RESEARCH ARTICLE

Dosimetric Evaluation of 3-D Conformal and Intensity-modulated Radiotherapy for Breast Cancer after Conservative Surgery

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Abstract

Background: Breast cancers are becoming more frequently diagnosed at early stages with improved long term outcomes. Late normal tissue complications induced by radiotherapy must be avoided with new breast radiotherapy techniques being developed. The aim of the study was to compare dosimetric parameters of planning target volume (PTV) and organs at risk between conformal (CRT) and intensity-modulated radiation therapy (IMRT) after breast-conserving surgery. Materials and Methods: A total of 20 patients with early stage left breast cancer received adjuvant radiotherapy after conservative surgery, 10 by 3D-CRT and 10 by IMRT, with a dose of 50 Gy in 25 sessions. Plans were compared according to dose-volume histogram analyses in terms of PTV homogeneity and conformity indices as well as organs at risk dose and volume parameters. Results: The HI and CI of PTV showed no difference between 3D-CRT and IMRT, V95 gave 9.8% coverage for 3D-CRT versus 99% for IMRT, V107 volumes were recorded 11% and 1.3%, respectively. Tangential beam IMRT increased volume of ipsilateral lung V5 average of 90%, ipsilateral V20 lung volume was 13%, 19% with IMRT and 3D-CRT respectively. Patients treated with IMRT, heart volume encompassed by 60% isodose (30 Gy) reduced by average 42% (4% versus 7% with 3D-CRT), mean heart dose by average 35% (495cGy versus 1400 cGy with 3D-CRT). In IMRT minimal heart dose average is 356 cGy versus 90cGy in 3D-CRT. Conclusions: IMRT reduces irradiated volumes of heart and ipsilateral lung in high-dose areas but increases irradiated volumes in low-dose areas in breast cancer patients treated on the left side.

Keywords: Breast cancer - radiotherapy - intensity-modulated - conservative surgery

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Introduction

Breast cancer is the most common cancer entity in women, representing a major health care problem. The disease is diagnosed in about 1.2 million patients and accounts for about 500,000 deaths yearly worldwide (Askoxylakis et al., 2010). The development of diagnostic strategies has led through the years to an earlier diagnosis of breast cancer, which resulted in the evolution from entirely surgical treatment into more conservative approaches, replacing mastectomy by breast-conserving surgery followed by radiation therapy in early-stage disease (Volker et al., 2011). Therefore, it has made the outcome of breast-conserving surgery comparable to mastectomy.

Nowadays, radiotherapy plays an important role in the treatment of breast cancer (Zhou et al., 2012; Liu et al., 2013; Nandi et al., 2014; Varol et al., 2014), and breast-conserving surgery followed by adjuvant radiotherapy (RT) is now the standard treatment for early-stage breast cancer (Veronesi et al., 2002). It allows the reduction to local recurrence and metastases, so these patients survive for long periods of time, mortality and morbidity are technique- and dose-dependent (Nesrin et al., 2007).

The challenge now is to minimize the morbidity caused by this treatment without losing its efficacy. Therefore, optimized radiation treatment planning plays a critical role in the care of breast cancer patients, there have been exciting advances in RT techniques, but generally these techniques require more resources and a higher work volume (Fisher et al., 2002).

In this study, we acheck the breast dosimetry obtained with simple conventional planning techniques and how it can be significantly improved with new modalities, such as IMRT and FiF-IMRT? Study objective, evaluates for breast cancer patients' the dose distribution of tangential beam IMRT of the breast in post conserving surgery compared to tangential beam 3D-CRT. Evaluates isodoses heart distribution and ipsilateral lung of tangential beam IMRT compared to tangential beam 3D-CRT.

Materials and Methods

Patients

Between January 2009 and December 2009, 20 women aged over 18 years with ductal carcinoma in situ (DCIS) or

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invasive carcinoma (T0–T3 N0–N1), all patients had left-sided breast cancer treated with breast conserving surgery were recruited for this study. Systemic chemotherapy was administered for high risk patients. Adjuvant endocrine therapy and trastuzumab were administered when indicated. Written informed consent was obtained for all patients. Age was (53-79 years), 56% were hormone receptor positive and 45% Her2 over expression negative. And median follow-up was 27.7 months.

