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Internal mammarial lymph node radiotherapy in obese patients with breast cancer, at what expense?

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► ***Original article***

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ABSTRACT

Background and Aim: The incidence of internal lymph node (IMN) involvement was 4- 65% in breast cancer patients. Despite studies indicating the positive effects of IMNRT on the oncological results, most of the clinicians avoided IMNRT because of the toxicity related to the increased dose of organs at risk (OAR). We aimed to compare the dosimetric results of RT plans with and without IMN containing planning target volumes (PTVs) using helical tomotherapy (HT) in obese patients. ***Materials and Methods:*** The PMRT data of 23 obese patients were evaluated retrospectively / dosimetrically. Two PTVs with and without IMN were defined and two separate plans were made with HT. Dose received by IMN and OAR were compared. ***Results:*** The untargeted IMN V_{40} were calculated between 0% to 99%. When the plans are evaluated in terms of critical organs, the inclusion of the IMN into the target volume, the most significant adverse effect was observed in heart doses in the left chest wall (CW) irradiation. The significant increases in cardiac V_5 (% 62.6 vs %48.6 p=0.007), V_{10} (%38.2 vs %23.2 p=0.011), V_{20} (%14.15 vs %9.06 p=0.045) and maximum heart dose (48.04 vs 43.2 p=0.043) were observed in the left-side CW irradiations that involving the IMN. In CW irradiation on the right side with IMN, only a significant increase in mean heart dose (5.44 vs 4.52 p=0.036) was observed. Lung V_5 doses were increased by inclusion with IMN in both sides. There was no difference in the contralateral breast doses in both plans for both sides. ***Conclusions:*** If the IMN is not targeted, some of the patients are getting appropriate doses in obese patients.

Keywords: *Internal Mammary Nodal Area, Breast Cancer, Intensity-modulated radiation therapy.*

INTRODUCTION

Postmastectomy radiotherapy (PMRT) has proven a survival benefit in T3-4 or node positive breast cancer [1,2]. Regional nodal irradiation (RNI) is a valuable component of the PMRT and the main targets are axilla, supraclavicular fossa (SCF) and IMN [3]. RNI improves overall survival (OS), disease free survival (DFS) and reduces mortality of the breast cancer patients [4-10].

IMN is anatomically located in the parasternal space medial to the breast. Malign drainage in this region is mostly observed in centromedial tumors, though it may also occur in all quadrants, even in the upper outer quadrant the most frequent breast cancer location. In surgical series, the incidence of IMN involvement in axillary node-negative patients was 4-9% and it varies between 16% and 65% in patients with nod-positive status [10].

Despite these high rates of IMN involvement, the recurrence rates reported in this field with PMRT are <1% [5]. The expected contribution from IMN RT does not only include prevention of local recurrence but does also increase DFS and

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OS. Survival benefit is proved with the metaanalysis by Budach *et al.* [11].

Several techniques can be used in breast cancer RT involving IMN (electron, photon IMN, wide tangents, and IMRT). Novel RT technics have provided dosimetric benefit in many disease sites in terms of doses received by OAR [10,12-14].

Additionally, obesity is a risk factor for breast cancer. However, the dose distribution of radiotherapy is also affected by the physical characteristics of the patient. In our study, the effect of IMN on radiotherapy was evaluated in obese patients. There are limited articles on this topic [1-5]. In this study, 23 obese patients who previously received chest wall radiotherapy with Helical Tomotherapy (HT) were re-planned with 2 different target volumes either containing IMN or not. We aimed to compare dosimetric outcome with or without IMN RT.

MATERIALS AND METHODS

The data of 30 patients with a median Body Mass Index (BMI) of 32 kg/m^2 (range 29-45) who are diagnosed with invasive ductal carcinoma (IDC) were evaluated dosimetrically and retrospectively. The study was conducted in accordance with the Helsinki Declaration, which was approved by the Ethics Committee of Ankara Atatürk Training and Research Hospital in April 2017. Modified radical mastectomy (MRM) were applied to all of the patients. After completing the adjuvant chemotherapy, the patients who were treated between 01.01.2016 to 01.01.2018 with HT were included in this study. Seven patients with missing data were excluded from the study. 11 patients who had right side chest wall (CW) and 12 patients who had left side CW RT were included. The planning target volumes (PTV) of 23 patients were again contoured and planned with and without IMN. IMN and OAR data were compared dosimetrically.

CT simulation

The planning computerized tomography (CT) simulation was made in the supine position with Aquilion LB Toshiba. The patients were laid down on the breast bed as the table would be parallel to the patient's midsternal line. The breast bed was inclined at 7-15 degrees, the arm on the RT side was removed, 90 degrees from the shoulder and elbow to the abduction position. Operation scars and drain areas were marked with lead wire. The simulation area was determined to be the C3 vertebra at the top and 5 cm below the end of the contralateral breast at the bottom. Tomography was performed at 3 mm cross section without contrast agent. The comfort of the patient was emphasized because the duration of the treatment was predicted to be longer with HT compared to 3D conformal RT.

