

The Effect of Internal Mammary Chain Radiotherapy After Post-Mastectomy on Coronary Arteries and Chambers of Heart: Dosimetric Comparison of Tangential Field FIF and d-IMRT Plans

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OBJECTIVE

The aim of this study was to compare tangential field field-in-field (FIF) and dynamic-intensity-modulated radiotherapy (d-IMRT) techniques in terms of changes in cardiac substructure and coronary arteries doses on dose-volume histogram (DVH).

METHODS

Fifteen patients with the left breast cancer who received radiotherapy to the chest wall (CW) were retrospectively selected. The left main coronary artery, left anterior descending (LAD), circumflex and right coronary arteries, and heart chambers were contoured. D_{mean} , V_5 , V_{10} , and V_{30} for heart chambers; D_{mean} and D_{max} for coronary vessels; and D_{mean} , V_{95} , V_{107} , CI and HI for planned target volume were compared between plans on DVH.

RESULTS

When the internal mammary lymph node (IMLN) field is added to the CW, high-dose volumes of the whole heart and ventricles (V_{30}) and LAD doses are significantly better protected with d-IMRT technique (whole heart V_{30} : 9.4% by 6.2%, ventricle L V_{30} : 17.1% by 9.9%, ventricle R V_{30} : 7.3% by 4.3%, and LAD D_{max} : 52.7 Gy by 51 Gy). All the low-dose volumes of the whole heart and ventricles (V_5 and V_{10}) and all coronary vessels excepting LAD were better protected in the FIF technique.

CONCLUSION

In patients who will undergo IMLN radiotherapy, especially if they have coronary disease, RT technique can be selected according to the vessel where the damage is located. However, more research is warranted on this subject.

Keywords: Coronary vessels; heart protection; heart substructure; internal mammary chain radiotherapy; left anterior descending; left breast cancer.

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Introduction

Post-mastectomy radiotherapy applied to the chest wall (CW) and regional nodes in node-positive breast cancer significantly reduce locoregional recurrences, general recurrences, and breast cancer mortality.[1] It has been shown that internal mammary lymph node (IMLN) metastases are detected at a rate of 28-52% in axillary lymph node (LN)-positive and 5-17% in axillary LNnegative patients.[2,3] After the most recent studies, National Comprehensive Cancer Network guidelines have been updated and IMLN radiotherapy recommendations since 2006 suggested "category 1" when axillary LN \geq 4 positive, and as "strongly considered" if 1-3 positive axillary LNs are found, both after mastectomy and lumpectomy. In a cohort study examining the effect of IMLN radiotherapy on survival, distant metastasis, and breast cancer mortality in early-stage node-positive breast cancer, it was shown that IMLN radiotherapy decreases breast cancer mortality, improves survival, and reduces rates of distant metastases.[4] While the greatest benefit was observed in node-positive medial/central disease, the same benefit was also detected in those with \geq 4 LN positivity independent of localization. No benefit was observed in patients with 1-3 LN positivity and lateral lesions.[4] In the light of these studies, in recent years, we, radiation oncologists, have increased our desire for radiotherapy applied to the field of IMLN. However, an increase in cardiac and pulmonary toxicities, especially in patients with the left breast cancer, is inevitable with the addition of IMLN to the radiotherapy protocol. The left-sided breast radiotherapy is significantly associated with radiation-induced coronary atherosclerosis and cardiac mortality.[5] Computed tomography (CT)-based radiotherapy plans allow for more effective protection of normal tissue structures and also determine the risk of toxicity. In this study, our aim was to compare conventional tangential field field-in-field (FIF) and dynamic-intensity-modulated radiotherapy (d-IMRT) techniques in terms of changes in cardiac substructure and coronary arteries doses on dose-volume histogram (DVH) when IMLN radiotherapy is added to post-mastectomy left CW radiotherapy.

