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The impact of anthropometric measurements on radiotherapy planning for patients with breast cancer

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▶ ***Original article***

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ABSTRACT

Background: In the management of breast cancer, radiotherapy plays a crucial role, especially in managing local tumor control. To achieve the best possible outcomes while fully protecting normal tissues, it is important to consider anatomic variations, which can differ between individuals and significantly impact treatment field designs. ***Materials and Methods:*** The study involved 40 patients with breast cancer who underwent breast-conserving surgery (BCS) and received both whole breast and lymph node irradiation. The study evaluated the impact of anthropometric characteristics including weight, mid-sternum thickness, Haller index, central lung distance (CLD), and breast volume on the doses of organs at risk (OARs). ***Results:*** Breast size was found to be an important factor in determining lung doses. Patients with larger breasts had higher ipsilateral lung doses compared with those with small or medium-sized breasts. On the other hand, patients with mid-sternum thickness above 1.7 cm had higher contralateral breast doses. As expected, patients who received internal mammary nodal irradiation had higher lung doses and contralateral breast doses compared with those who did not. ***Conclusions:*** In the radiotherapy of breast cancer, it is important to consider treatment portal designs based on anthropometric variables to reduce the doses of organs at risk. Contralateral breast doses in patients with high mid-sternum thickness and lung doses in patients with large breasts should be carefully and treatment options should be evaluated accordingly.

INTRODUCTION

Breast cancer accounts for 31% of all cancers in women and is the leading cause of cancer-related deaths among women aged 20 to 49 years [1]. Patients with breast cancer who are diagnosed at an early stage tend to have a longer life expectancy compared with those who receive radiotherapy for other malignant conditions. The importance of radiotherapy was revealed in the meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), showing that the administration of radiotherapy (RT) after breast-conserving surgery (BCS), could reduce the risk of breast cancer recurrence by almost 50%. Moreover, radiotherapy contributes to a reduction of breast cancer-associated deaths by around one-sixth [2].

Risk factors associated with tumor biology such as stage, grade, hormone receptor status, and cErb mutations are known to affect prognosis [3]. In addition, factors related to the adverse effects of radiotherapy are crucial for the patient's quality of life and complications. In the radiotherapy of breast cancer, the treatment field encompasses the ipsilateral lung, heart, and contralateral breast, resulting in cardio-pulmonary adverse effects together with the increased risk of secondary cancer development [4-6]. Accordingly, patients with left breast cancer receive higher heart doses due to the closer proximity of the cancer to the treated areas [7]. To overcome these challenges, the effective implementation of deep inspiration breath hold (DIBH) in patients with left breast cancer reduces cardiac movement, which enhances cardiac protection [8].

The elevation of cardiac doses increases the chances of developing coronary artery disease, which can lead to non-cancer-related deaths in the long term. Additionally, previous use of anthracycline, trastuzumab, and/or tamoxifen in the management can further increase cardiotoxicity [9]. Even when the heart is not within the irradiation field, the cardiac injury may worsen due to the abscopal effect, which emphasizes the importance of limiting the components that we can manage [10]. Both anatomic variations and different treatment positions can cause organs at risk (OARs) doses (such as heart, lungs, and contralateral breast) to vary, even with identical treatment protocols, highlighting the need for individualized treatment plans [11, 12]. Therefore, treatment field designs based on the anatomic variables of the patient could help to reduce the adverse effects [13]. This study aimed to evaluate the relationship between the dose distributions of organs at risk and the dosimetric changes that could be revealed by the differences in the treatment depending on the patient's anthropometric variables.

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The study is innovative in creating a quick tool for evaluating individualized risks before developing specific radiotherapy plans.

MATERIALS AND METHOD

Patient Population

Forty female patients with cT1-3 and cN1-3 pathologically confirmed invasive breast cancer who received adjuvant radiotherapy after undergoing breast-conserving surgery (BCS) at Akdeniz University Radiation Oncology Clinic between April 2017 and May 2019 were retrospectively selected. Exclusion criteria included the presence of distant metastases and mastectomy of the primary tumor. Axillary lymph node metastasis was confirmed through sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND).

