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Dosimetric assessment of left anterior descending, heart and brachial plexus in breast cancer patients irradiated with helical tomotherapy

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► ***Original article***

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ABSTRACT

Background: In this study, it was aimed to evaluate the radiation doses to the heart and uncommon critical organs such as left anterior descending (LAD) and brachial plexus (BP), in breast cancer patients irradiated with tomotherapy. ***Methods and Materials:*** Eighty patients with primary breast cancer received whole breast and supraclavicular region radiotherapy (RT) with helical tomotherapy were evaluated. The patients were divided into 4 groups according to the surgical procedure performed right mastectomy (RM-Group 1), left mastectomy (LM-Group 2), right breast-conserving surgery (R-BCS) (Group 3), and left breast-conserving surgery (L-BCS-Group 4). The homogeneity index (HI) for target volume, total volume (V), maximum doses (Dmax), and mean doses (Dmean) for LAD and ipsilateral BP and V, Dmean, V5 (volume of received 5 Gy) and V25 (volume of received 25 Gy) were determined for the heart to all groups. ***Results:*** According to the results, HI's were almost the same in all groups (~1.08). Although the dosimetric parameters for the heart were higher in the left breast irradiations there was a statistical difference between the groups. Dosimetric parameters of LAD are also similar to cardiac dose. However, the increase in the left breast is more pronounced. The brachial plexus dose parameters of all groups were close to each other. ***Conclusion:*** It is recommended that the brachial plexus dose should be included in routine dosimetric evaluation in terms of minimizing the risk of radiation-induced plexopathy. Also, the LAD dose should be evaluated with the heart dose to reduce the cardiotoxic effects that may occur after radiotherapy.

INTRODUCTION

Breast cancer is one of the most common types of cancer in the world. According to the statistics, 11.7% of diagnosed cancer types are breast cancer [1]. In recent years, one in 4 women has breast cancer and one in 8 women has died from breast cancer [2]. Radiation therapy (RT) remains an essential part of complex breast cancer therapy as it reduces the death from breast cancer and recurrence, but requires minimization of critical tissue and organ doses [3]. Heart, lung, and contralateral breast doses are limited in order to reduce side effects in breast RT, dosimetric evaluation of brachial plexus (BP) and left anterior descending (LAD) artery doses are not common in breast radiotherapy.

Radiation exposure to LAD in breast cancer radiotherapy causes an increase in cardiovascular complications such as pericarditis, coronary artery disease (CAD), conduction disorders, and heart failure [4]. Although studies have shown that the average dose of the heart is a main predictor of cardiac complications, some studies have shown an increase in high-grade coronary artery stenosis in LAD in left breast RT, suggesting a direct link between RT and coronary artery stenosis [5-7]. Therefore, left ventricular volume receiving a dose of 5 Gy is the most important prognostic dose parameter for the development of acute coronary complications, and the average dose to the LAD being greater than 5 Gy resulted in an increased need for coronary intervention in the LAD [8, 9].

Radiation can cause damage to the brachial plexus and lead to brachial plexopathy in the late period after RT [10]. Radiation-induced brachial plexopathy presents as pain, paresthesia, or motor weakness in the upper extremities and can cause significant morbidity, and affects the patient's quality of life [11, 12]. The tolerance dose is between 60-66 Gy according to RTOG constraints [10]. However, no specific dose value is given in QUANTEC [13]. Although the tolerance dose of the brachial plexus is high, it was observed that the brachial plexus was affected in patients after radiotherapy [14]. Brachial plexopathy is more frequently seen following treatment for breast cancer. Although the improvements in radiotherapy techniques reduced the risk of neurological toxicity, radiation-induced plexitis remains it is a severe form

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with few treatments available [15, 16].

As far as we know, in nearly all studies heart and lungs are considered as the only critical organs exposed to the dose in breast radiotherapy. However, due to the studies about the clinical findings of organs such as LAD and BP, it is determined that the doses of these organs should be included in routine dosimetric evaluation. In this study, we aimed to evaluate the doses of heart with LAD and ipsilateral brachial plexus in right and left-sided breast cancer radiotherapy with helical tomotherapy.