Contouring of target volumes and critical organs

The images were transferred to the contouring computers and the planning unit according to the electron density values in comparison with Hounsfield Unit (HU) values defined by a special phantom.

The RTOG guide was used to contour the patient's clinical target volumes (CTVs), and OARs. The PTV was created by an additional 3 mm margin around CTV. The patients included in the study were previously contoured by 6 different radiation oncologists. The researchers checked the appropriateness of the target volumes and OARs according to the RTOG criteria. Two different PTVs were generated according to the CTV; CTV with CW+ axilla + SCF + IMN and the same CTV without IMN. The IMN area was contoured with a 5 mm margin throughout the first 4 intercostal spaces. As a result, two separate plans for 2 different PTVs; PTV containing IMN (PC-IMN) and PTV not containing IMN (PNC-IMN) were created for each patient on the same planning tomography. Prescription and Treatment Planning: A total of 50 Gy in 25 fractions was prescribed.

The HT treatment planning system (version 4.8) is an inverse planning system that performs dose calculation with the Superposition-Convolution algorithm. 6MV single energy planning is done. When planning radiotherapy;

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it is necessary for the user to enter the TPS system for the non-3D-CTT specific parameters such as field width, modulation factor and pitch factor which was 5cm, 2.0 and 2.15-2.3 respectively. These parameters are determined by the user according to target position, shape and size and they directly affect the quality and duration of the treatment. The plans were evaluated by the dose volume histogram (DVH).

In all plans, the maximum dose in the PTV was not exceeded by 110% and the PTV was considered to be as comprehensive as the reference isodose (47.5 Gy of isodose, 95% of 50 Gy given as a prescription). In addition, the following parameters were determined for each PTV volume in order to be able to see doses in all OAR volumes and to evaluate them in terms of statistical significance.

IMN; D_{90}, D_{95}, V_{40}, V_{45}
Heart; D_{max}, M_{HD}, V_5, V_{10}, V_{20}, V_{25}, V_{30}
Ipsilateral and contralateral lung; MLD, V_5, V_{10}, V_{20}, V_{30}
Contralateral breast; V_3, V_4, V_5

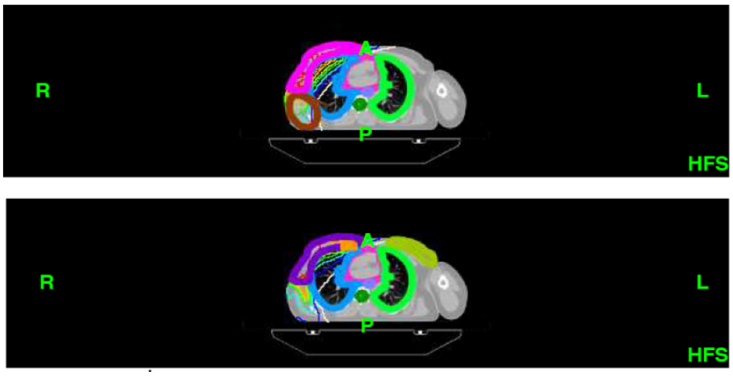

Figure 1. Patients were contoured in two separate volumes with and without the IMN.

Statistical analysis

SPSS Ver. 20 software package was used for statistical analysis. The characteristics of the patients and categorical data were evaluated by Chi-square test. The statistical and visual examination was performed to confirm if the data has distributed normally. Normal distribution was determined and parametric tests were used. Dependent and independent two-group data analysis were evaluated by student *t-test*. ANOVA was performed when there were three or more variables. Pearson correlation analysis was used for the relationship between variables. The significance limit was determined as $p< 0.05$.

RESULTS

23 non-metastatic breast cancer patients diagnosed between January 1, 2016 to February 2, 2018, who were treated with HT were evaluated retrospectively / dosimetrically. The median age of the patients was 53 (range 33-71). 11 patients had right side breast tumor and 12 patients had left side breast tumor. Sixteen (69%) of the patients were T2, 6 (26%) were T3 and only 1 (4.3%) were T4. 11 (47%) patients were N1, 6 (26%) patients were N2, and 6 (26%) patients were N3. The pathology of all the patients was invasive ductal carcinoma. 1 (4.3%) patient was grade 1, 6 (26%) patients were grade 2 and 16 (69%) patients were grade 3. Median tumor size was 5 cm (range 1.8-17 cm) (table 1). In patients with a right breast tumor, the median tumor size was 5.5 cm (range, 3.5-7), and the median tumor size of patients with the left-sided tumor was 4.65 cm (range 1.8 -7 cm). The mean volume of PTV was 999cc (SE: 65.5) and the median volume was 1004cc (range 519-1600). The mean PTV for patients with right localization was 1099cc (SE: 34), while the median was 1100cc (range 519-1600). The mean PTV for patients with left-sided tumors was 908.9cc (SE: 93, 9), while the median was 820cc (range 556-1595).