Materials and Methods

Patient Data

Fifteen patients with the left breast cancer who received radiotherapy to the CW after post-mastectomy at Tokat Gaziosmanpaşa University Hospital between January 2020 and June 2021 were selected. Fifteen patients were retrospectively recontoured. Cardiac vessels as the left main coronary artery (LMCA), both proximal and distal left anterior descending (LAD), circumflex (CX) and right coronary arteries (RCA), and heart chambers (right and left atria and ventricles) were contoured with reference to contouring atlas presented by the Danish Multidisciplinary Cancer Group. [6] According to the radiotherapy planning consensus defined by the Radiation Therapy Oncology Group, planned target volume (PTV) for CW was created and IMLN was contoured similarly in all patients as covering the first three intercostal areas (http://www.rtog. org/CoreLab/ContouringAtlases/BreastCancerAtlas. aspx.). The PTV encompassed the CW with the pectoralis muscle, CW muscles, and ribs, and eliminated the outermost 2 mm from the superficial skin surface. This retrospective dosimetric study was approved by the Institutional Review Board and Ethics committee.

Treatment Techniques

For each patient, CT simulation was created with the patient laid in the supine position on the breast board and vacuum bed, with his/her ipsilateral arm was elevated, and CT images were obtained at 3 mm intervals (slice thickness). Fraction dose of 2 Gy was prescribed amounting to a total of 50 Gy, and four different plans were created. These were the FIF and IMRT plans with and without inclusion of IMLN as follows: CW-FIF technique; CW+IMLN-FIF technique; only CW-IMRT technique, and CW+IMLN-IMRT technique. A total of 60 plans were made using the eclipse planning system version 13. In both FIF and IMRT plans, 6 MV photon energy was used as it provides better dose coverage on the CW. D_{mean} , V_5 , V_{10} , and V_{30} for the whole heart (incl. both right and left atria and ventricles); \mathbf{D}_{mean} and \mathbf{D}_{max} for coronary vessels incl. LMCA, LAD, RCA, and CX; and D_{mean}, V₉₅, V₁₀₇, CI (conformity index) and HI (homogeneity index) values for PTV were compared between plans on DVH. The homogeneity index was calculated with (D2-D98%)/ D50%) formula (HI of zero is ideal) and the conformity index was computed as volume of PTV covered by the 95% isodose curve/volume of PTV (CI of 1.0 is ideal).[7]

Figure 1 shows the contouring of the cardiac substructures and the dynamic-IMRT and FIF technique plan comparisons/isodose curves covering 95% of the prescribed dose. The study was analyzed in three parts. In the first part, when the IMLN field is added to the CW radiotherapy in the traditional tangential FIF technique, doses received by the heart and its substructures, in the second part, when the IMLN field is additionally covered by the CW radiotherapy in the d-IMRT tech-



curve representing over 95% of the prescribed dose delivered. Contouring: Right atrium (blue), left atrium (brown), right ventricle (cyan), left ventricle (dark blue), left main coronary artery (light green), left anterior descending (red), circumflex (pink), and right coronary artery (orange).

CT: Computed tomography; RT: Radiotherapy; FIF: Field-in-field; IMRT: Intensity-modulated radiotherapy; L: Left; R: Right; CX: Circumflex; LAD: Left anterior descending; LMCA: Left main coronary artery; PTV: Planning target volume; RCA: Right coronary artery.

nique, doses received by the heart and its substructures, and in the third part, FIF and d-IMRT techniques in the CW+IMLN radiotherapy were compared. The purpose of designing this dosimetric study was to find an answer to the question: "How are the cardiac substructures affected by IMLN radiotherapy and which RT technique protects the cardiac substructures better when IMLN is added to the radiotherapy protocol?"

Statistical Analysis

The results were represented as mean±standard deviation (SD). The two-sided paired t-test was used when the datasets were normally distributed. Otherwise, datasets were compared by Wilcoxon Cox test. These analyses were performed using SPSS version 17 (SPSS Inc., Chicago, USA). All reported P-values were two sided and p<0.05 was considered of statistical significance.

Results

For Cardiac Substructures

In the first part, when we added the IMLN field to the CW in the tangential FIF technique, the only unchanged constant was LAD D_{max} (p=0.195), while a significant increase was found in the doses of all other parameters (Table 1).