Simulation scanner

A non-contrast CT-simulation was performed in the supine position. A VacLoc is used in the region of the head, and neck to aid set-up reproducibility with the ipsilateral arm abducted and raised over-head and head turned to the contralateral side.

Radio-opaque wires were used to mark the lumpectomy scar and clinically palpable breast tissue, and reference indicators tattooed, from cricoide to diaphragmatic cupola The CT dataset was exported to the treatment planning system, Pinnacle version 8.

Target volume and critical structures

The target volumes were defined and he planning target volume (PTV) definition for breast was done according to the breast cancer atlas for radiation therapy planning consensus definitions of the Radiation Therapy Oncology Group (RTOG) http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.

The breast volume was defined in all slices using the markers and the glandular breast tissue that were visible on the CT, the volume of mammary tissue excluding, the pectoralis muscle to the skin. The ribs and superficial 5 mm of skin were also excluded, the borders of the contoured breast were defined by the mid-sternum medially, the anterior border of the latissimus dorsi muscle laterally, the pectoralis major muscle posteriorly, the inferior aspect of the clavicular head superiorly, and 2 cm below the mammary fold inferiorly.

The heart was defined as all visible myocardium, from the apex to the right auricle, atrium, and infundibulum of the ventricle, the pulmonary trunk, root of the ascending aorta, and superior vena cava were excluded. The lungs were delineated the small vessels extending beyond hilar region were included; trachea, main bronchus and hilars were not included (Volker et al., 2011).

Treatment planning technique

The dose prescribed according to the International Commission on Radiation Units and Measurement (ICRU) Reports 50 and 62 recommendations. The dose was prescribed to the ICRU reference point which was usually the isocenter located in the PTV volume centroid.

The prescribed total dose was 50 Gy in 25 fractions. All plans were generated by the same planner using Pinnacle planning system, version 7.6. Beam energy of 6 MV was used for all 3D-CRT and IMRT planing. Treatment delivery, an Elekta Synergy X-ray Volume Imaging (XVI) system. Accordingly, the target volume should be surrounded by the 95% isodose line.

At least 98% of the planned target should receive at least 95% of the prescribed dose, and 2% of the planned target should receive at the outside 107% of the prescribed dose, while a homogeneous dose within 95%-107% of the prescribed dose at target intended to obtain.

For organs at risk, lung, and heart were taken into consideration when prescribing the reference isodose (Jae-Goo et al., 2012).a dosimetric comparison of the heart was conducted using V30, V5, and the mean dose. The ipsilateral lung was also evaluated using V20 and V5 (Table 1).

Tangential beam 3D-CRT

Two tangential semi-opposed beams and a multileaf collimator were used for 3DCRT, Tangential fields that covered the contoured target volume with MLC blocks and wedges were designed. All possible combinations of wedges were chosen to optimize coverage of the PTV and to obtain the best planning, a minimum of two and a maximum of four tangential fields in different wedges and energies were used.

Gantry angles ranged from 300° to 310° for the medial fields and from 115° to 133° for the lateral fields for patients treated on the left side. The fields extended 2 cm anteriorly of the chest to provide coverage of the "flash"region (Figure 1).

IMRT technique

Plans were created for step-and-shoot multileaf collimator (MLC), IMRT optimization and segments were also generated using inverse planning. To optimize coverage of The PTV five to seven fields were used, Gantry angles ranged from 3° to 358° (Figure 2). The segment was combined with the segments into a single field. The dose was prescribed to the PTV.

Table 1. Dose–volume Constraints for Targets and Critical Structures

Structures	Type	Volume	Dose(GY)
PTV Left breast	Target	98%	47.5
PTV Left breast	Target	107%	53.5
Heart	Organ at risk		
V30		5%	30
V5		50%	5
Mean dose			26
Ipsilateral lung	Organ at risk		
V5		30%	5
V20		15%	20