MATERIALS AND METHODS

Patient groups

Before the study, Mersin University Clinical Research Ethics Committee approved the study dated 19/11/2021 and with registration number 2021/707. The study consisted of 80 patients who admitted to the Mersin University Hospital Radiation Oncology Department with the diagnosis of primary breast cancer received whole breast, supraclavicular fossa (SCF), and axillary lymph node region RT.

The patients included in the study were divided into four groups: Group 1: right breast underwent mastectomy (RM), Group 2: left breast underwent mastectomy (LM), Group 3: right breast-conserving surgery (R-BCS), and Group 4: left breast-conserving surgery (L-BCS)

Treatment planning

Before radiotherapy planning, patients were fixed using a T board. Computed tomography sections were obtained at 3 mm intervals to cover the inferior, superior, and lateral borders of the breast and critical organs (Canon, Aqulion Lightning, Japan).

Obtained CT sections were transferred to the contouring station (MIM) and organs at risk (heart, LAD, and ipsilateral brachial plexus) and target volumes as including breast or chest wall, SCF and axillary lenf nodes were delineations (MIM_64, MIM Software Inc., USA). The ipsilateral brachial plexus was delineation by a radiologist (figure 1). All contours were transferred from the contouring station to the treatment planning system. Tomotherapy plans were generated using the Accuray treatment planning system (Accuray, Precision 1.1. IDMS, USA). Helical IMRT dynamic jaw mode and inverse planning technique were used for all patients with 6 MV photon energy. Treatment plannings were optimized in the tomotherapy planning software using the convolution/ superposition dose calculation method. Planning parameters were as follows; dynamic jaw, 5 cm jaw field, 0.2 pitch factor in all patients but modulation factors in plannings varied between 2.2-3.0 values to achieve conformal dose distributions depending on the anatomy of the patient. Prescription doses were determined to give a total dose of 50 Gy in 25 fractions to the target volume for patients who underwent a mastectomy and 60 Gy radiation dose who underwent BCS (50 Gy to the entire breast in 25 fractions, axillary and supraclavicular region, and 10 Gy in 5 fractions to the tumor bed for boost dose), respectively. The entire target volume was aimed to receive 95% of the prescription dose.

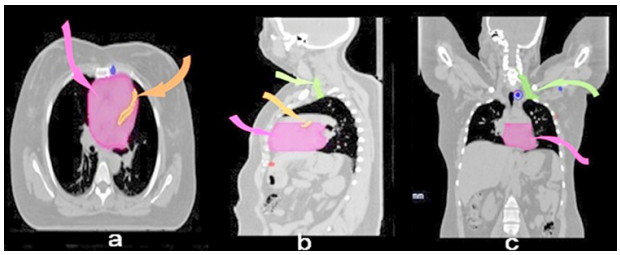


Figure 1. Regions and indicated arrows of heart, brachial plexus, and LAD contours in transverse **(a)**, sagittal **(b)**, and coronal **(c)** slices (pink: heart, orange: LAD, gren: brachial plexus).

Planning evaluation

The aim was to distribute the dose so that 95% of the prescribed dose would cover the target volume. In order to evaluate the dose homogeneity of the target volume, the homogeneity index (HI) of the patients in all groups was calculated. The homogeneity index (HI) was used in the equation (1) for dose homogeneity assessments.

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \quad (1)$$

In the equation (1), D2% is the dose received by 2% of the target volume, D98% is the dose received by 98% of the target volume, and D50% is the dose received by 50% of the target volume. HI should ideally be close to 0 [17].

To compare organ doses of the groups, total volume (V), maximum doses (D_{max}), and mean doses (D_{mean}) were determined for LAD and ipsilateral brachial plexus and V, D_{mean}, V5 (volume of received 5 Gy) and V25 (volume of received 25 Gy) were assigned for heart to all groups. Samples of dose distribution for the right and left breast treatment planning are shown separately in figure 2.

Statistical analysis

Planning data were analyzed using a statistical package program (SPSS v.20, IBM, Istanbul, Turkey). The checks of normality of the variable are tested with Kolmogorov-Smirnov test. Independent variables between the groups were compared using one-way ANOVA followed by the LSD (Least Significant Difference) *post hoc* test. P values less than 0.05 were considered statistically significant.

RESULTS

In this study, 80 patients receiving breast radiotherapy were examined. The mean and standard deviations of the values of the patients in each group

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were calculated and the statistical significance of the four groups was compared to each other. The dosimetric parameters, statistical results, and patient demographic information are shown in the table 1.