Computed Tomography (CT) simulation and Planning

CT images were obtained using a GE LightSpeedÔ RT CT scanner (GE Healthcare, USA) with a 2.5-mm slice thickness without any breathing adaption and contrast agent. The patients were positioned headfirst and supine on the breast board and the ipsilateral arm was abducted 90 degrees. Treatment plans were created using the Precise PLANÔ software (version 2.15) (Elekta, Stockholm, Sweden) treatment planning system (TPS) using transferred 3D-CT image datasets. Patients were treated using an Elekta SynergyÒ Platform Linear Accelerator (LINAC) (Elekta, Stockholm, Sweden) with 6 MV photons using an opposed tangential, field-in-field intensity modulated radiation therapy (IMRT) technique (figure1).

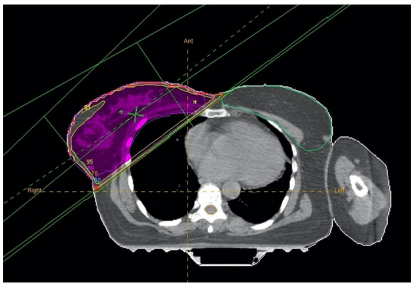

Figure 1. Dose distribution of opposed tangential, field-in-field intensity modulated radiation therapy (IMRT) technique.

Delineation of target volumes and OARs

The clinical target volume (CTV) was defined as the visible breast on the contouring CT. The nodal CTV was created by incorporating axillary and supraclavicular lymph nodes; internal mammary lymph nodes (IMN) were included in nodal CTV if indicated. A CTV boost field encompassed the tumor bed, surgical clips, and postoperative changes. The planning target volume (PTV) was created by adding a 5-mm margin around the CTV. Delineation was performed by a single radiation oncologist and a second radiation oncologist reviewed the targets and OARs. Target delineation was performed according to the Radiation Therapy Oncology Group (RTOG) Breast Cancer Atlas for Radiation Therapy Planning. A dose of 50 Gy is prescribed for patients to cover whole-breast CTV and nodal CTV, and a dose of 10 Gy is prescribed to boost volume. The International Commission on Radiation Units and Measurements (ICRU-50) guidelines were followed to create an optimal plan and the prescribed dose was intended to cover 95% of the PTV.

Anthropometric evaluations

Patient pretreatment weights were measured and noted. Haller index (HI), central lung distance (CLD), and mid-sternum thicknesses were measured from the CT simulation images for each patient. Haller index (HI) was calculated by dividing the widest transverse diameter of the thorax by the sterno-vertebral distance on axial image of the CT simulation images (figure 2) [14]. The patients were divided into two groups based on the median HI values (median HI: 2.2). Mid-sternum thicknesses were measured by determining the distance between the sternum and skin at the level of the opposite nipple using tomography images (figure 3). The median mid-sternum thickness was found as 1.7 cm, and patients were divided into two groups, ≤1.7 cm and > 1.7 cm. CLD was acquired by measuring the distance between the posterior tangential field edge and the anterior chest wall [15]. The median CLD was 3.1 cm and patients were divided into two groups, ≤3.1 cm and >3.1 cm. Cut-off values were determined based on the median of HI, CLD, and mid-sternum thickness. Patients were grouped by irradiated breast volume as large (≥1600 cc), medium (975-1600 cc), and small (≤975 cc) [16].

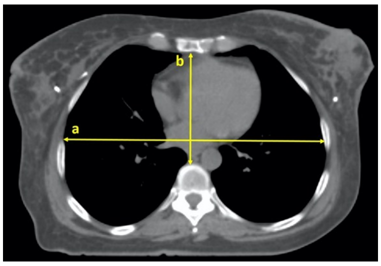

Figure 2. The Haller index is calculated by dividing the widest transverse diameter of the thorax **(a)** by the sterno-vertebral distance **(b)**, using a computed tomography simulation image.

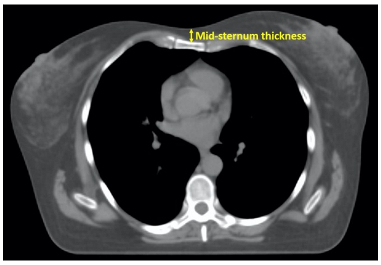

Figure 3. Mid-sternum thickness is estimated by measuring the perpendicular distance from the sternum to the skin at the level of the opposite nipple using an axial computed tomography image.

