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Are incidental IMRT doses to internal mammary lymph nodes reliable enough, as they were in the past with conformal RT in breast cancer?

Incidental IMRT doses to internal mammary lymph nodes

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Abstract

Aim: Intensity-modulated radiotherapy (IMRT), applied in combination with several other methods, has gradually become common practice in breast cancer treatment. The dose distribution in this area has become even more critical since the benefits of regional lymph node irradiation were demonstrated in disease-free survival (DFS) and distant metastasis-free survival (DMFS) rates, particularly in the early phase of the disease. Our main aim in this dosimetric study was to compare IMRT and conformal RT plans, excluding internal mammary lymph node field (IMLN) planning, and to investigate the dose distribution incidentally received by the IMLN.

Material and Methods: A PTV-total was created excluding the IMLN field in 15 right-sided and 15 left-sided breast cancer patients, and two different plans were designed for each patient to receive the defined target doses using both conformal and IMRT techniques. The incidental IMLN field dose distributions in the conformal and IMRT plans were compared in regards to the D95, Dmax, Dmin, Dmean, V40, V45, V47.5, and homogeneity index (HI) values.

Results: The incidental distributions of D%95, D%98, D%2, maximum dose, minimum dose, mean dose, V40, V45, and V47.5 in IMLN were found to be significantly lower in the IMRT plans compared to the conformal plans.

Discussions: IMRT requires a more careful reevaluation of the incidental doses received by the IMLN field. The use of IMRT in breast cancer radiotherapy may lead to a potential for increased recurrence rates in the internal mammary lymph nodes area compared to the rates observed in the conformal technique due to the lower doses received by the adjacent tissues.

Keywords

Breast cancer; Radiotherapy; Incidental doses; Nodal irradiation

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Introduction

The contribution of radiation therapy (RT) in breast cancer treatment has long been the subject of investigation. Another major issue is to determine the characteristics of the patients, in whom IMLN field will be treated [1,2]. The characteristics of patient subgroups, in which the contributions of the IMLN field RT are observed in the rates of local control (LC), overall survival (OS) or disease-free survival (DFS) rates, have been among the major questions waiting to be answered today. The IMLN field is difficult to reach surgically, which increases the duration of the intervention associated with increased risks [3]. In addition, due to the potential of additional pulmonary and cardiac toxicity associated with the IMLN RT, the benefit-to-risk ratio should be studied with care for every patient during the planning phase.

The doses, to which the surrounding tissues are exposed, have been reduced currently, owing to the advances in technology during the evolution of breast RT from 2D to 3D, as well as towards IMRT. Although the inverse planning period is longer in IMRT, side effects are less frequently observed because the surrounding tissues are exposed to lower doses [3].

The exposure of the surrounding tissues to lower doses by means of IMRT requires a more careful re-evaluation of the incidental doses received by the IMLN field. Then, the question arises, could this modification in the technique of the treatment lead to a change (potential increase) in the IMLN recurrence rates? In this article, we tried to shed light on the answer to this question.

Material and Methods

Patient selection

Patients previously irradiated at our center were reviewed and 30 cases were selected for the present study. Three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) were retrospectively planned for 15 right-sided and 15 left-sided breast cancer patients treated with breast-conserving surgery and whole breast radiation therapy.

Simulation, volume definition, and radiotherapy technique

CT simulations were done with a GE Light Speed16 CT scanner in the supine position with a slice thickness of 2,5 mm. Target volumes and organs at risk were delineated by a single radiation oncologist using Varian Eclipse TPS station Version 13.0.1 (Varian Medical Systems, Sao Paulo).

Regardless of tumor stage and lymph node involvement, axillary levels I- II-III, supraclavicular region and internal mammary lymph nodes were retrospectively contoured in all cases, according to radiation therapy oncology group (RTOG) breast cancer atlas.

The contralateral breast, heart, lungs were delineated as organs at risk (OAR). Dose constraints for OAR are shown in Table 1.

For whole breast radiation planning, PTV-total (PTV-breast and PTV-lymphatic) included ipsilateral breast, axillary levels I- II-III, and supraclavicular lymphatic (except internal mammary lymph nodes) with a 3 mm expansion and the PTV-boost included lumpectomy cavity with a 10 mm expansion limited to 3 mm from the patient's surface. The prescribed doses were 50 Gy to PTV-total and 60Gy to PTV-boost at 2Gy per fraction.