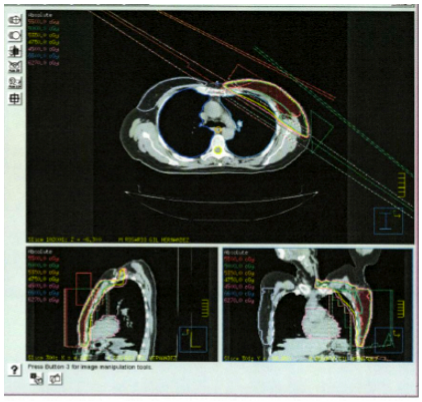

Figure 1. Fields used in IMRT Planning

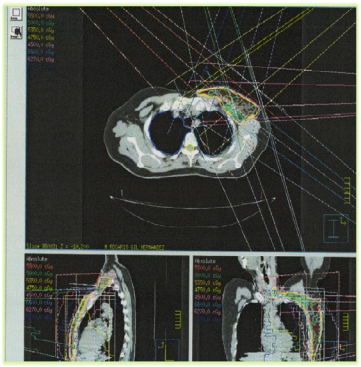

Figure 2. Fields used in IMRT Planning

Comparison dose volume histogram

Dose volume histograms of the PTV and organs at risk of the 3D-CRT and IMRT plans were generated using mean doses received by D98, D2, of the breast volume and the mean volumes that received, V95, V100, V107 of the doses and dose parameters compared.

As well as the dose homogeneity index (DHI) and the conformity index (CI), defined as follows: the Homogeneity index (HI) was defined as the fraction of the PTV with a dose between 95% and 107% of the prescribed dose (V95%-V107%).

$$DHI=(D2-D98)\div Dpres\times 100\%$$

D98 is the dose received by 98% of the target volume on the c-DVH; D2 is the dose received by 2% of the target volume on the c-DVH; Dpres is the prescribed dose.

The DHI should be less than 15 for an acceptable plan, and lower DHI values indicate a more homogeneous dose distribution. The Conformity Index (CI) was defined as the fraction of the PTV surrounded by the reference dose (V95%) multiplied by the fraction of the total body volume covered by the reference PTV dose [(PTV95%÷PTV)×(PTV95%÷V95%)].

The CI values ranged from 0-1. A higher CI value indicates higher dose conformity to the target (Askoxylakis et al., 2010). The monitor unit counts (MU) required for treatment were recorded and compared between the techniques, between 564/fraction (fr) and 1054/fraction with IMRT, and between 328/(fr) and 517/(fr) en 3DCRT. Treatment position was verified daily using clinical assessments with treatment light fields and megavoltage electronic portal imaging.

Results

Dose coverage PTV

In this study, the dosimetric outcomes of 3D-CRT, and IMRT in treating the intact breast were thoroughly investigated. The dosimetric comparisons of the treatment volume and MU for the tow planning techniques are shown in (Table 3). p value ≤0.05 was considered statistically significant.

PTV coverage V95: in order to identify the most favorable planning method for PTV coverage, IMRT S&S planning was compared to 3D-CRT planning methods using V95 criteria shows a comparison of the two planning methods on the proportion of the PTV receiving 95% of the prescribed dose, it can be seen that the proportion of PTV receiving 95% of the prescribed dose appeared

Table 2. Patient and Tumor Characteristics

		Mean	Range	% of patients
Age (years)		61.65	(39-83)	
Breast volume (cm^3)		745.854	(324-1384)	
Pathological tumour size (mm)		19.85	(6-32)	
Margenes(mm)		17.6	(8-4)	
Stage	I			35
	II			60
	III			5
Axillary node-positive				55
Histological grade	1			60
	2			25
	3			15

Table 3. Dosimetric Summary of the Treatment Volumes and Monitor Units for the Tow Planning Techniques

	Mean 3D-CRT	Mean IMRT
V95 (%)	97.8	99
V100 (%)	74	87
V107(%)	11	1.3
CI	0.95	0.96
DHI	12.5	11.6
MU	399.31	802.06