Dosimetric Evaluations

Dose volume histogram (DVH) parameters were calculated for total lung (TL) and ipsilateral lung (IL) were V_5, V_{10}, V_{20} (the percentage of lung volume covered by 5 Gy, 10 Gy and 20 Gy, respectively) and mean lung dose (MLD). For the evaluation of DVH of the heart, mean dose (D_{mean}), V_{10}, V_{25} (percentage of volume covered by 10 Gy, 25 Gy, respectively) and D_{33} (dose received by 33% of the heart) were calculated for each patient. For contralateral breast doses D_{max}, D_5 (dose received by 5% of the contralateral breast), V_5 (contralateral breast volume that received 5 Gy dose), and D_{mean} were calculated. In addition, volumes of heart, contralateral breast, irradiated breast, and boost volumes were measured from treatment plans. Anthropometric measurements and dosimetric values were compared for each.

Statistical Analysis

Descriptive statistics were used to present baseline characteristics. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine if the parameter distribution was normal. The independent t-test or Mann-Whitney U test was used to analyze parameter differences among groups formed according to breast size. In the analysis of treatment fractions, either repeated measures analysis of variance (ANOVA) or the Friedman test was used. Pearson's correlation coefficient was used to evaluate the relationship between changes in dimension and dose. Any results with a p-value less than 0.05 were considered statistically significant. The data analysis was performed using the IBM SPSS Statistics version 23.0 software (Armonk, NY: IBM Corp. 2016).

RESULTS

All patients included in the study were female and the mean age of the patients was 49.1±8.7 years. The characteristics and anthropometric features of the patients are given in table 1 and table 2. Out of 40 patients, 19 were diagnosed as having left-sided breast cancer. The heart doses (D_{mean}, V_{10}, V_{25}, D_{33}) were significantly higher, and total lung doses (V_5, V_{10}, V_{20}, MLD) were lower in patients with left-sided breast cancer compared with those with right-sided breast cancer (table 3). IMN region was added to irradiated nodal volumes in 37.5% of patients; in this IMN irradiated group (table 3), the ipsilateral and total lung doses (V_5, V_{10}, V_{20}, MLD), and contralateral breast doses (D_{max}, D_5, and V_5) were significantly higher compared with the non-irradiated group. The median body weight was 72 (IQR: 64.2 - 77.7) kg and the breast volume was larger with increasing body weight (p=0.014).

Table 1. Anthropometric features of patients.

	Median	Interquartile range (25%-75%)
Body weight (kg)	72	64.2 - 77.7
Haller index (HI)	2.2	1.9 - 2.4
Central lung distance (CLD)(cm)	3.1	2.6 - 4.4
Mid-sternum thickness (cm)	1.7	1.5 - 2.5

Table 2. Descriptive features of the tumor and covered treatment fields.

		Number of patients (n)	Percentage (%)
Localization of tumor (Laterality)	Left	19	47.5
	Right	21	52.5
Internal mammary nodal irradiation	Yes	15	37.5
	No	25	62.5
Irradiated breast volume	Small (≤ 975 cc)	7	17.5
	Medium (975-1600 cc)	19	47.5
	Large (≥ 1600 cc)	14	35

Table 3. Dose data according to Internal Mammary Nodal irradiation and breast laterality.

	IMN irradiated (n =15)	IMN non-irradiated (n=25)	p-value	Left breast (n=19)	Right breast (n=21)	p-value
Total Lung						
MLD	10.24 Gy	8.69 Gy	**0.002**	8.32 Gy	10.13 Gy	**<0.001**
V_5	31.69%	26.26%	**0.007**	26.10%	30.28%	**0.035**
V_{10}	20.51%	17.78%	**0.011**	16.92%	20.51%	**<0.001**
V_{20}	17.08%	14.76%	**0.014**	13.93%	17.17%	**<0.001**
Ipsilateral lung						
MLD	18.38 Gy	16.24 Gy	**0.002**	16.89 Gy	17.17 Gy	1
V_5	58.97%	51%	**0.002**	55.77%	52.38%	0.64
V_{10}	38.19%	34.81%	**0.041**	36.48%	35.71%	0.52
V_{20}	31.87%	28.90%	**0.011**	29.92%	30.10%	0.87
Heart						
D_{mean}	3.35 Gy	4.69 Gy	0.22	6.41 Gy	2.18 Gy	**<0.001**
D_{33}	3.02 Gy	3.08 Gy	0.89	12.17 Gy	0.24 Gy	**<0.001**
V_{10}	3.47%	7.37%	0.15	9.57%	0.00%	**<0.001**
V_{25}	2.07%	6.04%	0.11	3.55%	2.61%	**<0.001**
Contralateral Breast						
D_{max}	40.01 Gy	24.99 Gy	**0.014**	26.31 Gy	34.52 Gy	0.12
D_5	6.75 Gy	4.23 Gy	**0.010**	5.81 Gy	4.61 Gy	0.40
V_5	5.24%	3.39%	**0.021**	4.46%	3.74%	0.52
D_{mean}	1.73 Gy	1.31 Gy	0.057	1.46 Gy	1.47 Gy	0.37