The IMLN field was delineated in every patient to cover the first three intercostal spaces extending to the margin of the 4th rib. The margins of IMLN were defined as a distance of 5 mm mediolaterally and 2 mm anteroposteriorly around the vessels. A PTV-total was created excluding the IMLN field in every patient as described above, and two different plans were designed for each patient to receive the defined target doses using both conformal and IMRT techniques. The incidental IMLN field dose distributions in the conformal and IMRT plans were compared in regards to the D95, Dmax., Dmin., Dmean, V40, V45, V47.5, and homogeneity index (HI) values. The HI was calculated according to the (D2-D98)/Dp formula. The DVH parameters, on which the plans were based, are presented in Table 2. A boost plan to be directed to the lumpectomy cavity was designed in each patient to ensure that the closest doses to real ones would be received by the adjacent tissues.

Radiotherapy Planning:

3DCRT plans with field-in-field technique

A single isocentric treatment approach was used in this planning. For this purpose, two parallel tangential fields covering the target breast tissue together with the regional lymphatics (level I-II-III) and two opposing anterior-posterior (AP) parallel fields covering the supraclavicular region were used. The isocenter of these four basic fields was primarily located inferior to the clavicular head. Then the isocentre was revised to match it inferiorly to the field, as it was predicted that the tangential field distance would be a maximum of 20 cm on the superior-inferior plane when the jaw was completely closed and located superiorly to the isocenter. Gantry angles of the tangential fields were determined, selecting the angles to show none or the least of the posterior breast tissue volume in the “beam's eye view”. The source-to-skin distance (SSD) on the forehead was equalized on both sides. The tangential field distance was set to zero for superior jaws, but a 2 cm-width was set at the outer margin of the PTV inferiorly to compensate the respiratory motion. The subfields were created within the total calculated field with MLCs, primarily to cover the volumes receiving a dose over 110% and then to reduce the volumes subject to doses 107% and 105%. The sum of the weights of the subfields was designed in such a way that it would not be over 20% of the weight of each plan.

Seven-Field Inverse IMRT Plans

Seven fields were used in inverse IMRT plans, created at the gantry angles of three internal and three external tangential fields and one vertical field with respect to PTV breast. After the tangential areas used in 3DCRT plans were diverted externally in the range of 5-15 degrees, two more areas were selected, directed internally at 15-20 degrees. The last field was selected at an angle so that it would be positioned perpendicularly. The coach angles were set to zero in the field configurations. Aligning all created fields to the point where all targeted PTVs were intersected, the centre of gravity for the total PTV was selected to be the isocenter. Fluence smoothing of all fields was designed to be proportional to the maximum and minimum optimization priority values defined for PTVs. In addition, normal tissue optimization was set to equal values to those of the PTV priority values in the automatic mode.

Statistical methods:

Frequencies and statistics were performed using SPSS 20

(SPSS Inc.) statistical software. The statistically significant threshold was accepted as p=0.05. As the data set was not distributed normally, the Wilcoxon signed rank test was used to compare the doses delivered by the conformal and IMRT plans to the IMLN regions.

Results

The long and short median diameters of the target volume of IMLN were 1.5 cm and 0.8 cm, respectively, based on the anatomical section. The median height of the patients was 160 cm (range: 141-168 cm) and their median body weight was 73 kg (range: 43-125 kg). The median volume of the breast tissue was 1200cc (range: 443-2339 cc). According to the body mass index (BMI) classification, 33% of the patients were obese or extremely obese. The median BMI was 29 (range: 21-46). The doses received by the target volumes and organ-at-risk (OAR) doses are presented in Table 1.

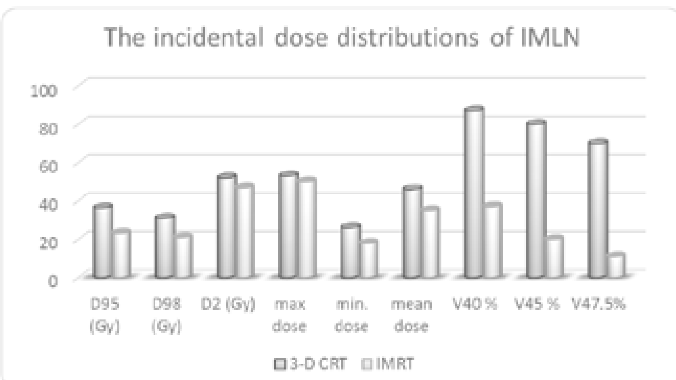

Figure 1. The incidental dose distributions of IMLN

The incidental distributions of D%95, D%98, D%2, maximum dose, minimum dose, mean dose, V40, V45, and V47.5 in IMLN were found to be significantly lower in the IMRT plans compared to the conformal plans (Figure 1). The homogeneity of the incidental dose distributions was found to be more favorable in the conformal plans in 63% of the patients compared to IMRT plans, however, no statistically significant difference was observed (Figures 2, 3).

