreased in patients with right-sided breast cancer.
Tuohinen et al, 2017	(18)	80	Patients with right-sided breast cancer experience a reduction in strain and pulsed tissue Doppler costs in the basal anterior LV myocardium, but those with left-sided breast cancer experienced a reduction in GLS.
Tuohinen et al, 2017	(17)	73	Although there was an increase in LV myocardial mass, LV systolic performance remained the same.
Trivedi et al, 2019	(23)	40	GLS and lateral tricuspid annulus peak systolic velocity is abbreviated to S' velocity reduced 12 months after RT, LVEF remained unchanged, and diastolic parameters (E/A ratio) decreased at 12-month follow-up. Global late diastolic (A-Sr) strain rates increased at 12 months.

Table 3. Studies reporting whole-heart and LAD doses from left-sided breast cancer radiation therapy

First Author, year	References	Patients	Mean heart dose (Gy)	Mean LAD dose (Gy)
Chung et al, 2013	(26)	32	2.82	7.22
Tuohinen et al, 2016	(16)	78	2.85	18.77
van den Bogaard et al, 2019	(27)	109	4.29	20.57
Jacob et al, 2019	(28)	104	2.9	15.7

radiation-related heart problems are an important issue for survivors of breast cancer. In recent decades, the advancement of RT techniques has reduced heart dose. Using cardiac imaging techniques can help diagnose of CV complications from RT.

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Authors' contribution

Conceptualization: KT and KK.
Methodology: KT and KK.
Investigation: KT, KK, MR, SP.
Resources: KT, KK, MR, SP.
Data curation: KT, KK, MR, SP.
Writing—Original Draft Preparation: KT, KK, MR, SP.
Writing—Review and Editing: KT, KK, MR, SP
Supervision: KT, KK, MR, SP.
Project Administration: KT, KK, MR, SP.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Kermanshah University of Medical Sciences approved this study. The institutional ethical committee at Kermanshah University of Medical Sciences approved all study protocols (IR.KUMS.REC.1398.104). This study was extracted from MSc thesis of Kolsoum Teimouri at this university (Thesis #980107). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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