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Clinical implementation of IMRT step and shoot with simultaneous integrated boost for breast cancer: A dosimetric comparison of planning techniques

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Original Article

Abstract

Purpose: Radiotherapy post-lumpectomy with two coplanar tangent beams is the standard treatment for women with early stage breast cancer. Despite the use of wedges as tissue compensators, the resultant plans often contains a significant dose gradient and 'hot spots' in excess of 15% or more of prescribed dose. In recent years a field-in-field (FIF) dose-compensation technique, which use two standard tangent fields and one or two (rarely three) small beams within these, was developed. It allows to obtain a more uniform dose throughout the target volume in the majority of cases but not in all. This study presents our experience to develop optimal intensity modulated radiation therapy (IMRT) techniques to be applied clinically in those cases where the traditional technique with two tangent fields or its variant field in field (FIF) are unable to achieve a satisfactory planning target volumes (PTVs) coverage and dose objectives to the organs at risk (OARs). **Methods:** We investigated two pure IMRT plans (named 3F-IMRT and 4F-IMRT) and a hybrid one (H-IMRT). Treatment plans were performed for 7 left-sided and 4 right-sided breasts using simultaneously integrated boost (SIB) planned technique with inverse optimization. Results were compared with those obtained with FIF technique. Dose prescribed was 45 Gy/20 fractions to the breast and 50 Gy /20 fractions to the lumpectomy cavity delivered in 5 fr/week. Dose–volume histograms were generated and parameters as target dose coverage, conformity and homogeneity as well as OARs dose distribution were analyzed. Finally the secondary cancer risk to contralateral breast due to radiation was evaluated as a further parameter for the choice of the optimal plan. **Results:** Compared to the FIF, the three IMRT plans provided the same target coverage and a better dose conformation, but a worst dose homogeneity of the boost target. The volume of the OARs, receiving higher doses than 15 Gy was reduced but was increased the volume receiving low doses. This causes the increase of the risk of radiation induced cancer, especially for the contralateral breast. For this organ, the highest value of the excess absolute risk (EAR) was associated to the 4F-IMRT, while the lower, to the FIF. **Conclusion:** The intensity-modulated radiation therapy techniques 5F-IMRT and 4F-IMRT were the best to be applied clinically in those cases, where the traditional technique of irradiation of the breast is unable to achieve the PTVs coverage and dose objectives to the OARs. However, all the IMRT techniques showed an increased volume of healthy tissues receiving low doses, so they should not be used in extensive manner and in particular should be avoided in the cases of young women due to the excess of risk to develop a secondary cancer.

Keywords: Breast cancer, Radiotherapy, IMRT, Treatment planning, Dosimetry, Contralateral breast dose, Second cancer risk.

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1. Introduction

Breast cancer is the most common malignancy among women.[1,2] The standard of care is the conserving surgery or mastectomy followed by adjuvant radiotherapy. Various studies have shown that radiation treatment significantly improves local control and long-term survival,[3,4] an additional boost to the tumor bed further reduces local recurrences.[5,6] Conventionally, breast radiation therapy of 50 Gy in 25 fractions is prescribed, with up to an additional 10 Gy in 5 fractions to the tumor bed. The boost is usually delivered after the last fraction of the whole breast treatment (sequential boost), but it is also widely used the irradiation technique in which boost is given in the same fraction just after the whole breast treatment (concomitant boost) reducing the total treatment period. When IMRT came, the SIB technique was introduced where the two target volumes (whole breast and lumpectomy cavity) were treated simultaneously with different dose levels. Anatomically, the breast presents a very challenging geometry. Doses to the lungs and heart must be kept low to avoid long-term complications, because most patients have a long life expectancy, as well as the dose to the contra-lateral breast, out of concern for possible induced second malignancies.

Three-dimensional conformal radiation therapy (3DCRT) with 2 opposed tangent fields is the standard treatment technique with the aim to achieve suitable target volumes coverage and to spare the neighboring healthy tissue. Wedges are frequently employed to compensate for different thicknesses across the breast. The efficacy of this treatment method has been proved in many clinical studies, which report positive results in terms of local control rate.