Discussion

IMLN positivity reaches 40-65%, especially in the presence of centromedial localization, axillary involvement or large tumor. Furthermore, the involvement of IMLN reached a "5-7%" rate even in an N0 disease [4]. Such factors strengthen the rationale of applying an elective IMLN RT [3,5-7]. However, the RT field widens by including the IMLN area, leading to increases in toxicity primarily in the heart and lungs [1]. The incidence of adverse coronary events has been reported to increase by 7.4% with an increase in one Gray unit in the mean dose to which the heart was exposed [8]. Furthermore, IMNL RT has been shown to be associated with an 18%-increased risk of coronary artery disease compared to a 7% increase in breast radiotherapy without IMLN RT [9]. These findings have long caused the MILN RT indication to be decided cautiously and limitedly. In addition, the prevalence of recurrence in the IMLN field is 1% [10], with the conformal RT technique, which has a common use today. This recurrence rate was associated with the incidental IMLN doses received during the breast radiotherapy [3]. Due to these reasons, the evaluation of the doses to which the IMLN area was exposed, has always been a subject of primary importance, even in selected patients, in whom the IMLN area was not

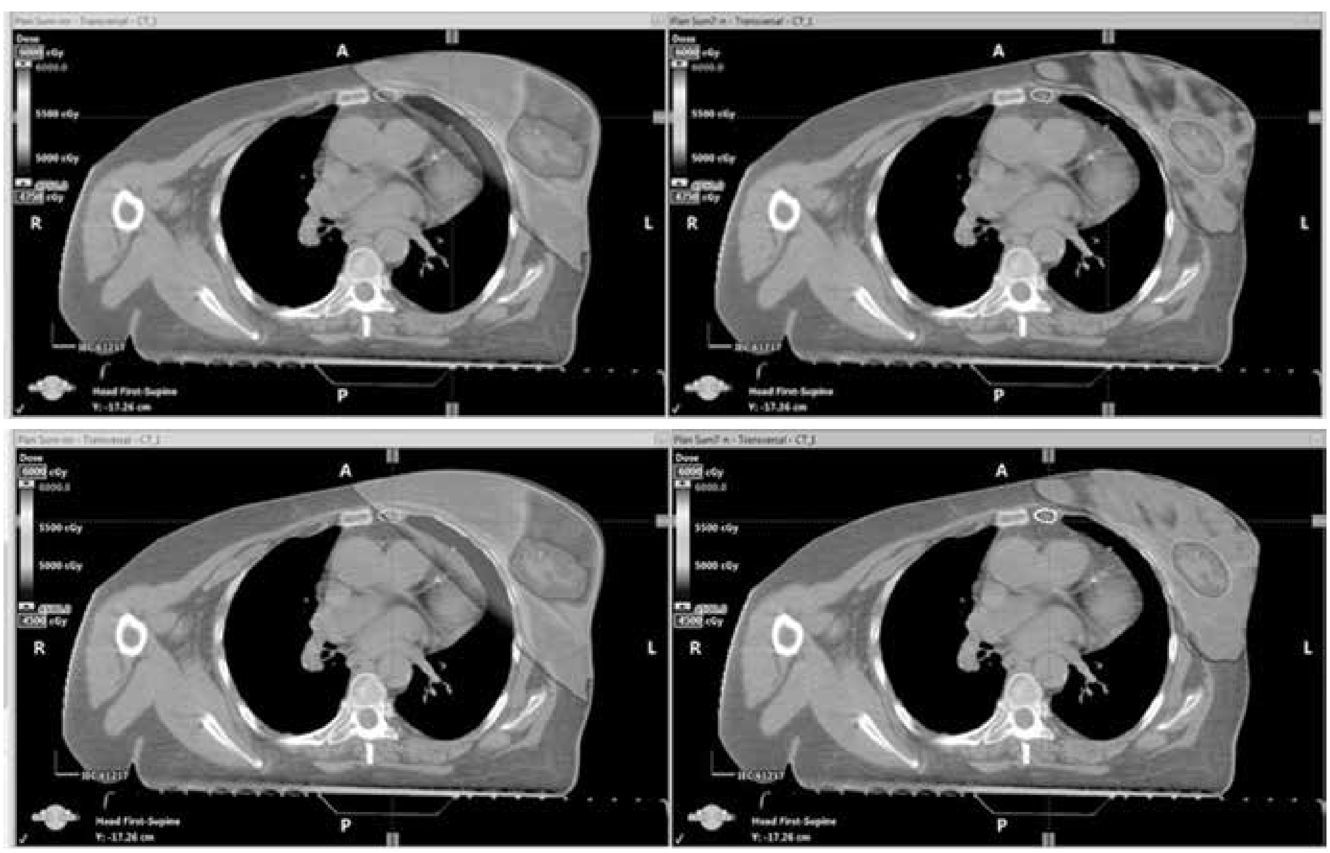

Figure 2,3. The incidental dose distributions in the conformal and IMRT plans for 4750 cGy and 4500cGy

Table 1. Dose constraints used for organs at risk (OAR) and dose–volume parameters for target and organs at risk in the 3D-CRT and IMRT plans

Dosimetric planning constraints			Dose /volume parameters	
Organ/volume			3-D CRT (median)	IMRT (median)
Ipsilateral breast	V95	>95%	95%	95%
	V115%	<1%	3,5%	0,4%
	V110%	<10%	12%	4%
	V105%	<14%	32%	18,5%
Ipsilateral lung	V5	<30%	60%	92%
	V20	<20%	39%	27%
	mean	<14 Gy	19 Gy	17 Gy
Contralateral lung	V5	<10%	<1%	20%
Whole lung	V10	<35%	25%	35%
Heart	Dmean	<5Gy	4,5Gy	7Gy
	V10	<30%	9%	18%
	V20	<10%	5%	1,3%
	V30	<3%	3%	<1%
Contralateral breast	Dmean	<5Gy	0,8Gy	4Gy
Esophagus	Dmean	<34Gy	7Gy	9,5Gy
	V35	<50%	9%	5%

Table 2. The incidental IMLN field dose distributions in the conformal and IMRT plans (Wilcoxon signed ranks test)

MILN	3-D CRT (mean±SD)	IMRT (mean±SD)	p-value