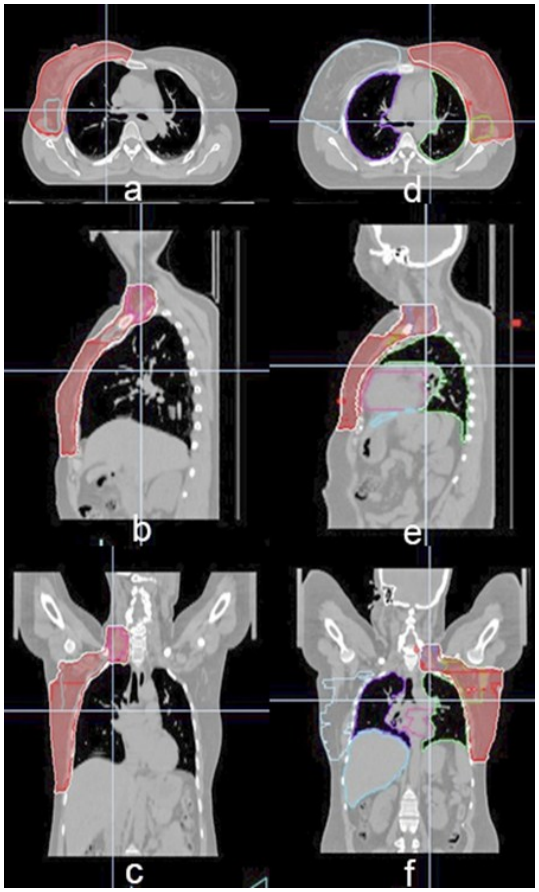


Figure 2. Isodose distributions of right **(a, b,c)** and left **(d,e,f)** breast tomotherapy treatment plannings on coronal, sagittal, and transverse slices, respectively (Red overlay: 95% of the prescribed dose and white overlay: 90% of the prescribed dose).

Table 1. Age, HI, dosimetric parameters of brachial plexus, heart and LAD results, and satistical values (mean ± standard deviation) for all groups.

	Group 1 (RM)	Group 2 (LM)	Group 3 (R-BCR)	Group 4 (L-BCS)
Age (year)	51.3±14.06	47.45±10.61	55.00±10.45	53.8±11.62
HI	1.08±0.02	1.08±0.01	1.07±0,03	1.08±0,01
Brachial Plexus				
V (cc)	9.72±1.42	8.35±1.01	11.01±3.18	8.20±1.89
D_{mean}*(Gy)*	38.21±3.23	36.20±3.65	36.11±2.48	34.63±3.24[a]
D_{max} *(Gy)*	52.74±0.62	52.40±1.49	53.44±2.48	52.61±0.82
Heart				
V (cc)	583.23±92.71	559.41±79.20	560.10±80.28	579.26±73.53
D_{mean}*(Gy)*	3.70±0.50	4.50±0,40[a,c,d]	3.78±0.52[b,d]	4.86±0.26[a,b,c]
V5 (%)	19.64±3.40	21.33±2,42	19.38±5.43[d]	23.32±5.57[a,c]
V25 (%)	0.02±0.63	1.40±0,92[a,c]	0.59±0.20[b,d]	1.62±1.14[a,c]
LAD				
V (cc)	3.89±2.33	2.87±1.14	4.15±1.16	3.89±1.29
D_{mean}*(Gy)*	6.07±1.88	14.49±5.56[a,c]	5.63±1.53[b,d]	13.19±2.79[a,c]
D_{max} *(Gy)*	10.97±3.96	33.04±6.78[a,c]	10.27±3.7[b,d]	35.46±5.41[a,c]

Group1: right breast underwent mastectomy (RM), Group 2: left breast underwent mastectomy (LM), Group 3: right breast-conserving surgery (R-BCS), Group 4: left breast-conserving surgery (L-BCS).
[a]Different from Group 1 (p<0.05), bDifferent from Group 2 (p<0.05), [c]Different from Group 3 (p<0.05), dDifferent from Group 4 (p<0.05) (Group 1: right breast underwent mastectomy, Group 2: left breast underwent mastectomy, Group 3: right BCS, Group 4: left BCS), Anova.