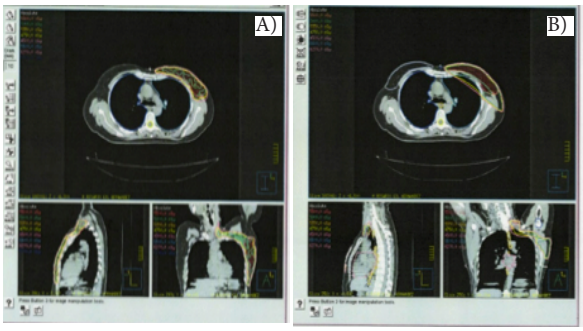

Figure 3. A) IMRT Planning: Isodose Distribution; B) 3DCRT Planning: Isodose Distribution, IMRT Plans Would Give a Much More Homogenous Dose Distribution

on average to be higher and thus better with the IMRT S&S planning method (99%) compared with the method 3D-CRT planning (97.8%), so the difference was no significant p=1, Odds Ratio: one confidence interval 95% (0.2439, 4.1007). However IMRT planning methods gave more consistency in terms of average coverage. In all cases of the IMRT plans there was at least 95% coverage of the 95% Isodose. This would seem to suggest that IMRT plans in these cases would give a much more homogenous dose distribution (Figure 3). IMRT plans would give a much more homogenous dose distribution.

PTV coverage V107: the plans were then assessed to see if the IMRT planning method could reduce the reportable hot spots of V107, in the PTV shows the percentage of the PTV volume receiving a dose of 107% of the prescribed dose.

It can be seen clearly that in all cases the IMRT planning method showed a much reduced% of V107 as compared with the 3DCRT planning method. The mean V107% for each of the plans were calculated giving values 11% for the 3DCRT planning method compared with a much smaller 1.3% for the IMRT planning method., The difference was significant p value: 0.02; Odds Ratio:

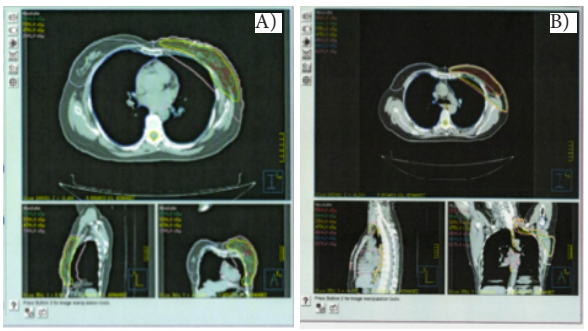

Figure 4. A) IMRT Planning; B) 3DCRT Planning, IMRT Planning Method Showed a Much Reduced% of V107 as Compared with the 3DCRT Planning Method

Plan Summary Sheet

Beam Setup

Beam	Machine	Energy	Modality	Prescription	Isocenter	SSD (cm) Start / Avg	MU Per Fraction Wedged/Open
tan int	1426	6 MV	Photons	PTV Mama	iso	92.59 / 92.59	66.612 / 97.788
tan ext	1426	6 MV	Photons	PTV Mama	iso	89.75 / 89.75	63.829 / 93.271
tan int red	1426	6 MV	Photons	PTV Mama	iso	92.59 / 92.59	6.4
tan ext red	1426	6 MV	Photons	PTV Mama	iso	89.75 / 89.75	7.4
s obl 335	1426	6 MV	Photons	PTV Supra	iso	95.26 / 95.26	34.029 / 49.071
s obl 25	1426	6 MV	Photons	PTV Supra	iso	96.73 / 96.73	43.080 / 61.720
s obl 120	1426	6 MV	Photons	PTV Supra	iso	90.21 / 90.21	211.641 / 40.459

	Collimators (cm) (Control Pt 1)				Gantry						
Beam	Y1	Y2	X2	X1	Start / Stop	Couch	Coll	Block	Wedge	Bolus	Comp
tan int	0.00	20.00	8.00	3.50	303 / 303	0	90	MLC	MOTORI...	No	No
tan ext	18.60	0.00	8.00	3.00	127 / 127	0	270	MLC	MOTORI...	No	No
tan int red	8.00	3.10	20.00	0.00	303 / 303	0	0	MLC	None	No	No
tan ext red	3.10	8.00	18.63	0.00	127 / 127	0	0	MLC	None	No	No
s obl 335	7.10	0.00	5.00	10.73	335 / 335	0	90	MLC	MOTORI...	No	No
s obl 25	6.60	0.00	6.00	10.00	25 / 25	0	90	MLC	MOTORI...	No	No
s obl 120	0.00	6.80	4.00	8.78	120 / 120	0	270	MLC	MOTORI...	No	No