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Comparison of internal mammary nodal doses

IMN doses were assessed in 23 patients with two separate plans, based on the D_{90}, D_{95}, and the V_{40}. The data are summarized in table 2 and table 3 D_{90} in IMN plans were around 40 Gy in 21.7 % of the patients.

Table 1. Patient's Demographics

Localization	Right	11 (47.8%)
	Left	12 (52.2%)
T Stage	T_2	16(69.6%)
	T_3	6(26.1%)
	T_4	1(4.3%)
N Stage	N_1	11(47.8%)
	N_2	6(26.1%)
	N_3	6(26.1%)
Grade	Grade 1	1(4.3%)
	Grade 2	6(26.1%)
	Grade 3	16(69.6%)
Age	Median	53 (range 33-71)
PSFT	Median	1.87 cm(range1.32-3.4)
BMI	Median	32.8(27.4-45.7)

Table 2. Comparison of IMN doses for the right chest wall.

		Mean(Gy)(SE)	Median(Gy)	p
D_{90}	İMN+	47.34 (1.078)	48 (range 39-52)	<0.001
	İMN-	32.033 (2.69)	32 (range 11.09-42.87)	
D_{95}	İMN+	46.09 (1.36)	47.30 (range 36.48-52.3)	<0.001
	İMN-	29.19 (2.82)	28 (range 9.19-42.37)	
V_{40}	İMN+	98.41 (0.94)	98 (range 89-100)	<0.001
	İMN-	52.28 (9.87)	43.08 (range 0-99)	
V_{45}	İMN+	87.93 (5.16)	99 (range 46-100)	<0.001
	İMN-	24.93 (9.37)	10.73 (range 0-74)	

IMN = internal mammary node, D_{90} = the dose at which 90% of the volume was taken, D_{95} = the dose at which 95% of the volume was taken, V40 = volume receiving 40 Gy, V_{45} = volume receiving 45 Gy

Table 3. Comparison of IMN Doses for left chest wall.

		Mean (Gy) (SE)	Median (Gy)	p
D_{90}	İMN+	48.2 (0.63)	48.94 (range 42.16-50.5)	<0.001
	İMN-	31.27 (2.57)	32.74 (range 18.71-47)	
D_{95}	İMN+	47.36 (0.68)	47.94 (range 41.11-50.2)	<0.001
	İMN-	29.64 (2.61)	31.22 (range 16.09-46)	
V_{40}	İMN+	99.78 (0.21)	100 (range 97.43-100)	<0.001
	İMN-	49.66 (9.98)	42.73 (range 2.45-99)	
V_{45}	İMN+	97.23 (2.04)	100 (range 75.21-100)	<0.001
	İMN-	28.68 (9.09)	14.89 (range 0-96)	

IMN = internal mammary node, D_{90} = the dose at which 90% of the volume was taken, D_{95} = the dose at which 95% of the volume was taken, V_{40} = volume receiving 40 Gy, V_{45} = volume receiving 45 Gy

Comparison of ipsilateral lung doses

V_5, V_{10}, V_{15}, V_{20}, V_{30} and mean lung doses (MLD) were calculated and compared. In the left chest Wall irradiation; the left lung V_5 doses were found to be higher in the PC-IMN than PNC -IMN (p=0.049). Similarly, in patients with the right chest wall irradiation, the right lung V_5 was lower in the PC-IMN than those in the PNC-IMN (p=0.063). Differences in other measures were not significant. The results are given in table 4.

Comparison of contralateral lung doses

V_5, V_{10}, V_{15}, V_{20}, V_{30} and mean lung doses (MLD) were calculated and compared. Consistent with the results of the ipsilateral lung, there was a significant difference only in V_5 in both sides. In addition, MLD of the contralateral lung was higher in the PC-IMN compared to the PNC-IMN (table 5).

Comparison of cardiac doses

With the extraction of the IMN fields for the right CW, the mean cardiac dose (MCD) was significantly reduced. In patients with left side disease, the significant decreases in V_5, V_{10}, V_{20},

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and maximum cardiac dose were seen when the IMN was not included in the treatment area. The data is given in table 6.

Table 4. Evaluation of ipsilateral lung dose.