In the second part, when we added IMLN field to CW in the d-IMRT technique, while parameters of atrial L V10 (p=109), atrial R V₅ (p=0.317), ventricular L V₃₀ (p=0.292), LMCA D_{mean} (p=0.286), LMCA D_{max} (p=0.549), and LAD D_{max} (p=0.485) did not change, parameters of other cardiac substructures increased statistically significantly when IMLN field was included in the radiotherapy of CW (Table 2).

In the third part, in the comparison of FIF and d-IMRT techniques in CW+IMLN radiotherapy, the whole heart, ventricular L and ventricular R V_{30} values, and LAD D_{mean} and D_{max} were found to be significantly superior in d-IMRT technique. Other parameters (LMCA, RCA, and CX D_{max} and D_{mean} ; V_5 and V_{10} of the ventricles; and the whole heart) were found to be statistically significantly superior in the FIF technique (Table 3).

For PTV

PTV coverage (V_{95}), V_{107} , and HI did not change, but CI worsened (p<0.001) when IMLN field was added to the CW in the FIF technique. All parameters related to PTV (D_{mean} , V_{95} , V_{107} , CI, and HI [for all p>0.05]) did not change when IMLN field was added to CW in IMRT technique. In the third part, in the comparison between FIF and d-IMRT techniques in CW+IMLN radiotherapy, PTV D_{mean} , V_{95} , V_{107} , and CI values were found to be significantly superior in the d-IMRT technique (for all p<0.001). Only PTV homogeneity index was not significantly different (p=0.203).

FIF technique D _{mean} , D _{max} as cGy V ₅ , V ₁₀ , V ₃₀ , V ₉₅ , and V ₁₀₇ as %	CW		CW+IMLN		р
	Mean	SD	Mean	SD	
Whole heart					
D _{mean}	640.3	171.2	689.1	186.6	0.001
V ₅	17.9	4.5	19.1	4.7	0.004
V ₁₀	11.9	3.7	13.2	4.1	0.002
V ₃₀	8.4	3.2	9.4	3.3	0.007
Atrium L					
D _{mean}	63.8	14.0	67.3	15.2	0.001
Atrium R					
D _{mean}	126.3	256.7	64.1	14.3	0.010
Ventricle L					
D _{mean}	1076.3	292.7	1138.0	299.4	0.001
V ₅	31.1	7.0	33.4	7.8	0.002
V ₁₀	21.6	6.5	23.3	6.7	0.004
V ₃₀	15.7	5.7	17.1	5.9	0.004
Ventricle R					
D _{mean}	597.7	300.0	674.9	367.3	0.001
V ₅	19.8	10.4	22.5	12.0	0.001
V ₁₀	10.9	7.6	12.5	9.0	0.013
V ₃₀	5.6	5.2	7.3	6.9	0.012
LMCA					
D _{mean}	92.5	31.7	99.1	35.3	0.001
	116.9	39.1	125.3	43.0	0.001
RCA					
D _{mean}	88.6	32.5	96.2	33.6	0.001
	254.2	115.6	293.3	155.5	0.001
LAD					
D _{mean}	3723.1	670.1	3838.1	597.7	0.002
D _{max}	5270.1	97.2	5270.7	91.3	0.195
CX					
D _{mean}	106.0	27.0	111.5	28.2	0.001
D _{max}	214.5	86.6	228.6	91.2	0.001
PTV					
D _{mean}	5183.0	23.8	5186.5	24.0	0.026
V _{95%}	97.0	1.0	97.1	1.0	0.191
95% V _{107%}	15.2	5.6	15.8	6.1	0.219
CI	1.4	0.1	1.5	0.1	< 0.001
HI	0.1	0.0	0.1	0.0	0.999

Table 1	Comparison of CW and CW+IMLN fields in FIF technique (mean±SD)
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CW: Chest wall; CW+IMLN: Chest wall+internal mammary lymph node; FIF: Field-in-field; SD: Standars deviation; L: Left; R: Right; LMCA: Left main coronary artery; RCA: Right coronary artery; LAD: Left anterior descending; CX: Circumflex; PTV: Planning target volume; CI: Conformity index; HI: Homogeneity index; V₃: The volume receiving a dose of 5 Gy; V₁₀: The volume receiving a dose of 10 Gy; V₃₀: The volume receiving a dose of 30 Gy; PTV: V₉₅₆ the volume receiving 95% of the prescribed dose; PTV: V₁₀₇₅₆ the volume receiving 107% of the prescribed dose; D_{max}: Maximum dose; in bold values are not statistically different (p>0.05)

