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Risk of Heart Disease in Left-Sided Breast Cancer Radiotherapy: With Considering Baseline Risk of Heart Diseases

Hamid Ghaznavi[1*], Amir Jafari[2]

1. Department of Radiology, Faculty of Paramedical School, Kurdistan University of Medical Sciences, Sanandaj, Iran.
2. Radiation therapy division, Ayatollah Khansari Hospital, Arak University of Medical Sciences, Arak, Iran

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Introduction: After lumpectomy, radiation therapy is used to control the tumor and increase patient survival. Following radiation therapy, the organs at risk are vulnerable to toxicity and secondary cancer.
Material and Methods: Thirty-two patients with early-stage of left breast cancer were selected for this study. Intensity-modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3DCRT) were planned to deliver the prescribed dose to the target volume. Considering baseline risk of heart disease, the excess absolute risk (EAR) of heart disease was calculated using the Reynolds risk score for ages 50-70.
Results: There was a significant difference in 10-year EAR of heart disease when comparing 3DCRT plans to IMRT ($p < 0.05$). The 10-year EAR for IMRT in the low, median, and high-risk groups was superior to 3DCRT. Among factors involved in baseline risk, by increasing the age, the impact of smoking on increasing EAR was clearer compared to a family history of heart disease.
Conclusion: IMRT had a more uniform dose distribution and a better conformity-homogeneity index than 3DCRT. However, the mean heart dose and subsequently the risk of heart disease significantly were lower in 3DCRT. Considering baseline risk leads to accurate estimates of the heart disease risk after breast cancer radiotherapy.

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Introduction

Breast cancer is one of the most common malignancies among women, and it has the highest morbidity and mortality for women after lung cancer [1]. Lumpectomy- surgery to remove cancer or other abnormal tissue from the breast- is considered the main treatment for early-stage of this cancer with a small tumor size. Following this surgery, radiation therapy is utilized to control the tumor and increase patient survival [2, 3].

Different techniques such as 3DCRT (three-Dimensional Conformal Radiation Therapy), IMRT (Intensity Modulated Radiation Therapy), and VMAT (Volumetric Modulated Arc Therapy) are used for whole breast radiotherapy. The 3DCRT method uses two opposing tangential fields to radiate the breast, and it is also used in order to uniformly distribute the dose throughout the breast and reduce the dose at the interface region between the breast and the lung. In the VMAT and IMRT methods, the target volume coverage increases by applying more fields at different angles and rotating the gantry at different angles [4, 5].

In radiotherapy, in addition to the target organ, the organs inside the field of view may receive a noticeable dose. In addition to these organs, those outside the field of view receive a small dose due to the scatter and leakage of radiation from the patient's body and the facilities. These organs are recognized as organs at risk (OAR), and depending on the received dose are vulnerable to toxicity and secondary cancer [6, 7].

The most common injuries to the organs during breast radiotherapy are secondary lung cancer and heart disease such as coronary disease, heart attack, myocardial infarction, and ultimately cardiovascular death [8-10]. A comparison of coronary heart disease in left-side vs. right-side breast cancer radiotherapy in the early stages has shown that coronary disease is several times more common in patients with left-side than in those with right-side breast cancer [11].

Nowadays, the development of advanced techniques in radiotherapy such as free flattering filter and Deep Inspiration Breath Hold (DIBH) and image-guided Radiation Therapy (IGRT), has resulted in dose reduction to OARs. In left-sided breast cancer, the DIBH technique has been able to considerably reduce lung and heart doses [12]. The risk of heart disease in patients with breast cancer radiotherapy increases linearly in proportion to the heart-received dose [8]. Therefore, minimizing the heart dose during radiotherapy is important in order to prevent these patients from heart disease and mortality.