	Right CW IMN+ (%)(SE)	Right CW IMN- (%) (SE)	p	Left CW IMN+(%)(SE)	Left CW IMN-(%)(SE)	p
V_5	64.63 (2.3)	59.67 (1.27)	0.063	63.28 (2.13)	59.75 (1.90)	0.049
V_{10}	44.76 (1.06)	42.66 (1,6)	0.30	42.02 (2.14)	42.48 (1.54)	0.65
V_{15}	36.02 (1.0)	34.24 (1.95)	0.40	32.76 (2.23)	32.56 (1.56)	0.87
V_{20}	29.64 (1.01)	28.52 (1.86)	0.59	24 (2.4)	23.8 (1.4)	0.33
V_{30}	18.87 (1.07)	18.02 (1.83)	0.93	17.08 (1.81)	16.65 (1.35)	0.69
MLD	14.98 (0.39)	14.38 (0.62)	0.47	13.99 (0.63)	12.99 (1.02)	0.33

IMN = internal mammary node, CW= Chest wall, V_5 = volume receiving 5 Gy, V_{10} = volume receiving 10 Gy, V_{15} = volume receiving 15 Gy, V_{20} = volume receiving 20 Gy, V_{30} = volume receiving 30 Gy, MLD=Mean Lung Dose

Table 5. Evaluation of contralateral lung doses.

	Right CW IMN+ (%)(SE)	Right CW IMN-(%)(SE)	p	Left CW IMN+(%)(SE)	Left CW IMN-(%)(SE)	p
V_5	17.14 (3.17)	10.73 (1.27)	0.044	15.32 (4.16)	10.03 (2.36)	0.10
V_{10}	6.33 (1.60)	3 (0.97)	0.11	1.76 (0.79)	1.42 (0.5)	0.58
V_{15}	2.19 (0.88)	0.83 (0.52)	0.21	0.25 (0.13)	0.075 (0.05)	0.16
V_{20}	0.51 (0.36)	0.22 (0.2)	0.55	0	0	NS
V_{30}	0.45 (0.4)	0	NS	0	0	NS
MLD	3.98 (0.59)	2.63 (0.21)	0.016	3.69 (0.89)	2.44 (0.39)	0.083

IMN = internal mammary node , CW= Chest wall, V_5 = volume receiving 5 Gy, V_{10} = volume receiving 10 Gy, V_{15} = volume receiving 15 Gy, V_{20} = volume receiving 20 Gy, V_{30} = volume receiving 30 Gy, MLD=Mean Lung Dose

Table 6. Evaluation of cardiac doses.

	Right CW IMN+ (%)(SE)	Right CW IMN-(%)(SE)	p	Left CW IMN+(%)(SE)	Left CW IMN-(%)(SE)	p
V_5	38.19 (10.01)	30.81 (7.49)	0.21	62,67(9,32)	48.63 (7.59)	0.007
V_{10}	13.96 (3.9)	9.43 (2.55)	0.097	38.23 (6.1)	23.32 (3.99)	0.011
V_{20}	2.93 (1.22)	0.67 (0.26)	0.069	14.15 (2.9)	9.06 (1.69)	0.045
V_{25}	0.615 (0.27)	0.057 (0.005)	0.086	9.76 (2.6)	6.07 (1.4)	0.081
V_{30}	0.24 (0.12)	0	0.088	5.49 (1.6)	3.8 (0.96)	0.162
MHD	5.44 (0.88)	4.52 (0.68)	0.036	9.5 (0.86)	8.7 (1.31)	0.55
Max.	32.34 (3.3)	26.17 (2.44)	0.057	48.04 (1.07)	43.21 (1.84)	0.043

IMN = internal mammary node , CW= Chest wall, V_5 = volume receiving 5 Gy, V_{10} = volume receiving 10 Gy, V_{20} = volume receiving 20 Gy, V_{30} = volume receiving 30 Gy, MHD=Mean Heart Dose, Max.= Maximum Heart dose

Evaluation of contralateral breast

In patients with right side breast tumor, the mean contralateral breast volume (left breast) was 1001cc (SE: 117), median was 1100cc (range 320-1963); In patients with left side breast tumor, the mean volume of the contralateral breast was 1089cc (SE: 155), median volume was 935cc (range 434-1903). No significant effect of IMN was observed in both field irradiation.

Treatment duration

Median of treatment duration was 502 seconds (range 351-845) in PC-IMN and 510 seconds (range 344-1001) in PNC-IMN (p=0.84).