D95 (Gy)	36,34 ± 13,42	23,21 ± 6,14	<0,001
D98 (Gy)	31,11 ± 14,62	21,42 ± 5,69	0,002
D2 (Gy)	52,68 ± 2,66	47,60 ± 5,22	<0,001
max dose (Gy)	53,53 ± 3,47	50,66 ± 4,78	0,002
min. dose (Gy)	26,83 ± 13,72	18,26 ± 5,36	0,002
mean dose (Gy)	46,24 ± 5,96	35,91 ± 5,58	<0,001
HI	0,43 ± 0,28	0,52 ± 0,12	0,109
V40 (%)	87,26 ± 19,81	37,52 ± 27,74	<0,001
V45 (%)	80,80 ± 25,54	20,37 ± 20,54	<0,001
V47,5 (%)	70,50 ± 29,37	11,99 ± 15,11	<0,001

included in the target treatment field in the RT plans.

In the MA 20 study [11], one of the studies providing the strongest evidence for the importance of MILN field RT, showed favorable results in DFS (77% vs 82%, respectively) and regional recurrence rates (2.7% vs 0.7%, respectively) in patients receiving IMLN + SCV + Level- III irradiation compared to the remaining patients who did not receive this treatment at an early stage of the disease with 1-3 positive nodes or in the node-negative patients with T2-T3 unfavorable disease (disseminated LVSI, inadequate axillary dissection, etc.). In EORTC 22922 [12], patients with positive axillary lymph nodes or patients with central/medial tumors were examined based on the treatment with IMLN + SCV RT. The study reported that the mortality of breast cancer was reduced, and the DFS and distant DFS rates were improved. With the addition of improved OS rates, these results were highlighted in a meta-analysis, including a French study, too [13], In the light of these randomized studies, the NCCN (National Comprehensive Cancer Network) guidelines were updated, strongly considering the irradiation of the regional lymph nodes, including the IMLN region, in the patients who underwent breast-conserving surgery and had 1-3 positive lymph nodes. Furthermore, even in patients with central/medial tumors without any positive lymph nodes or in patients having a tumor size larger than 2 cm with disseminated LVSI, the importance of "regional nodal RT" was stressed. This is a major milestone in the evolution of breast cancer radiotherapy. In the near future, we may even discuss the usefulness of IMLN RT intensively in some selected node-negative patients or patients with micrometastatic involvement, as well as patients with 1-3 positive lymph nodes.