The average age of the patients was 51.89±11.69 years. The average age of the patients in the entire group is close to each other. According to the results, HI's were almost the same in all groups, so there was no statistical difference between the groups. Also, brachial plexus, heart, and LAD doses are given in table 1.

Brachial plexus

Since SCF and axillary lymph node regions were included in all patients, the change in Dmax values was not statistically significant for the brachial plexus. In addition, there is no statistically significant difference between right and left breast irradiation, resulting from bilateral brachial plexus dose values were evaluated. In our study, the maximum dose of the brachial plexus was found to be between 52 Gy and 53.5 Gy in all patients. The increase in D_{mean} for Group 1 (RM) was statistically different from Group 4 (L-BCR) only ($p<0.05$).

Heart

For D_{mean} of heart, Group 1 (RM) and Group 2 (LM) are statistically different from all groups. It is seen that Group 3 (R-BCS) is different from Group 2 (LM) and Group 4 (L-BCR) ($p<0.05$). The mean doses were less than 4 Gy for the right breast and less than 5 Gy for the left breast and D_{mean} in left breast irradiation were higher than right breast irradiation and statistically different from each other. As expected, the mean doses in right breast irradiation were less than the left breast irradiation. It was observed that V5's were less than 20 % for right breasts and they were less than the left breasts radiotherapy (21.33% and 23.32%).

Although there was no statistically significant difference between the V5, group 1 (RM), and Group 2 (LM) patients given 50 Gy radiotherapy, the difference between group 3 (R-BCS) and Group 4 (L-BCS) patients was statistically significant. The statistical difference is due to the 10 Gy boost treatment applied for BCS patients. V25 values are quite low in all groups. Group 3 (R-BCS) is a significant difference from Group 4 (L-BCS), while Group 4 (L-BCS) is a significant difference from group 1(RM) for the V5 value. When compared with the left breasts (Grup 2 (LM) and group 4 (L-BCS)), V25 values of the right breasts (Group 1 (RM) and Group 3 (R-BCS)) significantly increased ($p<0.05$).

LAD

It was observed that Dmean values of LAD increased in left breast groups (Group 2(LM) and Group 4 (L-BC)). These statistical increases are different from right breasts (Group 1(RM) and Group 3 (R-BCS)), ($p<0.05$). In addition, there is a significant difference between Group 2 (LM) and Group 4 (L-BCS) since an additional dose was given with a 10 Gy boost.

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D_{max} values in left breast groups (group 2 (LM) and group 4 (L-BCS)) increased statistically significantly from right breast groups (group 1(RM) and group 3 (R-BCS)) ($p<0.05$). The mean LAD dose was less than 4 Gy and 5 Gy and the maximum LAD dose was less than 20 Gy about 23 Gy for the left breast and right breasts irradiation, respectively. As a result, LAD dose values are higher in left breast irradiation than in the right breast.

DISCUSSION

Although disease management and mortality are quite high in breast cancer RT, side effects occurring in OaRs can cause serious problems [18]. Irradiation techniques such as helical IMRT with tomotherapy, IMRT, volumetric arc therapy which have emerged in the last decade, play an important role in controlling normal organ doses [19, 20]. In this study, the brachial plexus dose, which is not commonly used in routine dosimetric evaluation in breast radiotherapy, and the doses of the heart and LAD were evaluated together for 80 patients with BCS and mastectomy who underwent breast irradiation with tomotherapy.

In order to reduce the cardiotoxic effects after radiotherapy, the heart dose should be reduced. Studies have shown that the cardiotoxic risks after left breast irradiation is higher when compared to the right breast irradiation [21-23]. Darby *et al.* stated that 1 Gy increase in the mean dose of the heart increases the cardiac risk by 7.4%, and when the mean dose is above 3 Gy, cardiac mortality increases by 0.3%-0.7% for women older than 50, depending on cardiac risk factors [24]. In the studies evaluating the mean heart dose with different radiotherapy techniques, although the dose values are in the range of 5.09 Gy-6.3 Gy for left-sided breast irradiation, these values are lower for right-sided breast irradiation, as expected [3, 25, 26]. In two different studies conducted with the VMAT technique, the mean doses to the left sided breast were found to be 3.82 Gy and 9.24 Gy [27, 28]. In the same studies using the helical tomotherapy technique, the mean doses to the left breast are 5.13 Gy and 4.03 Gy [27, 28]. Erdis *et al.* reported that the mean heart dose was 5.4 Gy received radiotherapy with helical tomotherapy for BCS [29]. In our study, the mean doses were lower than 4 Gy in the left breast and 5 Gy in the right breast.