DISCUSSION

According to our results; in adjuvant breast irradiation with HT, the IMN does not receive

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appropriate doses unless included in the target volume. Approximate D_{90} doses were under 40 Gy in 80% of the patients. In addition, the doses of untargeted IMN were varied. Doses of untargeted IMN V_{40} were between 0% and 99% in PNC-IMN. Surprisingly, about 1/5 of patients received 45 Gy to IMN even when it is not included in the target volume. The addition of IMN negatively affected heart doses, mostly in the left GD irradiation. In the left side PC-IMN, significant increases in cardiac V_5, V_{10}, V_{20}, and maximum heart doses were observed. A significant increase in MHD was observed in the right-side PC-IMN. Both ipsilateral and contralateral lung V_5 doses were increased by the addition of IMN for both sides. No significant effect has been observed in the doses of the contralateral breasts or the duration of treatment.

Un-planned IMN doses were previously evaluated dosimetrically with 2D and 3D techniques. In the study by Proulx *et al.,* 50 breast patients treated with 2D technique were evaluated [15]. Even if the IMN is not targeted, it was inside the target volume completely in 14% of the patients, and partially in 40% of the patients. They also evaluated the relationship between IMN dose variability and anatomical structures and found an inverse relationship between presternal fat tissue thickness and IMN doses. Of the 11 women with more than 1 cm of presternal fat tissue, none of the IMN fields were in the standard PTV. In addition, Anterioposterior (AP) and transverse (T) thoracic differences, and skeletal diameter ratios (AP: T ratio) were also assessed and no significant correlation was found. Similarly, Hare et al., showed that IMN were inside RT field partially in 73% of patients, and completely in only 14% of the patients treated with the standard tangential field. They also found out that IMN coverage was inversely proportional to the pre-sternal fat thickness (PSFT) [16]. In another study by Sapienza *et al.*, 112 breast patients were evaluated with 3D technique, IMN area was inside PTV completely in only 6 patients, partially in 83 patients, while 23 patients had IMN completely outside PTV area [17]. D_{mean} was measured as 45 Gy if the IMN is completely inside the area, as 23.1 Gy if IMN is partially inside, and as 9.97 if IMN is outside the area. In our study, unplanned IMN doses in the IMRT technique were evaluated on obese patients. PSFT measurements of all of our patients were above 1 cm. IM/IGRT technique was used with Tomotherapy. Although this provides a significant advantage in preserving the OAR, it has made it very clear that the target areas must be clearly defined. Dose received by IMN were highly variable with PNC-IMN plans. İf IMN is not targeted in this patient group, it is not known whether it has received the appropriate doses.

In the standard tangential fields, it is obvious that IMN area was not adequately covered. When the area was expanded to include IMN in the target volume, lung and cardiac doses were increased. Especially in the left breast irradiation, cardiac toxicity is a concern [18]. It is known that there is a 10-15 years period between the clinical findings of heart disease and radiation exposure. Many studies have also found that cardiac damage associated with RT can occur earlier, even within the first five years. In a study by Verma, Cardiovasculer disease (CVD) was observed more frequently in patients receiving left side PMRT. Modern techniques provide better OAR doses with fewer side effects [8]. And may contribute to stabilize the increased radiation induced heart disease (RIHD) risk in the presence of IMNRT [19]. Significantly higher cardiac doses were also observed in PC IMN in the left side RT plan.

The risk of prolonged major cardiac complications is increasing in correlation with mean heart dose. An average 1 Gy rise in mean heart dose (MHD) causes an estimated 7.4% increase in heart disease risk [20]. In a study by Popescu, thirty patients with IMN field were planned with both IMRT and 3D technique and compared dosimetrically. With IMRT, better HI (HI 0.95 vs 0.74,), CI (CI 0.91 vs 0.48), cardiac V_{30} dose (1.7% vs 12.5%, $p < 0.001$), V_{20} ipsilateral lung dose (17% vs 26.6% $p < 0.001$) at the expense of increased contralateral lung V_5 (13.7% vs 2%, $p < 0.001$) and contralateral breast V_5 (29% vs 7.9%, $p < 0.001$) [21]. In another dosimetric study using IMRT with deep

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inspiration breath hold (DIBH), a 20% (p=0.0002) reduction in MHD and a 9% (p<0.001) reduction in LAD dose were observed. In a dosimetric comparison of VMAT and IMRT; in IMRT plans, lower heart and LDA doses were obtained compared to VMAT [22]. Proton therapy, a novel technique, enables lower cardiac doses, such that MHD can be reduced from 8 Gy to 2.6 Gy. Although the availability of proton therapy increases, a small number of patients have access yet [23]. In this study, there was a significant increase in cardiac doses in PC- IMN, especially in the left CW irradiation. MHD was 8.4 Gy in left breast PC-IMN, and dropped to 4.2 Gy in PNC-IMN (p <0.001) [12]. According to our results, cardiac doses were significantly increased, especially in left CW irradiation. Moreover, planning optimizations to reduce cardiac doses have resulted in prolonged treatment times. When right and left side RT plans were evaluated; MHD was 7.5 Gy in PC IMN and 6.7 Gy in PNC IMN (p=0.2). Lower MHD doses were achieved in right side in both plans. The addition of IMN to the target volume resulted an increase in MHD of 0.9 Gy (p=0.036), in the right side and 0.8 Gy (p=0.55) in the left.