Discussion

Cardiac toxicity is an issue that should be given great importance, especially in the radiotherapy planning of patients with the left breast cancer. There are many studies in the literature showing the dosimetric benefits of IMRT compared to 3D conformal radiotherapy. However, in recent years, the tendency to extend coverage field of the IMLN has increased, and the IMLN field is included in the radiotherapy protocol, however, studies of the IMLN radiotherapy on its additional effect on cardiac and coronary vascular toxicity are still

IMRT technique D _{mean} , D _{max} as cGy V ₅ , V ₁₀ , V ₃₀ , V ₉₅ , and V ₁₀₇ as %	CW		CW+IMLN		р
	Mean	SD	Mean	SD	
Whole heart					
D _{mean}	844.1	115.4	913.9	129.2	<0.001
V ₅	54.4	7.0	56.9	6.8	<0.001
V ₁₀	20.9	6.5	26.0	8.3	<0.001
V ₃₀	5.5	1.8	6.2	1.9	0.017
Atrium L					
D _{mean}	284.1	66.6	295.1	74.3	0.009
V ₅	11.4	9.3	13.7	10.2	0.007
V ₁₀	0.1	0.3	0.3	0.6	0.109
Atrium R					
D _{mean}	225.9	48.7	231.5	50.4	0.024
V ₅	1.5	4.7	0.4	1.1	0.317
Ventricle L					
D _{mean}	1241.9	129.6	1315.4	132.3	0.001
V ₅	87.7	7.6	89.9	6.6	0.003
V ₁₀	34.5	8.1	42.1	11.7	<0.001
V ₃₀	10.2	3.3	9.9	3.4	0.292
Ventricle R					
D _{mean}	873.5	262.3	978.4	313.4	<0.001
v ₅	69.2	14.4	71.7	14.4	<0.001
V ₁₀	25.1	17.9	31.1	18.8	<0.001
V ₃₀	2.9	3.5	4.3	4.9	0.007
LMCA					
D _{mean}	509.4	167.1	491.4	148.9	0.286
D _{max}	644.1	262.8	629.0	226.5	0.549
RCA					
D _{mean}	247.2	59.6	263.0	61.3	0.002
D _{max}	564.6	209.7	674.9	326.8	0.001
LAD					
D _{mean}	3249.3	521.6	3399.2	448.4	<0.001
D _{max}	5089.7	257.2	5106.5	265.3	0.485
CX					
D _{mean}	450.2	92.1	598.0	285.4	0.001
D _{max}	1012.6	318.1	1151.1	319.0	0.010
PIV					
D _{mean}	5145.2	30.2	5139.8	23.1	0.500
V _{95%}	99.2	0.5	99.2	0.4	0.689
V _{107%}	4.2	3.8	3.7	2.4	0.507
CI	1.0	0.1	1.0	0.1	0.434
HI	0.1	0.0	0.1	0.0	0.655

CW: Chest wall; CW+IMLN: Chest wall+internal mammary lymph node; IMRT: Intensity-modulated radiotherapy; SD: Standard deviation; L: Left; R: Right; LMCA: Left main coronary artery; RCA: Right coronary artery; LAD: Left anterior descending; CX: Circumflex; PTV: Planning target volume; CI: Conformity index; HI: Homogeneity index; V; The volume receiving a dose of 5 Gy; V₁₀: The volume receiving a dose of 10 Gy; V₃₀: The volume receiving a dose of 30 Gy; PTV: V_{95%} the volume receiving 95% of the prescribed dose; PTV: V_{107%} the volume receiving 107% of the prescribed dose; D_{max}: maximum dose; in bold values are not statistically different (p>0.05)

scarce in number. Our study showed that when the IMLN field is added to the CW, high-dose volumes of the whole heart and ventricles (V_{30}) and only LAD