Abbreviations: Internal mammary nodes (IMN), mean lung dose (MLD), maximum dose (D_{max}), mean dose (D_{mean}), V_5, V_{10}, V_{20}, V_{25} (the percentage of organ volume covered by 5 Gy, 10 Gy, 20 Gy and 25 Gy respectively), D_5 and D_{33} (dose received by 5% and 33% of the organ respectively).

In this study, we divided the patient cohort into two subgroups based on mid-sternum thickness: those with a mid-sternum thickness of ≤1.7 cm and those with a mid-sternum thickness >1.7 cm. The subgroup with mid-sternum thickness ≤1.7 cm had a contralateral breast V_5 of 2.40% and D_5 of 3.97 Gy. On the other hand, the subgroup with mid-sternum thickness >1.7 cm showed higher contralateral breast V_5 of 5.95% and higher D_5 of 6.51 Gy (p=0.006 and p=0.001, respectively). Based on the analysis of contralateral breast D_{max} and D_{mean} values, the subgroup of patients with a mid-sternum thickness of ≤1.7 cm had a D_{max} of 20.68 Gy and a D_{mean} of 1.19 Gy, whereas the subgroup with mid-sternum thickness >1.7 cm had a higher D_{max} of 41.60 Gy and D_{mean} of 1.77 Gy. The difference between the two subgroups was statistically significant (p<0.001 for D_{max} and p=0.01 for D_{mean}). Analysis comparing two groups that were divided according to the CLD and HI revealed no statistically significant difference in terms of OAR doses. The mean breast volume of the

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patients was recorded as 1333 ± 573 cc. The patients were originally separated into three groups according to irradiated breast volume. However, due to the small sample size in the group with small breast volumes, the decision was taken to merge the small and medium-sized breast groups. This resulted in the analysis of only two groups. The ipsilateral lung V_{10}, V_{20}, and MLD values were higher in patients with large breast volumes compared with those with small and medium breasts ($p=0.034$, $p=0.039$, and $p=0.018$, respectively), as well as total lung V_5, V_{10}, V_{20}, and MLD ($p=0.006$, $p=0.001$, $p=0.002$, and $p<0.001$, respectively). There was no difference regarding contralateral breast doses according to the breast volume.

DISCUSSION

For node-positive or high-risk node-negative breast cancer, adding medial supraclavicular and internal mammary irradiation can significantly improve disease-free survival and reduce disease-related mortality rates (17). Moreover, the Danish Breast Cancer Cooperative Group (DBCG) trial showed that for node-positive early-stage cases, adding IMNI to designed fields improved disease-free survival, as well as breast cancer mortality (18). Despite the benefits of irradiating internal mammary lymph nodes, attention should be paid to its potential toxicity, particularly in patients with breast cancer on the left side.

Ensuring the delivery of a safe dose for the heart is a substantial concern when adding IMN to treatment fields due to its well-known risk of increasing doses and cardiovascular disease risk (19-22). Studies showed that the use of modern radiotherapy techniques such as IMRT, volumetric modulated arc therapy (VMAT), helical tomotherapy, and proton therapy, doses to OARs could further be reduced (23-25). The DIBH technique has repeatedly been shown to decrease heart and lung doses while appropriately covering the targets (26-29). In instances of increased heart and lung doses, DIBH can be another helpful tool (30). In less developed countries, radiotherapy techniques may not be sufficient. Especially in these countries, when applying internal mammary lymph node irradiation, patients should be selected carefully, considering toxicity.