Another important risk factor for PMRT is pulmonary toxicity. In the EORTC, MA.20, Danish studies, IMN-RT slightly increased the pulmonary toxicities, but they remained below the predictions [16]. In current studies, mean lung doses are 7-18 Gy in the ipsilateral and 0.1-3 Gy in the contralateral lung [23]. V_{20} limitations have significantly reduced radiological changes after RT for breast cancer. Symptomatic pneumonia is rare since current dose limits are used. However, using only doses of V_{20} and MLD to determine pulmonary risks may not be sufficient. Goldman *et al*. Reported that V_{13} showed a stronger correlation with radiation changes in CT than V_{20} and MLD[24]. IMRT and tangential plans were performed on 30 breast cancer patients who were treated with breast conserving surgery (BCS) and received whole breast RT and significantly better CI, HI, pulmonary V_{20}, heart V_{30} was obtained with the IMRT technique. However, the contralateral lung V_5-V_{10} and contralateral breast V_{10} were increased in the case of IMRT [25]. In the case of irradiation with IMN using the IMRT technique, although a better target volume coverage was achieved, a significant increase in lung V5 doses was observed [26]. This can lead to decreased rates of acute radiation pneumonitis and chronic pulmonary fibrosis. But increased low dose areas and prolonged RT periods increase the risk of secondary cancer. In our study, the contralateral lung V_5 increased about 7% (p=0.044); for the right side in PC IMN compared to PNC-IMN and increased by 5% (p0.1) for the left side. MLD is 1.35 Gy in the right CW (p=0.016); while the left CW increased by 1.25 Gy (p=0.083).

Data based on breast cancer research have shown that radiotherapy significantly reduces the risk of recurrence and breast cancer mortality but at the expense of increased secondary cancer risk such as lung, esophagus, soft tissue, contralateral breast and leukemia [27]. Between 1983 and 1992, increased risk of lung cancer was observed in breast cancer survivors who received RT. After 1993, in parallel with significant developments in the RT and surgical techniques, the risk of developing secondary cancer decreased. It could be related not only to the dosimetric advantage of newer techniques but also the less preference of IMN-RT [23]. For example, in the 1980s, after breast-conserving surgery, 62% of women were irradiated with IMN-RT, but after 1990s this ratio decreased to 1% [28]. The risk of developing lung cancer is higher for ipsilateral lung than contralateral. The prolonged duration of treatment with IMRT and associated increased scattering exposure and high low-dose volumes increase the risk of secondary cancer in patients with long-term survival [29]. In our study, there is a significant increase in lung V_5 of PC-IMN.

Most studies have not provided clear data on the effect of IMN-RT on contralateral breast cancer. Since breast cancer patients have already a predisposition to develop second breast cancer, it is difficult to assess secondary breast cancer risk related to the irradiation. The tangential field for IMN RT is defined as the 1cm lateral from the midline which causes radiation exposure to the contralateral breast either directly or by scattering [30]. In a study

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comparing IMRT and conventional techniques dosimetrically, an increase was observed with IMRT in breast V_5 (29% vs 7.9% P <0.001) [31]. In another study comparing 2D, 3D, and IMRT dosimetrically, contralateral breast V_3 was examined and it was found to be significantly higher with IMRT than the other two methods (P = 0.010, P = 0.005), but no significant difference was observed between 2D and 3D (P = 0.790) [32]. Similarly, increased V_3 and V_4 was reported with the IMRT in the contralateral breast [33]. In our study, two IMRT plans were compared and the presence or absence of the IMN did not appear to have a significant effect on the dose of CB V_3, V_4, V_5.

Like many modern techniques, helical Tomotherapy has prolonged treatment durations. This may cause increased intrafractional uncertainties. Ricotti *et al*. evaluated the intrafractional motion during normal breathing in 20 breast patients with a median age of 51 using the Spectra monitoring system. A median of 6 evaluations was performed for each patient. It was observed that the baseline deviation of the body caused more pronounced uncertainties than the respiratory motion [34]. In our study, the mean duration of treatment for patients is 502 seconds (range 351-845) for PC-IMN and 510 seconds (range 344-1001) for PNC-IMN plans (p=0.84). Addition of IMN to the target volume did not prolong treatment duration.

In addition to dosimetric studies, IMN-RT benefit was assessed in randomized trials. It was shown that old techniques did not contribute to survival and cause increased side effects. Unlike them, a survival benefit without increased cardiac toxicity was observed with current RT techniques in expense of increased pulmonary toxicity [8, 33]. A Danish prospective study reported a 4% survival benefit with IMN-RT [35].