**Corresponding Author:* Tel: +98- 9188835030; Email: h.ghaznavy@yahoo.com

There have been many studies on the superiority of advanced techniques such as IMRT and VMAT over 3DCRT in providing higher and more effective radiation doses to the tumor; however, in some cases, the dose of OARs has been reported to be higher in advanced techniques in comparison to 3DCRT. Comparing the treatment techniques of VMAT, multi-beam IMRT(m-IMRT), tangential IMRT, 3DCRT in breast cancer radiotherapy, it was found that the contralateral breast and lung received lower doses in 3DCRT technique compared to other techniques [13], while in left-sided breast cancer radiotherapy, the average dose of heart in 3DCRT was significantly lower than VMAT. As a result, the 10-year excess absolute risk (EAR) of coronary heart disease is reduced for these patients [14]. A study was carried out on comparing the risk of secondary cancers and heart disease in left-sided breast cancer radiotherapy using IIMRT and VMAT techniques, and its results showed that the 10-year EAR of heart in IMRT was lower than in VMAT [15].

Previous studies have not examined the risk of heart disease by considering other important factors such as cigarette smoking, blood factors, and a family history of heart disease in the development of cardiovascular disease. It is noteworthy to consider these factors in estimating the incidence of heart disease after radiotherapy so that we can calculate the risk of heart disease more accurately. This study aimed to compare the risk of heart disease in radiation therapy patients with left-sided breasts by considering the factors mentioned in the Clinically Simplified model in two treatment techniques of m-IMRT and 3DCRT.

Materials and Methods

Patients

CT scans of 32 patients with left-sided breast cancer were used at an early stage without lymph node involvement. The patients' age range was 33-64. CT scans of these patients were performed on a Siemens 64 slice with a thickness of 3 mm.

Treatment planning

The treatment planning was performed using PROWESS PANTHER V5.50 treatment planning software of PROWESS Company. In the plane of treatment, according to RTOG 1005 report, the breast as the target tissue and the heart as a healthy OAR were contoured [16]. Accordingly, CTV contouring includes all breast tissues which extend from the second rib to the tissue that is seen on CT scan. Eventually, due to uncertainty about the patient's condition, PTV was contoured with CTV with a 7 mm margin.

In treatment planning, photon 6 MV and a prescribed dose of 50 Gy were used to PTV in 25 fractions with two techniques of 3DCRT as planning using two tangential fields facing each other and IMRT as inverse planning with nine fields with angles of 115-280 degrees according to the patients' anatomical features.

In order to evaluate and compare treatment techniques, using DVH, the average dose of PTV and heart, and the conformity index (CI) and homogeneity index (HI) were examined which were obtained using the following relationships:

$$CI = V_{PTV} \times \frac{V_{TV}}{TV_{PV}} \quad (1)$$

$$HI = \frac{D_2 - D_{98}}{D_{prescribtion}} \times 100 \quad (2)$$

Where *V*TV is the treatment volume of the prescription isodose line, *V*PTV is the volume of the PTV, and TVPV is the volume of *V*PTV within *V*TV. High conformal coverage in the plan is indicated by a small CI value, also *D*2% and *D*98% are the minimum doses delivered to 2 and 98% of the PTV. A small HI value indicates high homogeneity.

Heart disease risk assessment

Based on studies conducted in recent decades, it has been revealed that in patients undergoing breast cancer radiotherapy, heart disease caused by radiation toxicity includes heart attack, coronary heart disease, myocardial infarction, and ultimately cardiovascular death. In addition to the received dose of the heart following radiotherapy, the development of cardiovascular disease is affected by other factors like history of heart disease in the family, smoking, diabetes, and many other blood factors. Therefore, the model for calculating the EAR of the heart is as follows [17]:

$$EAR = \delta_{Darby} * D * Baseline\ Risk \quad (3)$$

The coefficient $\delta_{Darby} = 0.074\ Gy^{-1}$ shows the linearity of heart disease rate with an increasing mean dose of heart which may occur from the first years following radiotherapy to at least 20 years after radiotherapy (8). D represents mean heart dose (Gy), and the baseline risk based on the algorithm of the Clinically Simplified model (Reynolds risk score) for ages 50-70 years was estimated. According to Reynolds score 10-year heart disease risk (%) is calculated as the following formula:

$$1 - 0.98634^{(\exp[B-22.325])} \quad (4)$$

where B= 0.0799 × age + 3.137 × natural logarithm (systolic blood pressure) + 0.180 × natural logarithm (high-sensitivity C-reactive protein) + 1.382 × natural logarithm (total cholesterol) − 1.172 × natural logarithm (high-density lipoprotein cholesterol) + 0.134 × hemoglobin A1c (%) (if diabetic) + 0.818 (if current smoker) + 0.438 (if family history of premature myocardial infarction. It was used for all factors involved in this model, baseline risk was obtained in three groups by considering the history of heart disease in the family, smoking, or having both as low, medium, and high-risk groups, respectively. The mean values of these blood factors were considered for all groups [18].

As OARs receive a non-uniform dose, this non-uniform dose should first be converted to a uniform dose throughout the whole volume of OARs. For this purpose, a parameter called organ equivalent dose

(OED) is used, which is considered equal to the mean dose of the heart and is calculated using the following equation [19]:

$$OED_{linear} = \frac{1}{V_t} \sum_i V_i * RED(D_i)$$

Where V_t is the total volume of the organ of interest, V_i is the Volume and RED_i is the risk-equivalent dose in the i_{th} DVH bin. RED in the linear model equals D_i.

Results

The table 1 shows a difference between PTV, mean heart dose, mean of heart OED, and conformity-homogeneity indices in the two treatments. In the IMRT technique, the mean heart dose and heart OED were 2.4 and 0.8 times as high as the 3DCRT technique, respectively. Since conformity index is close to one and the homogeneity index is close to zero, the treatment is more effective. According to these indices, IMRT has been able to provide a more effective dose to PTV.

Table 1. Dosimetric parameters in two treatment techniques.

	3DCRT	IMRT-9Field
PTV($V_{98\%}$)	99.6±0.07	99.27±0.04
Conformity index	0.934	0.971
Homogeneity index	0.208	0.155
Heart mean dose(Gy)	3.43±1.55	8.26±3.41
Heart OED_{linear} (Gy)	0.92±0.57	1.69±1.32

The figure 1 shows treatment planning and DVH for a patient with left-sided breast cancer in both 3DCRT and IMRT methods.