Figure 5. MU Calculated with IMRT Planning Method

Table 4. Doses to Organs at Risk for the Tow Planning Techniques

		Mean 3D-CRT	Mean IMRT
Ipsilateral lung	V20 (%)	19	13
	V5 (%)	25	90
Heart	V30 (%)	7	4
	Mean dose (cGy)	1400	495
	Minmal dose (cGy)	90	356

Table 5. Late and Acute Toxicity Developed by Patients in Followup

Toxicity	3D-CRT	IMRT
Acute toxicity		
Dermatitis		
Grade 1	5	2
Grade 2	1	6
Grade 3	1	0
Pneumonia	1	0
Myocardial infarction	0	1
Late toxicity		
Skin fibrosis		
Grade 1	0	0
Grade 2	1	0
Grade 3	0	0
Lung fibrosis	0	0
Cardiomyopathy	0	0

0.0969 one confidence interval 95% (0.0019; 0.8799) (Figure 4).

This corresponded to a mean reduction of V107 of 9.7% when the data sets were IMRT planned.

Homogeneity index/conformity index

The DHI in IMRT was found to be average 11.6 it was better than 3DCRT as average 12.5, p value: 0.28; Odds Ratio: 0.3855 confidence interval is 95% (0.0528; 2.1335). The CI was in IMRT (0.96) and better than 3D-CRT (0.95); p=1.

The MU that were calculated to treat the patients were 399.31 MU in 3D-CRT It was lowered to 802.06 MU in IMRT; p value: 0.02; Odds Ratio: 3.3464 confidence interval is 95% (1.0928; 11.2841) (Figure 5).

Organs at risk (OAR)

The average dosimetric characteristics of the OAR for the tow planning techniques are presented in (Table 4).

Lung doses: the mean volum for V20 lung doses were 13 and 19% for the IMRT and 3DCRT planning respectively. p value: 0.48117542846903; Odds Ratio: 0.6879 confidence interval is 95% (0.2403; 1.9314).

IMRT planning method contributed to no more dose that the 3DCRT. Following on from this it can also be seen that IMRT planning had an increasing effect on the V5 Lung dose giving a mean V5 doses of 90% versus 25% for the 3DCRT planning method: p value: 0.05, Odds Ratio: 3.5545 confidence interval is 95% (0.754; 16.798). It shows that IMRT contributes to more lung dose at the lower values than the 3DCRT planning methods. However IMRT contributes to low lung dose at the high dose values than 3DCRT.

Heart doses: lastly, the Heart V30 was measured for each of the planning methods. It can be seen that the IMRT results showed a reduction of the cardiac V30 dose 4% versus 7% for 3DCRT and mean heart dose 495 cGy versus 1400 cGy for 3DCRT, however IMRT results showed increase of minimal heart dose, average 356 cGy in IMRT versus 90cGy in 3DCRT planning method, when analyzed for dose-volume parameters. Significant difference: p value: 0.034; Odds Ratio: 0.2476 confidence interval is 95% (0.0557; 1.1004). The c-DVH values of the tow treatment techniques.

IMRT only seems to reduce the V20 dose of the ipsilateral lung, the heart V 30 dose and mean heart dose, when compared with 3D-CRT, however, the V5 dose of the ipsilateral lung and minimal heart dose seems increased with IMRT.

Acute toxicity

Four weeks post-radiotherapy, seven (35%) patients had acute dermatitis grade 1 according to the last CTCAE_4.02, two of them treated with IMRT, seven (35%) patients had grade 2, and six of them treated with IMRT, one (5%) patient developed grade 3 radiation dermatitis treated with 3D-CRT.

IMRT seem did not allow a gain on the dermal acute toxicity. No patients had any residual toxicity.

One case had acute pneumonia diagnosed by X-ray treated with 3D-CRT, received chemotherapy and hormone therapy, the dose constraint has been met for the lungs.

One case of myocardial infarction two months after the end of radiotherapy, HER2 negative, received chemotherapy based on Epirubicin and hormone therapy, dose constraint was respected in the heart, treated by IMRT.