Radiotherapy planning is a major challenge for the treatment team in widely separated large-volume breasts, in which homogeneity is difficult to achieve in daily practice. In these patients, IMRT provides a more homogeneous dose distribution in this type of breast tissue having a characteristic convex anatomical structure. Despite the long planning time and associated high costs, the use of IMRT has gradually become more common owing to the benefits including the esthetic/ long-term cosmetic effects, reduction in the cardiac dose, and lower acute or late toxicity [14,15]. However, we must realize during the evolution of RT practices that more effective elimination of the microscopic disease associated with the incidental doses of the 3D conformal therapy may not be achieved with IMRT, because, based on the algorithm plans, the reduction in the dose is faster at the margins of the treatment field in IMRT, compared to the conformal therapies [4,16]. Therefore, it is anticipated in the patients receiving IMRT that IMLN area will receive lower doses along with the adjacent tissues. Therefore, at least in the planning phase, it would be beneficial to contour the IMLN site to review the received incidental doses, even though it is not included in the PTV, especially for the grey-zone patients with relatively high risk; these reliable IMLN doses in the conformal therapy might lose their effect in IMRT. This condition reminds the question of whether an increase in the recurrence rates will occur in IMLN in the near future.

The results of our study supported a positive answer to this question. Several previous results are available in the literature examining the incidental doses received by IMLN during 2D or 3D conformal therapies [17-19]. Despite the limitations, our study is one of the first studies to investigate the incidental doses of IMRT and to compare their distribution with those of conformal RT. The patient population in our study included patients with a larger volume of breast and high BMI, in whom homogeneity was difficult to achieve in daily clinical practice, so we tended to apply IMRT. The median breast volume in the study patients was 1200cc (443-2339 cc). According to the the BMI classification, 33% of the study patients were extremely obese. IMRT is preferred more in these patients, in whom RT planning is challenging and dose constraints are difficult to achieve. Within this scope, we may emphasize that the incidental doses received by the OAR and IMLN were close to the ones applied in real clinical practice. The incidental dose distributions in the IMRT plans in our study was significantly lower in terms of D%95, D%98, D%2, maximum dose, minimum dose, mean dose, V40, V45, and V47.5. Thus if we discuss the enhancing benefits of the IMLN field RT, and, in the light of the randomized studies, if we recognize the benefits of IMLN field RT in some selected subgroups of patients with 1-3 positive nodes, or even the ones without positive nodes, we may conclude that we must exercise extra care in observing the doses received by the IMLN field in IMRT plans, or we must consider including this region to PTV and not rely on the incidental doses to be received in the presence of robust indications. Unfortunately, robust data on the recurrence rates in the IMLN field are not available today as IMLN field is excluded from PTV in current IMRT practice. In order to be able to conclude stronger recommendations, further large-scale studies providing more robust data are required.

Conclusion:

In light of the results of large-scale randomized studies, it has been observed that the inclusion of the internal mammary lymph node area to RT plans is associated with reductions in local or distant overall recurrence rates and cancer-related mortality rates, especially in the early-stage breast cancer [11,12,20]. Associated treatment benefits have been reported in patients with 1-3 positive axillary nodes or even in patients without axillary node involvement but having the tumor centrally or in the inner quadrant, as well as benefits observed in patients with four or more positive lymph nodes [21,22]. This is a promising result in the sense that the local benefits of IMLN field RT can be observed in larger patient subgroups. Particularly in patients with the involvement of 1-3 nodes or in the high-risk patients without positive nodes (such as central/medial location, T2-3 tumor, etc.), it is more important to achieve a balance between the benefits of RT on survival rates, DFS, and LC rates; and its potential pulmonary or cardiac, etc. toxicity. In this context, it will be useful to consider that, with IMRT in breast cancer radiotherapy, there may be a potential of increased recurrence rates in the internal mammary lymph nodes area compared to the rates observed in the conformal technique due to the lower doses received by the adjacent tissues. Therefore, contouring the IMLN area and a careful evaluation of the doses to which this area is exposed will provide treatment benefits.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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