CLD shown to be correlated with ipsilateral lung dose in 2D conformal radiotherapy (31). Even with 3-dimensional conformal radiotherapy (3D-CRT) and IMRT techniques, CLD is a useful parameter that suggests increased lung doses, but correlation with multi-field IMRT was weaker (32). CLD has been suggested to be related to the irradiated volume of the heart besides the irradiated volume of the lung in a study evaluating breast-conserving surgery followed by 3D-CRT (33). Vees *et al.* demonstrated similar results in 3D-CRT plans regarding CLD and heart doses (V_{20}, V_{40}, irradiated volume) (34). In addition, in a study that predicted the need for IMRT in breast cancer using anatomic measurements, it was reported that an increase in CLD increased the frequency of the need for IMRT (35). We found no correlation between CLD and lung and heart doses. This is likely due to the use of forward IMRT, which allows more conformal plans and lower doses to the heart.

Stahl *et al.*'s research evaluating patients with breast cancer with pectus excavatum (PE) showed that a higher HI was predictive for higher mean cardiac dose, and the potential use of the HI in guiding cardiac avoidance techniques should be kept in mind (36). On the other hand. Lee *et al.* investigated the impact of anatomic factors on mean cardiac dose in a study including a cohort of 80 patients with left-sided breast cancer treated with two opposed tangential fields, and no significant association was found between the HI and mean cardiac dose (37). The researchers speculated that the lack of association might be due to the limited presence of individuals with PE (HI ≥3.3) because the mean HI of the cohort was 2.5 (37). Likewise, our results revealed no clear link between the HI and the cardiac radiation doses. It is believed that the lack of correlation could be attributed to the lower HI mean of our cohort compared with those with PE.

A study evaluating the effect of anatomic measurements on normal tissue protection in patients with small-sized breasts with left-sided cancer showed that greater mid-sternum thickness increased cardiac protection (38). Patients with high mid-sternum thickness should be careful about their contralateral breast doses in terms of secondary cancer development. In a study evaluating patients with left-sided breast cancer treated with 3D-CRT, patients with breast volume greater than 650 cc were suggested as a predictive group for increased irradiated heart volumes (34). Bhatnagar *et al.* showed that for patients treated with IMRT with larger breast volumes, the contralateral breast dose increased significantly, believed to be due to scattered dose. However, the results showed no increment in IL and heart doses (39). Hannan *et al.* revealed that increasing breast volume led to higher mean and maximum heart doses, albeit within acceptable limits, in IMRT planning (40). In patients with large breast volume, techniques such as DIBH, IMRT, and VMAT should be considered in terms of lung protection. Applying radiation therapy in the prone position for treating breast cancer increases lung protection, regardless of the radiotherapy technique, especially for patients with pendulous breasts (41). Patients with large breasts can also be treated in the prone position to reduce OAR doses. However, the prone position may not be suitable for patient comfort.

There is a concern about scattered radiation

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causing contralateral breast cancer [42]. Moreover, increased peripheral aromatization of androgens (testosterone and androstenedione) to estradiol and estrone, which is a very well-known risk factor for hormone-positive breast cancer, is much more prominent in patients with higher body weight due to the excess fat tissue [43]. It is crucial to consider this in the planning of treatment and follow-up of patients.

CONCLUSION

In the plans with forward IMRT, CLD exhibits limited efficacy for predicting an escalation in OAR doses. Our results showed that it is important to pay attention to contralateral breast doses in patients with high MST, and lung doses in patients with large breast size. Although the use of IMRT plans is commonly preferred, for selected patients, considering simpler 3D-CRT plans to save time and reduce costs may be warranted, by considering anthropometric parameters. Looking ahead, computer-guided artificial intelligence data processing systems may be able to design individualized treatment fields and beam angles based on the patient's anthropometric variables.

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Ethical statement: The authors are accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part are appropriately investigated and resolved. This study was approved by the Akdeniz University Clinical Research Ethics Committee on May 22nd, 2019, (Decision no: 496) and conducted in accordance with the Helsinki Declaration (1964). Informed consent was not obtained from the patients because patient data were collected retrospectively,

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