There are some limitations to this study. Firstly, data are evaluated retrospectively. Secondly, only obese patients are included and the results of the study cannot be generalized for all breast cancer patients. Lastly, Helical Tomo Therapy was used as IMRT technique and HT is only available in a limited number of centers.

In this study, it was seen that the PNC-IMN received highly variable doses in overweight patients. Moreover, it was observed that one in 5 patients received a dose over 40 Gy even if not targeted. This can lead to confusion when evaluating the survival effect of IMN-RT. Therefore, it may be more accurate to analyze the plans dosimetrically and identify the patients who received IMN-RT and those who did not to assess the benefit in studies using modern techniques.

CONCLUSION

The indication of IMN-RT is based on an individual assessment of the benefit-loss balance based on the characteristics of the patient and the tumor since cardiac and bilateral lung V5 doses increase with IMN-RT. Even if the IMN is not targeted, some of the patients are getting appropriate doses in obese patients. Therefore, in studies using modern RT techniques, dosimetric evaluation of the distinction between groups undergoing IMN-RT and not undergoing IMN-RT may help to clarify survival benefit.

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REFERENCES

1. Recht A, Comen EA, Fine RE, Fleming GF, Hardenbergh PH, Ho AY, *et al.* (2016) Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. *Pract Radiat Oncol, **6**: 219-34*.
2. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, et al. (2014) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet, **383**: 2127-35*.
3. Bedrosian I, Hu CY, Chang GJ (2010) Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. *J Natl Cancer Inst, **102**: 401-9*.
4. Poortmans PM, Kirkove C, Limbergen EV, Budach V, Struikmans H, Collette L, *et al.* (2015) Internal Mammary and

[DOI: 10.18869/acadpub.ijrr.18.2.191]