The common fear with rotational techniques such as IMRT and VMAT was that low-dose volumes would be high [30]. Yeh *et al*., Hacıislamoğlu *et al*. and Hou *et al.* reported V5 to be 19.98%-33.84%, 38% and 28.83% in helical tomotherapy techniques for left sided breast, respectively [26-28]. According to Hou *et al.* and Hacıislamoğlu *et al.* studies, V5 was 28.83% and 69% VMAT and helical tomotherapy, respectively [27, 28].

According to QUANTEC guidelines, if the V25 of the heart is less than 10%, the probability of long-term cardiac mortality will be less than 1% after RT [4]. Yeah *et al*. V25 in their study is 3.41% and 5.45% [26]. In Kuzba *et al*.'s study, V25 reported 6.88% for IMRT and 14.06% for VMAT [30]. Arslan *et al*. found V25 as 2.76% for breast irradiation performed by a breast-conserving surgeon [31]. In the Hou *et al.*'s study, V25 was 2.16% for VMAT and 2.66% for helical tomotherapy [27]. In the study of Erdiş et al. for breast conserving surgery, V25 was 0% [29]. In this study, although V25's were higher in breast-conserving radiotherapy, they were generally less than 1% in the right breasts and less than 2% in the left breast radiotherapy.

In breast radiotherapy, LAD is exposed to radiation, causing a cardiotoxic effect and the mean dose of LAD is the determinant of semptoms. The maximum dose of LAD is clinically more important, as only partial occlusion of the LAD causes symptomatic heart disease [32, 33]. However the threshold dose for LAD remains unclear [4]. Studies have reported that LAD dose is higher in left breast irradiation and tried to be kept as low as possible. In the left breast study, Beaton *et al.* found a mean LAD dose of 8.4 Gy and the Max LAD dose of 36.4 Gy [4]. In the study by Göksel *et al*., the mean and maximum doses of LAD were 8.96 Gy and 24.92 Gy with helical tomotherapy and 8.33 Gy and 19.49 Gy with VMAT [34].

Although the brachial plexus dose is not considered in breast irradiation, brachial plexus neuropathy (BPN) is one of the important late morbidities that developing after radiotherapy involving the supraclavicular fossa region [35]. In the study of Emami, the maximum dose of the brachial plexus was defined as 60 Gy and it was reported that the maximum dose should be taken into account since it is a serial organ [36]. No dose tolerance is specified for the brachial plexus in QUANTEC [13]. Currently, the incidence of brachial plexopathy after radiotherapy is less than 1-2% at doses less than 55 Gy [36]. According to the literature study by Galecki *et al*., the risk of brachial plexus injury is 1.7-73% if the maximum dose of the brachial plexus is in the range of 43.5-60 Gy [37]. In the study of Kültür *et al.*, they observed brachial plexus stiffening associated with fibrotic processes in the breast side brachial plexus receiving radiotherapy [14]. Jin *et al*. reported that the maximum LAD dose was 64.5 Gy and 54.5 Gy in a patient who received a boost and not a boost, respectively [35]. Maksimum LAD doses were 56.4 Gy and 55.2 Gy for VMAT and combining 3D with VMAT, respectively in Dumane *et al*.'s study [38]. In the study of Goyal *et al*., it was observed that the maximum dose of brachial plexus ranged from 53.64 Gy to 56.61 Gy [12].

CONCLUSION

It is recommended that brachial plexus doses should be included in routine dosimetric evaluation in

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terms of minimizing the risk of plexopathy and that LAD should be evaluated together with the heart dose in order to reduce the cardiotoxic effects that may occur after radiotherapy.

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Ethical consideration: This study was approved by Mersin University Clinical Research Ethics Committee.

Authors' contribution: S.B.U., study conception and design, treatment planning, analysis and interpretation of result, draft manuscript preparation; E.B.Y., target and critical organs delineation; Y.B., Brachial plexus delineation; M.B.Ç., treatment planning. All authors reviewed the results and approved the final version of the manuscript.

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