There was a suggestion of a possible association

between heart toxicity and increase cardiac low dose with IMRT.

Late toxicity

Tree-years late toxicity data are available on all 20 patients (Table 5).

No grade 3-4 toxicity has occurred. One case was identified at 3 year of grade 2 toxicity, palpable induration (fibrosis) of both the lumpectomy site and whole breast was found. Patient treated with 3D-CRT.

Discussion

A number of studies have demonstrated a dosimetric benefit of IMRT compared to 3D-CRT for the whole breast in early breast cancer patients (Smith et al., 2011). The IMRT plans appeared to be the planning method of choice both in terms of coverage and hot spot reduction (Barnett et al., 2011; Rajni et al., 2012).

This study was undertaken to evaluate the dose distribution of tangential beam IMRT of the whole breast compared to tangential beam 3D-CRT in early breast cancer patients.

Our data show that tangential beam IMRT of the whole breast compared to 3D-CRT reduces the ipsilateral lung dose-volume (V20) and heart dose-volume (V30) in patients treated on the left side.

Similar results have been reported for tangential beam IMRT for the whole breast in early breast cancer patients in a recent study Smith et al. (2011).

A significantly better sparing of the high-dose volume of the heart in early breast cancer patients has been reported by the use of multifield IMRT compared to 3DCRT, multifield IMRT reduced the heart volume receiving ≥30 Gy by 87%, or ≥35 Gy by 81%.

On the other hand, multifield IMRT significantly increased the mean heart dose by an average of 24.4% (Lohr et al., 2009). the left lung D30% by 143%, and the volume of the left lung receiving ≥20 Gy by 47% (Coon et al., 2009).

In our study we found that IMRT planning increase the minimal dose V5 of the heart and lung.

Clinically recognized presentations of radiation induced heart disease have been observed in patients who received therapeutic doses of about ≥35 Gy to partial volumes of the heart. Recent studies based on atom bomb survivors

Also suggest a relationship between cardiac mortality and low radiation doses in the range of ≤4 Gy (Vicini et al., 2003; Pignol et al., 2008).

Specially if pre-existing cardiovascular risk factors as smoking, obesity, and hypertension as well as the use of cardiotoxic agents such as anthracyclines, paclitaxel and trastuzumab are likely to contribute to the development of radiation-related heart disease (Fares et al., 2012). In aour series one patient had developed myocardial infarction two months after the end of radiotherapy, treated by IMRT, so she had cardiovascular risk factors as arterial hypertension and she had received chemotherapy based on anthracyclines and hormone therapy,

Multifield IMRT has been discussed to possibly increase the risk of second cancers. The reason for this is that compared to larger volume of healthy tissue is being irradiated with lower doses due to the use of multiple beams and the high number of monitor units. Prospective studies with long follow-up times are needed to fully evaluate the cardiac toxicity and secondary lung cancer risk in breast cancer patients treated with multifield IMRT (Remouchamps et al., 2003; Schubert et al., 2011).

Even though cosmetic results are poorly documented after 3D-CRT, encouraging outcomes have been reported, such as in this present study: 98% excellent/good cosmetic results after 1 year of median follow-up (FU) (Chie et al 2009).

This is in contrast with other studies using a 3D-conformal technique as described by Vicini et al. (2003) and Hepel et al. (2009) report excellent/good cosmetic results in 81.7% of patients at 15 months of FU. In the study by Jagsi et al. (2010) the authors describe 78% of patients with excellent/good cosmetic results using an IMRT technique (at 2.5 years of median FU), in our study cosmetic results was excellent at 1 month of follow-up in 65% with 3D-CRT and 60% with IMRT, so at 3 years of median FU results was excellent in 95% with 3D-CRT and 100% with IMRT. So the sample size was small and thus further study would be required to confirm the consistency of results

In conclusion, IMRT takes more time to plan so advantages of the IMRT technique it's seem improved a long-term skin protection, improved homogeneity, reductions Cardiac and Lung high-dose areas but increased irradiated volumes in low-dose areas.

so IMRT has been discussed to possibly increase the risk of second cancers and cardiac complications. More studies would be required to confirm this results, however would suggest that IMRT should be made available when dose constraints cannot be met by conventional planning 3D-CRT.

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