However, the traditional method, in some cases as large size breast, induces significant dose inhomogeneity as large as 15–20% in the superior and inferior regions of the breast, making relatively large hot regions and excessive exposure of normal tissue. In order to treat such cases, since 2006, we replaced the standard wedged tangential fields with FIF technique. FIF is a simple form of direct IMRT in which one or two small beams manually defined by the planner are added within the two standard tangent fields, shape and weight are optimized by planner using the multi-leaf collimator to create the best dose distribution.

Sometimes, however, also the FIF solution is not sufficient for patients with particular anatomical conformations. Thus, we started with a study which aimed to find an IMRT-SIB step and shoot technique, which allowed us to obtain better results respect to FIF treatment as: 1) a better dose coverage and conformation of the targets; 2) a lower dose to the OARs; 3) a time delivering dose comparable to the FIF technique.

In this work we report our investigation of three IMRT techniques, the results are compared with FIF concomitant boost and the risk of secondary tumor to contralateral breast is calculated.

2. Methods and Materials

2.1. Patients selection

In our hospital about 500 plans for the breast cancer are performed every year. In most of these the FIF technique is performed because it provides satisfactory dose conformation and uniformity of the targets and the respect of the OARs dose constraints. IMRT is implemented for that cases in which FIF technique is not enough to obtain an optimal dose distributions to the breast: as bottle breast (pectus excavatum) or particular anatomic conformation that implies an excessive irradiation of lung or heart. Mandatory for patient inclusion in IMRT is their ability to maintain the position during the treatment, which can take up to 20 min.

In the present study, we have selected 11 breast cancer cases post lumpectomy (7 left sides and 4 right sides) for which the standard technique did not reach satisfactory results. The tumor grading was G1-G3 (1 G1, 7 G2 and 3 G3), and the patient median age was 52 (range 32-73). In order to find a good IMRT technique to apply, four different models of planning was performed for each patient and dose distribution obtained was compared analyzing the difference in PTV dose uniformity and coverage, exposure of organs at risk and risk of second cancer induction to contralateral breast.

2.2. CT scanning

Computed tomography (CT) scans of patients were obtained using a Philips Brilliance CT (Philips Medical Systems, Andover, MA, USA) with 5-mm slice thickness. Patients were supine on a carbon fiber (breast board) in the treatment position with the ipsilateral arm positioned above the head. The clinical breast borders and lumpectomy scar were marked with radiopaque catheters. CT axial images were acquired for the area extending from 1cm above the head of the clavicle to including the entire bilateral lungs in free breathing in the lower part.

2.3. Delineation of target volumes and OARs

PTVs and OARs, defined as recommended by ICRU reports,[7,8] were delineated by expert radiation oncologist. Whole breast tissue was delimited: medially, from 2 cm to the edge of the sternum, laterally, to the midaxillary line; superiorly at the inferior edge of the medial head of the clavicle and inferiorly at the

inframammary fold. The posterior border was the junction with the chest wall or pectoralis major muscle. The breast planning target volume was obtained from the breast tissue plus a margin of 0.5 cm, then retracted from the skin by 5 mm and limited posteriorly to no deeper than the posterior surface of the ribs (to exclude the ipsilateral lung). The PTV boost was the surgical bed, based on postsurgical architectural distortion and surgical clips, correlated with the surgical scar, operative, and pathology reports.[9,10]

In this study the volume of PTV boost was called PTV2, while the whole breast volume with subtracted PTV2 was called PTV1. The organs selected as OARs including lungs, contralateral breast, heart (from its apex to the junction of the great vessels with the myocardium) and left anterior descending (LAD) coronary artery, were contoured.

An additional structure specified as "healthy tissue" was defined with the aim of evaluating the dose to all the healthy tissue, it was obtained by subtracting to the body contour the whole volume PTV1 + PTV2.