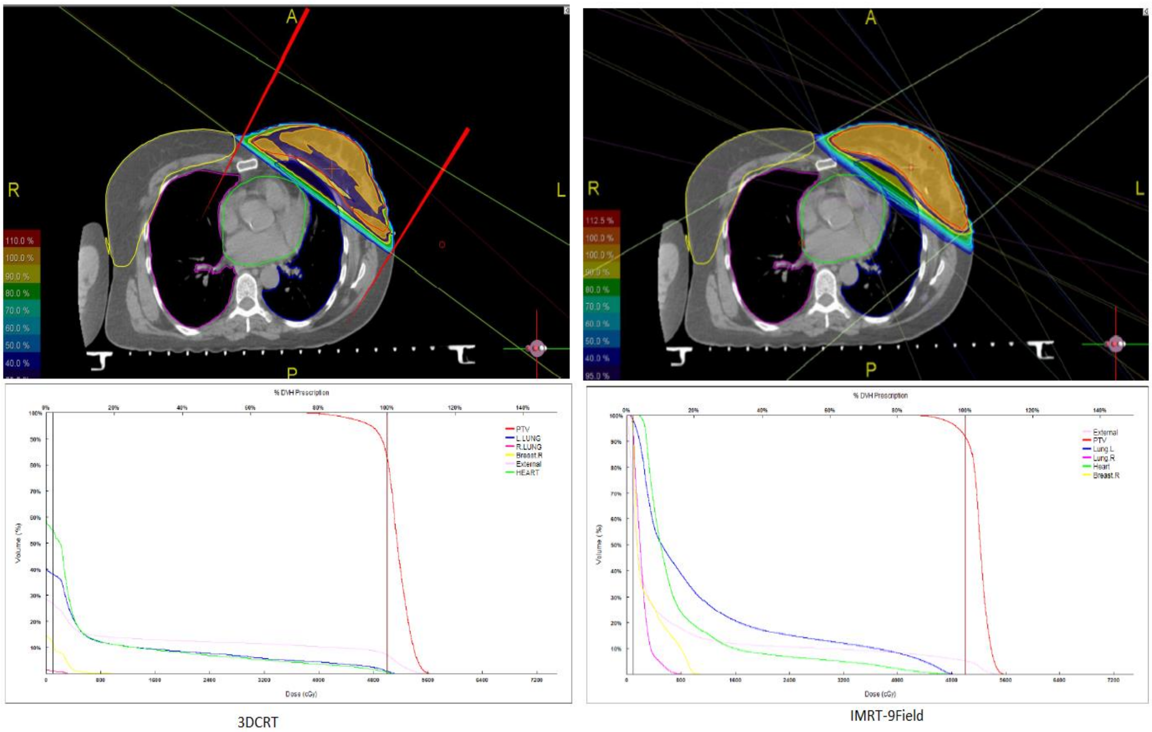


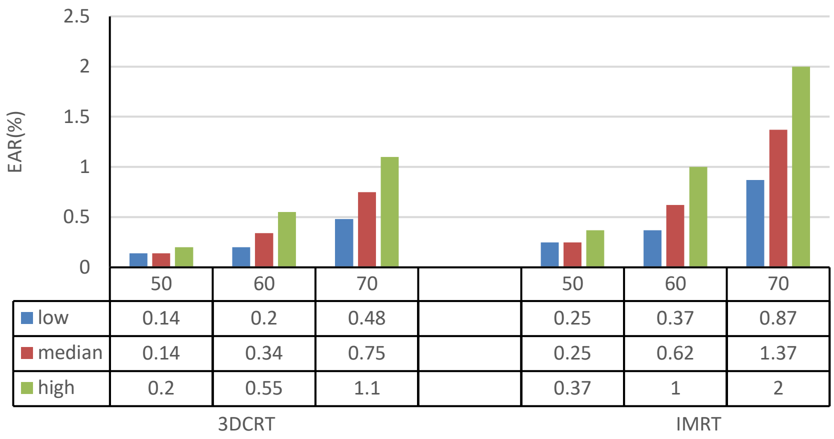
Figure 1. DVH for a patient in both 3DCRT and IMRT techniques.

The 10-year baseline risk values were obtained using a clinically simplified model (Reynolds score) for ages 50, 60 and 70. Since the effect of being a smoker and having a history of heart disease in the family was greater than that of blood factors(18), therefore, these values at the mentioned ages were obtained considering the history of heart disease in the family(group 1), being a smoker (group 2) or having both(group 3) in three categories of low, medium, and high risk using two techniques of 3DCRT and IMRT and assuming that the values of the blood factors were medium (Table 2). The values obtained are rounded off.

Table 2. The 10-year baseline risk for ages 50, 60, and 70 with considering the history of heart disease in the family, being a smoker or having both in low, medium, and high risk groups.

	Low	Medium	High
50	2%	2%	3%
60	3%	5%	8%
70	7%	11%	16%

10-years EAR for heart at the mentioned ages was calculated in low, medium, and high-risk groups for two techniques of 3DCRT and IMRT (Figure 2).



	50	60	70		50	60	70
low	0.14	0.2	0.48		0.25	0.37	0.87
median	0.14	0.34	0.75		0.25	0.62	1.37
high	0.2	0.55	1.1		0.37	1	2

Figure 2. 10-years EAR (%) of heart for patients in the range from 50 to 70 years using 3DCRT and IMRT techniques assuming that the values of the blood factors were medium.