Medial Supraclavicular Irradiation in Breast Cancer. *N Engl J Med, **373**: 317-27*.
5. Leite ET, Ugino RT, Santana MA, Ferreira DV, Lopes MR, Pelosi EL, da Silva JL, *et al.* (2016) Incidental irradiation of internal mammary lymph nodes in breast cancer: conventional two-dimensional radiotherapy versus conformal three dimensional radiotherapy. *Radiol Bras, **49**: 170-5*.
6. Vrana D, Gatek J, Cwiertka K, Lukesova L, Koranda P (2013) Internal mammary node management in breast cancer. A review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub, **157**: 261-5*.
7. Nikolaevich NS and Vasilevich KS (2017) Why do we need irradiation of internal mammary lymph nodes in patients with breast cancer: Analysis of lymph flow and radiotherapy studies. *Rep Pract Oncol Radiother, **22**: 37-41*.
8. Verma V, Vicini F, Tendulkar RD, Khan AJ, Wobb J, Edwards -Bennett S, Desai A, Shah C (2016) Role ofInternal Mammary Node Radiation as a Part of Modern Breast Cancer Radiation Therapy: A Systematic Review. *Int J Radiat Oncol Biol Phys, **95**: 617-31*.
9. Chang JS, Park W, Kim YB, Lee IJ, Keum KC, Lee CG, Choi DH, Suh CO, Huh SJ (2013) Long-term survival outcomes following internal mammary node irradiation in stage II-III breast cancer: results of a large retrospective study with 12-year follow-up. *Int J Radiat Oncol Biol Phys, **86**: 867-72*.
10. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, *et al.* (2015) Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med, **373**: 307-16*.
11. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C (2015) Adjuvant radiation therapy of regional lymph nodes in breast cancer – a meta-analysis of randomized trials- an update. *Radiat Oncol, **10**: 258.*
12. Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby S. (2015) Exposure of the heart in breast cancer radiation therapy: A systematic review of heart doses published during 2003 to 2013. *Int J Radiat Oncol Biol Phys, **93**: 845-53*.
13. Teke F, Doğan H, Kaya M, Gümüş M (2017). Dosimetric comparison of TomoDirect and TomoHelical plans in post-mastectomy chest wall radiation therapy. *Int J Radiat Res, **15:** 259-66.*
14. Koksal C, Kesen N, Akbas U, Kalafat U, Ozkaya K, Okutan M, et al (2017). Dosimetric comparison of 3-dimensional conformal and intensity-modulated radiotherapy techniques for whole breast irradiation in the prone and supine positions. *Int J Radiat Res, **15:** 353-62.*
15. Proulx GM, Lee RJ, Stomper PC (2001) Internal mammary lymph node inclusion in standard tangent breast fields: effects of body habitus. *Breast J, **7**: 111–6*.
16. Hare GB, Proulx GM, Lamonica DM, Stomper PC (2004) Internal mammary lymph node (IMN) coverage by standard radiation tangent fields in patients showing IMN drainage on lymphoscintigraphy: therapeutic implications. *Am J Clin Oncol, **27**: 274–8*.
17. Sapienza LG, Chen MJ, Gomes MJL, Mansur DB (2016) Unintended irradiation of internal mammary chain – Is that enough? *Reports of Practical Oncology and Radiotherapy, **21**: 25-30*.
18. Kaidar-Person O, Zagar TM, Oldan JD, Matney J, Jones EL, Das S, *et al.* (2017) Early cardiac perfusion defects after left-sided radiation therapy for breast cancer: is there a volume response? *Breast Cancer Res Treat, **164**: 253- 62*.
19. Rygiel K (2017) Cardiotoxic effects of radiotherapy and strategies to reduce them in patients with breast cancer: An overview. *J Cancer Res Ther, **13**: 186-92*.
20. Mondal D and Sharma DN (2018) External beam radiation techniques for breast cancer in the new millennium: New challenging perspectives. *J Egypt Natl Canc Inst, **28**: 211-8*.
21. Popescu CC, Olivotto IA, Beckham WA, Ansbacher W, Zavgorodni S, Shaffer R, WaiES, *et al.* (2010) Volumetric modulated arc therapy improves dosimetry and reduces treatment time compared to conventional intensity-modulated radiotherapy for locoregional radiotherapy of left-sided breast cancer and internal mammary nodes. *Int J Radiat Oncol Biol Phys, **76**:287-95*.
22. Sakka M, Kunzelmann L, Metzger M, Grabenbauer GG (2017) Cardiac dose-sparing effects of deep-inspiration breath-hold in left breast irradiation : Is IMRT more beneficial than VMAT? *Strahlenther Onkol, **193**: 800-11*.
23. Henson KE, McGale P, Taylor C, Darby SC (2013) Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. *Br J Cancer, **108**: 179-82*.
24. Blom Goldman U, Wennberg B, Svane G, Bylund H, Lind P (2010) Reduction of radiation pneumonitis by V20-constraints in breast cancer. *Radiat Oncol, **5**: 99*.
25. Ayata HB, Güden M, Ceylan C, Kücük N, Engin K (2011) Comparison of dose distributions and organs at risk (OAR) doses in conventional tangential technique (CTT) and IMRT plans with different numbers of beam in left-sided breast cancer. *Rep Pract Oncol Radiother, **16**: 95-102*.
26. Kaija H and Maunu P (1995) Tangential breast irradiation with or without internal mammary chain irradiation: results of a randomized trial. *Radiother Oncol, **36**: 172-6*.
27. Morton LM, Gilbert ES, Hall P, Andersson M, Joensuu H, Vaalavirta L, Dores GM, *et al.* (2013) Risk of treatment-related esophageal cancer among breast cancer survivors. *Ann Oncol, **23**: 3081-91*.
28. Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, *et al.* (2017) Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. *J Clin Oncol, **35**: 1641-9*.
29. Berrington de Gonzalez A, Curtis RE, Gilbert E, Berg CD, Smith SA, Stovall M, Ron E (2010) Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. *Br J Cancer, **102**: 220-6*.
30. Courdi A, Ferrero JM, Hannoun-Lévi JM (2013) Influence of internal mammary node irradiation on long-term outcome and contralateral breast cancer incidence in node-negative breast cancer patients. *Radiother Oncol, **108**: 259-65*.

[DOI: 10.18869/acadpub.ijrr.18.2.191]

31. Beckham WA, Popescu CC, Patenaude VV, Wai ES, Olivotto IA (2017) Is multibeam IMRT better than standard treatment for patients with left-sided breast cancer? *Int J Radiat Oncol Biol Phys,* ***69****: 918-24*.
32. Zhang F and Zheng M (2011) Dosimetric evaluation of conventional radiotherapy, 3-D conformal radiotherapy and direct machine parameter optimisation intensity-modulated radiotherapy for breast cancer after conservative surgery. *J Med Imaging Radiat Oncol,* ***55****: 595-602*.
33. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C (2015) Adjuvant radiation therapy of regional lymph nodes in breast cancer – a meta-analysis of randomized trials- an update. Radiat Oncol, 10:258.
34. Ricotti R, Ciardo D, Fattori G, Leonardi MC, Morra A, Dicuonzo S, Rojas DP, *et al.* (2017) Intra-fraction respiratory motion and baseline drift during breast Helical Tomotherapy. *Radiother Oncol,* ***122****: 79-86*.
35. Thorsen LB, Offersen BV, Danø H, Berg M, Jensen I, Pedersen AN, et al. (2016) DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer. *J Clin Oncol,* ***34****: 314-20*.

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