2.4. Evaluation of respiratory movements

Accurate and reproducible patient setup is a prerequisite to correctly deliver fractionated radiotherapy and can be of great relevance especially when using highly conformal techniques as IMRT. For this reason, in the preliminary phase of clinical implementation, a study of chest's movement for the respiratory excursion was done using the optical surface tracking system Align RT 5.0 by Vision RTLtd (Dove House Arcania Avenue, London UK). Align RT is a video based three-dimensional surface imaging system that is used to image the skin surface of patients before and during radiotherapy treatment. In order to minimize the setup errors that can result from respiratory motion, the system acquire real time imaging of patient. The following maximum movements of isocenter position and its projections on the patients' skin were measured: ±2 mm in the posterior-anterior direction; ±1 mm in cranio-caudal direction; ±1 mm in latero-lateral direction. In order to evaluate how respiratory excursion influence the dose-volume histogram (DVH) all the combinations of maximum isocentre's shift in x, y, z directions due to the breath were simulated and dose's distribution recalculated. The obtained results showed that the volume covered by the isodose 95% ranged between 99% (no isocenter shift) and 97.5% for the targets while as regards all the OARs the dose variation was between 0% and ± 2.5%. In all cases the dose constraints were always respected. To accommodate respiratory motion, in all the IMRT plans a skin margin in air was given to the fields enlarging at least 1.5 cm out of the body contour.

2.5. Dose prescription and constraints

The prescribed dose for all patients was 45 Gy/20fr (2.25 Gy/fr) to the PTV1 and 50 Gy/20fr (0.25 Gy/fr) to the PTV2 through concomitant boost technique for FIF and SIB for IMRT step and shoot plans. In Table 1 dose constraints for breast/boost target volumes and OARs are reported. Plans were normalized so that 95% of the prescription dose was delivered at least 95% of the target volumes.

Table 1: Dose constraints for breast/boost target volumes and organs at risk for a prescribed dose of 45 Gy to the PTV1 and 50 Gy to the PTV2

Tissue/Organ	Objective/constraints
PTV1/PTV2	$D_{95\%}$ ≥ 95%
Ipsilateral lung	$V_{20\%}$ ≤ 20%
Heart	$V_{30\%}$ ≤ 5%
	$V_{20\%}$ ≤ 10%
	$V_{10\%}$ ≤ 15%
	$V_{5\%}$ ≤ 20%
Contralateral breast	$V_{5\%}$ < 15%

Dx%=percentage of prescribed dose given to x% of volume target . Vx%=percentage of the volume receiving x% or more of prescription dose.

2.6. Planning technique

Four techniques have been investigated in order to determine the optimal one:

- field-in-field technique (it was the reference with which to compare the others);
- hybrid inverse planning (H-IMRT);
- IMRT inverse planning with 4 fields, 2 medial and 2 lateral (4F-IMRT);
- IMRT inverse planning with 5 fields, 2 medial, 2 laterals and 1 anterior (5F-IMRT).

All plans were generated using Oncentra Masterplan V.4.3 TPS. Beam gantry angles were chosen mainly on the basis of the internal and external anatomy of patients by using 6 MV photon beams delivered by an Elekta Precise linac. Collapsed cone convolution algorithm was used for the dose calculation. For all the IMRT Inverse planning, step and shoot technique was applied.

The FIF technique is a 3DCRT technique but can be seen also as a very simple IMRT forward planning. Since 2006 it is performed in our hospital using two standard tangent field and one or two small beams within these (Figure 2-a1). These subfields were designed to reduce hot volumes in the breast and the dose to the OARs due to the large tangent fields. About 90% of the prescribed dose to the breast was delivered by the primary fields while the remaining 10% by the FIF (Figure a1). Additional 5 Gy was given to the lumpectomy cavity by concomitant boost (Figure 2-a2). The H-IMRT combined two open standard tangent fields directly optimized, weighted 20%, and the same beams plus two

additional fields at optimal angles, to cover the PTV Boost inversely optimized, weighted 80%[10] (Figure 2-b). The 4F-IMRT used the same beams of the H-IMRT but entirely inversely optimized (Figure 2-b). Lastly, the 5F-IMRT was obtained adding to the 4F-IMRT, an oblique anterior beam with a low weight (Figure 2-c). As regards the treatment delivery time of the IMRT techniques, it was not too longer than the field-in-field (20 min vs. 15min), but, the pre-treatment steps (contouring of organs, planning and pre-treatment verification) were time expensive for physicist and physician staff.