There was a significant difference in 10-year excess absolute risk of heart diseases when comparing 3D-CRT plans in IMRT ($p<0.05$).

The effects of the family history of heart disease and smoking were nearly identical at younger ages. However, the effect of smoking on increasing baseline risk was slightly higher. The EAR values were equal to the baseline risk ones due to the rounding of these values. Compared to a family history of heart disease by increasing age, the effect of smoking on increasing EAR was clearer. EAR was almost 80% higher than 3DCRT for IMRT techniques at all ages.

Discussion

In this study, the risk of heart disease in patients undergoing left-sided breast radiotherapy was calculated in two techniques, 3DCRT and IMRT-9Field. The IMRT technique had a more homogeneous dose distribution than the 3DCRT. The conformity index for PTV on IMRT was 4% higher than 3DCRT. Furthermore, the homogeneity index in IMRT improved by 26% compared to 3DCRT, which could be a result of an increase in the number of fields. In the IMRT and 3DCRT techniques, the mean heart dose was 3.41 and 1.55 Gy, respectively. This increase in IMRT dose could be due to an increase in the number of radiation fields and radiation angles. These values were lower than the criteria set by RTOG and Emami’s article [16, 20].

Regarding the chest radiotherapy for patients with breast cancer who were irradiated with IMRT-7field and 3DCRT techniques, the conformity-homogeneity index in PTV was better in the IMRT technique, but the mean heart dose in IMRT technique was 56% higher than in 3DCRT [21]. In a comparison of 3D-CRT and IMRT-9field for patients with left-sided breast cancer, it was found that the dose homogeneity was better using IMRT compared to 3DCRT, but the mean dose heart in ۳D-CRT was 12% lower than IMRT-9field [22].

Comparing different therapeutic techniques such as 3DCRT, IMRT, HT(helical tomotherapy), and VMAT for whole breast radiotherapy, it was found that the highest dose uniformity in the target volume is related to HT techniques, but the mean heart of contralateral lung and breast in HT was higher than any other technique. In addition, the heart dose in HT was lower than that in other methods, but the mean heart dose in 3DCRT and forward IMRT was not significantly different. This suggests that in advanced treatment techniques, where there is better homogeneous dose distribution in the target volume in comparison to other methods, the dose of the OARs may be higher than that in other methods. Also, compared to FB, the DIBH technique for left-sided breast cancer radiotherapy using 3DCRT could be a useful method to reduce heart dose. [23,24].

In patients with breast cancer radiotherapy, the risk of heart disease increases linearly with the dose received by the heart. In addition to the dose received, factors like diabetes, a history of heart disease, smoking, and alcohol increase this risk significantly (8, 21). By using advanced techniques in radiotherapy such as free flattering filters, DIBH and IGRT, the dose of organs at risk has been reduced. In left-sided breast cancer, the DIBH technique was able to significantly reduce the mean heart dose [12].

In this study, 10-year EAR risk for heart disease was compared in 3DCRT and IMRT techniques using the Clinically Simplified model. This model unlike radiobiological models, in addition to dose, other risk factors such as a history of being a smoker and a history of heart disease in the family which affect the incidence of heart disease are also considered in the EAR. Since diabetes has little effect on heart disease, it is not included in the Reynold score calculation. It is only recommended that the patients inform their physician about their diabetes and reduce it by performing physical activities and going on diets [18].

Our study revealed that the highest risk of heart disease came from a smoking group with a family history of heart disease. In both treatment techniques, EAR in the high-risk group was 5.5 times higher in patients aged 70 years than in those aged 50 years. It shows the considerable effect of aging on the incidence of heart disease in patients with underlying problems such as a history of heart disease in the family and smoking. EAR in 3DCRT technique was lower than IMRT technique. EAR for IMRT at low risk was 78-85% ($p < 0.01$), medium risk was 81-85% ($p < 0.03$), high risk was 81-82% ($p < 0.02$) higher than 3DCRT. In EAR for 50 years of age, the effect of smoking and the history of heart disease in patients did not differ in the value of EAR. At age 60, the difference increased considerably for the smoking group, but at age 70, it was almost 13% lower than at age 60.