(both D_{max} and D_{mean}) from among the coronary vessels are significantly better protected when d-IMRT technique is used (whole heart V_{30} : 9.4% by 6.2%, ventricle

RT field: CW+IMLN D _{mean} , D _{max} as cGy V ₅ , V ₁₀ , V ₃₀ , V ₉₅ , and V ₁₀₇ as %	FIF technique		IMRT technique		р
	Mean	SD	Mean	SD	
Whole heart					
D _{mean}	689.1	186.6	913.9	129.2	<0.001
V ₅	19.1	4.7	56.9	6.8	0.001
V ₁₀	13.2	4.1	26.0	8.3	<0.001
V ₃₀	9.4	3.3	6.2	1.9	<0.001
Atrium L					
D _{mean}	67.3	15.2	295.1	74.3	<0.001
V ₅	0.0	0.0	13.7	10.2	0.001
V ₁₀	0.0	0.0	0.3	0.6	0.109
Atrium R					
D _{mean}	64.1	14.3	231.5	50.4	<0.001
v ₅	0.0	0.0	0.4	1.1	0.180
Ventricle L					
D _{mean}	1138.0	299.4	1315.4	132.3	0.017
v ₅	33.4	7.8	89.9	6.6	<0.001
V ₁₀	23.3	6.7	42.1	11.7	0.001
V ₃₀	17.1	5.9	9.9	3.4	0.001
Ventricle R					
D _{mean}	674.9	367.3	978.4	313.4	<0.001
V ₅	22.5	12.0	71.7	14.4	<0.001
V ₁₀	12.5	9.0	31.1	18.8	0.001
V ₃₀	7.3	6.9	4.3	4.9	0.005
LMCA					
D _{mean}	99.1	35.3	491.4	148.9	<0.001
D _{max}	125.3	43.0	629.0	226.5	<0.001
RCA					
D _{mean}	96.2	33.6	263.0	61.3	<0.001
D _{max}	293.3	155.5	674.9	326.8	0.001
LAD	2020 1	507 7	2200.2	440.4	.0.001
D _{mean}	3838.1	597.7	3399.2	448.4	<0.001
D _{max}	5270.7	91.3	5106.5	265.3	0.010
СХ	111 -	20.2	500.0	205.4	0.001
D _{mean}	111.5	28.2	598.0	285.4	0.001
D _{max} PTV	228.6	91.2	1151.1	319.0	<0.001
D _{mean}	5186.5	24.0	5139.8	23.1	<0.001
V 95%	97.1	1.0	99.2	0.4	<0.001
V _{107%}	15.8	6.1	3.7	2.4	<0.001
CI	1.5	0.1	1.0	0.1	<0.001
HI	0.1	0.0	0.1	0.0	0.203

CW+IMLN: Chest wall+internal mammary lymph node; FIF: Field-in-field; IMRT: Intensity-modulated radiotherapy; RT: Radiotherapy; SD: Standard deviation; L: Left; R: Right; LMCA: Left main coronary artery; RCA: Right coronary artery; LAD: Left anterior descending; CX: Circumflex; PTV: Planning target volume; CI: Conformity index; HI: Homogeneity index; V₃: The volume receiving a dose of 5 Gy; V₁₀: The volume receiving a dose of 10 Gy; V₃₀: The volume receiving a dose of 30 Gy; PTV: V_{95%} the volume receiving 95% of the prescribed dose; PTV: V_{107%} the volume receiving 107% of the prescribed dose; D_{max}: Maximum dose

L V₃₀: 17.1% by 9.9%, ventricle R V₃₀: 7.3% by 4.3%, LAD D_{mean}: 38.3 Gy by 33.9 Gy, and LAD D_{max}: 52.7 Gy by 51 Gy). All the low-dose volumes of the whole

heart and ventricles (V_5 and V_{10}) and all coronary vessels excepting LAD (incl. both D_{max} and D_{mean}) were better protected in the FIF technique. In this respect,

PTV D_{mean} , V_{95} , V_{107} , and CI were significantly superior in the d-IMRT technique (for all p<0.001), while HI was not significantly different (p=0.203).