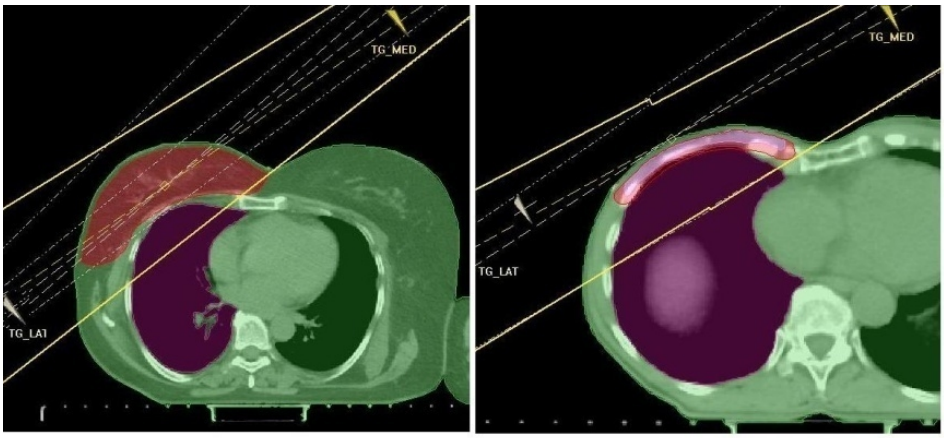

Figure 1: Examples of patients candidate for IMRT. On the left, a case of sternum re-entered, on the right a particular anatomic conformation with a large lung volume included in the tangential fields.