In evaluating the risk of heart disease in left-sided breast cancer radiotherapy using a clinical model in two treatment techniques of 3DCRT and VMAT, it was revealed that medium risk which considers blood factors regardless of smoking and history of heart disease in the family, 10-year EAR in the 3DCRT and VMAT techniques at age 50 was 0.09% and 0.11%, respectively, and at age 70, it was 0.53% and 0.63%, respectively. Using the DIBH technique, the EAR of the heart was significantly reduced, and this value was more noticeable in 3DCRT technique (14). In our study, according to assumptions of calculating baseline risk this study, the EAR value in 3DCRT technique at ages 50 and 70 was 0.03% and 0.19%, respectively. This difference could be attributed to the approximately 3-fold difference in mean OED of heart in this study compared to our study. Aging has been proved to increase the risk of heart disease following breast cancer radiotherapy. Therefore, using advanced techniques such as DIBH can have a significant effect on reducing heart disease after radiotherapy.

The Schneider model is another well-known radiobiological model for estimating the risk of secondary malignancies in radiotherapy [19]. Using this model, the risk of secondary cancers such as contralateral breast and lung cancer can be calculated by considering parameters such as dose fractionation and the ability for tissue repair and proliferation after each treatment session in breast cancer radiotherapy. Generalizing this model to estimate the risk of heart malignancy in breast cancer radiotherapy may not be correct, though, because the complications of breast cancer radiotherapy for the heart include pericarditis, coronary artery disease, and myocardial infarction, but not secondary cancer [15]. In breast cancer radiotherapy, the risk of secondary cancers for incidence of contralateral breast and lung cancers has been investigated using the Schneider model for different treatment methods such as 3DCRT, IMRT, and VMAT. The highest EAR was related to the ipsilateral lung, but the lowest EAR is changing between the contralateral lung and the contralateral breast. This can be attributed to applying different techniques and receiving different doses in these two organs [13-15, 25-29]. The free flattening filter technique has been able to reduce EAR to an acceptable level for the contralateral breast in IMRT [27]; however, another study showed that the free flattening filter technique did not affect reducing the EAR of OARs [26].

Nadaie et al have used the BEIR VII model to evaluate secondary cancer risk of organs at risk after radiotherapy of breast cancer. They found that the EAR of the heart was 15.8 [30], the shortcoming of this paper come from using BEIR VII model instead of OED model for estimation of secondary cancer risk of the organ in the field which received a high dose, because BEIR VII model can estimate the cancer risk for low dose (below 1- 2 Gy) [31]. Also, this paper was not considered the effects of smoking, parental history of myocardial infarction, and blood factors for estimating EAR of heart disease following radiation therapy.

Using advanced treatment methods such as HT and VMAT and using the DIBH technique can result in the uniformity of dose distribution; in addition, it can reduce heart dose and subsequently reduce the risk of heart disease. In radiotherapy, in order to estimate the risk of disease and secondary cancers after radiotherapy for OARs such as the lungs and heart, using models that have considered factors other than ionizing radiation such as smoking, a family history of cancer or cancer, and blood factors can calculate the risk more accurately than the models that only included radiation in estimating the risk. The limitations of this study included lack of access to advanced radiotherapy devices such as HT, Free flattening filter technique, DIBH, IGRT and VMAT to estimate the risk of heart disease in these devices and treatment techniques.

Conclusion

The uniformity of dose distribution and conformity-homogeneity index in IMRT was better than 3DCRT technique. While the mean dose of heart and subsequently the risk of heart disease significantly were lower in 3DCRT. Adding risk factors that are effective in the development of heart disease leads to accurate estimates of the risk of heart disease after breast cancer radiotherapy. Compared to other factors, smoking significantly increases the heart disease risk. Also, aging has a considerable effect on this risk after breast radiotherapy.

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