In a study comparing tangential beam IMRT and 3D conformal RT techniques in postmastektomi CW radiotherapy with 20 unselected breast cancer patients, the PTV, and organs at risk (OAR) such as lung and heart doses were compared on DVH. Mean doses of ipsilateral lung and heart were lower in the tangential beam IMRT technique and for the PTV, homogeneity index did not differ, while the conformity index was found to be significantly better in the IMRT technique. [8] In our study, although we found a similar result for PTV, on the contrary, mean cardiac doses were found to be significantly higher in the IMRT technique. However, in the aforementioned study, not only the leftsided breast cancer patients but unselectively all breast cancer patients were included in the radiotherapy protocol, which may be the reason why the mean cardiac dose was lower in the IMRT technique in their study. However, in our study, in the 3D conformal radiotherapy (or FIF) technique, multi-leaf collimators pulled firmly toward target volume to protect the heart as much as possible so the mean and low-dose volumes of whole heart and ventricles were better protected.

In a prospective study conducted by Chargari et al.,[9] the contribution of IMLN radiotherapy to cardiac radiation dose was investigated in 36 patients with breast cancer. Radiotherapy at a dose of 50 Gy was applied with standard conformal radiotherapy technique and the effect of IMLN radiotherapy on the cardiac dose was investigated according to the type of surgery (breast conserving surgery [BCS] vs. mastectomy) and the laterality of breast cancer (left vs. right breast cancer). Compared to patients with the right breast cancer, patients with the left breast cancer received a statistically significantly increased cardiac dose. In the grouping made according to the type of surgery, the cardiac dose used was not statistically different in those who underwent mastectomy or BCS. The authors reported that the type of surgery performed did not affect the cardiac dose.[9] In another dosimetric study, 50 patients with the left breast cancer were analyzed dosimetrically by contouring the LAD and whole heart in tangential breast radiotherapy.[10] They found the mean LAD dose as 19.06 Gy and also detected a perfect correlation between the LAD and cardiac doses. For every 100 cGy increase in the mean cardiac dose, the mean LAD dose increased by 4 Gy. In this study, we found the mean LAD dose to be 38 Gy and 33 Gy in the classical tangential and d-IMRT techniques, respectively. The reason for our high value of LAD dose is that the patients in our study were locally advanced so the ribs were included in the target volume, however, the above-mentioned study was performed with patients with early-stage breast cancer who received only breast radiotherapy, which was formed by excluding the ribs in the target volume.

A similar dosimetric study was done by Zhang et al.[11] They dosimetrically compared volumetric modulated arc therapy (VMAT) and IMRT techniques, in terms of heart, lung doses, and PTV on DVH in the left CW and IMLN radiotherapies applied after mastectomy. VMAT provided slightly better but statistically insignificant protection in the mean, V_5 , V_{10} , and V_{30} of heart doses. The VMAT technique provided better PTV dose coverage, fewer monitor units, and shorter treatment time.[11]

Our study has some limitations. First of all, besides being a retrospective series, comparison with advanced radiotherapy techniques could not be made. In other words, breath-holding or respiratory gating systems could be used to provide better heart protection in patients with the left breast cancer. However, unfortunately, these facilities were not available, so applicable in our clinic and we were also working with a retrospective series.

Conclusion

Only LAD D_{max} did not increase with the addition of IMLN radiotherapy in the FIF technique. When the IMLN field was added in the IMRT technique, both maximum, and mean doses coronary vessels of LMCA and LAD did not change, while the doses of other coronary vessels were increased. Consistent with the literature data, all the low-dose volumes of heart and ventricles (V_5 and V_{10}) and all coronary vessels (excl. LAD) were better protected in the FIF technique when compared with the IMRT technique. In patients with the left breast cancer who will undergo IMLN radiotherapy, especially if they have coronary disease, RT technique can be selected according to the vessel where the damage is located. However, more research is warranted on this subject.

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Ethics Committee Approval: The study was approved by the Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee (No: 22-KAEK-011, Date: 20/01/2022).

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