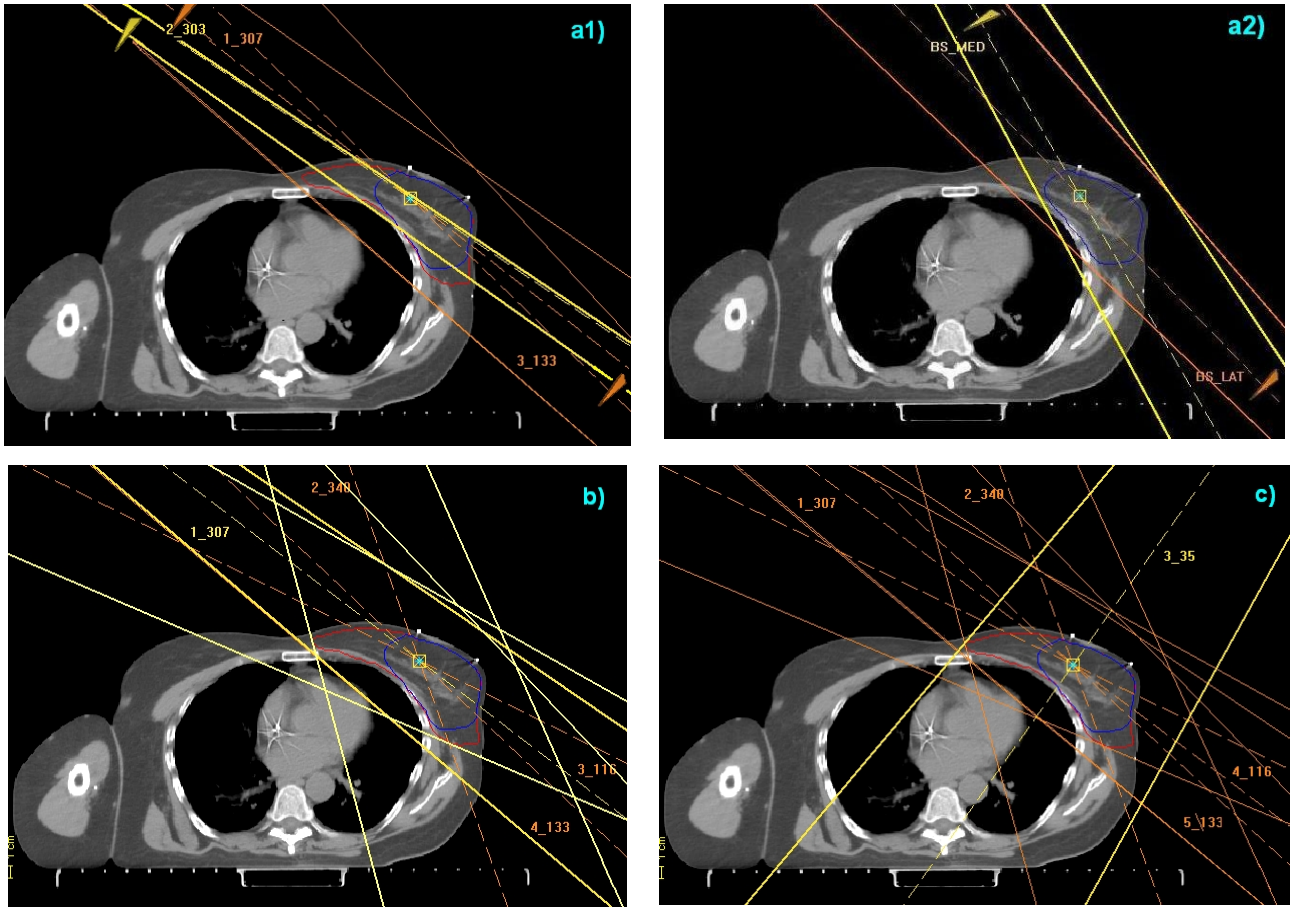

Figure 2: Beam orientation. a1) tangent beams of the FIF technique; a2) simultaneous boost of FIF; b) H-IMRT and 4F-IMRT; c) 5F-IMRT.

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2.7. Dose evaluation parameters

To evaluate the dose distribution to PTVs and OARs, the dose information was collected from DVHs. For the target dose coverage, conformity and homogeneity analysis, four indices were calculated for each plan assuming as reference isodose the 95% of the prescribed dose.

Target Coverage (TC), calculated with the formula of Salt-Lomax-Scheib:[11-14]

$$TC = \frac{V_{t,RI}}{V_t}$$

where, $V_{t,RI}$ is the volume covered by the reference isodose 95% and V_t is the target volume, is used to evaluate the target coverage by the reference dose and ranges between 0 and 1, where 1 is the ideal value.

Conformity Index (CI), defined as Lomax and Scheib suggest[11-14], by the ratio of the tissue volume covered by the reference isodose $V_{t,RI}$ (95%) and the volume enclosed by the reference isodose V_{RI}:

$$CI = \frac{V_{t,RI}}{V_{RI}}$$

is used to evaluate the conformity of the target by the reference dose; it can assume values between 0 and 1, where 1 is the best value (good conformation of target and lower dose to nearest organs), whereas values closer to zero indicates total absence of conformity.

Conformation Number (CN) by Riet *et al.*[13-14], is the product of the first two indexes and takes into account both the irradiation of the target volume and of healthy tissue:

$$CN = CI \times TC = \frac{(V_{t,RI})^2}{V_{RI} V_t}$$

As TC and CI, CN can assume values between 0 and 1, where 1 is the ideal value (good conformity and coverage of the target).

Homogeneity Index (HI), defined as the formula recommended in ICRU Report 83,[8] but assuming as minimum PTV dose $D_{95\%}$:

$$HI = \frac{D_{2\%} - D_{95\%}}{D_{50\%}} 100$$

HI assumes values ≥ 0 but, on the contrary of the other indexes, values closer to zero indicates a greater homogeneity.

3. Results and Discussions

3.1. Target

The obtained mean doses to PTV1 and PTV2, considering all the patients of the study, are showed in Table 2. The t-test was applied to determine the statistical differences between the dose volume data for IMRT versus FIF plans. The p-value calculated is two tailed and p-values < 0.05 are considered significant.

The average dose to the 100% of PTV1 in all the plans ranges between 46.07 Gy (102.3%) for 5F-IMRT and 47.33 Gy (105.1%) for FIF. The dose coverage, $D_{95\%}$, is about 43.3 (96.2%) for 4F-IMRT and 5F-IMRT against 44.3 (98.4) for FIF. The difference between $D_{2\%}$ (near maximum dose[8]) of FIF and IMRT plans is not statistically significant.

The same parameters are shows for PTV2. Here, on the contrary of PTV1, substantially no significant differences result between all values except in the case of the V_{100} that has the minimum value with the 4F-IMRT.

To have a visual immediate comparison between the different techniques about the dose coverage, conformity and homogeneity of the targets for each plan, the indices TC, CI, CN and HI were calculated and results for PTV1 and PTV2 showed in cumulative histograms of Figure 3 and Figure 4.

The ideal value for CI, TC and CN is 1 so, for the 11 patients of this study, the best value obtainable in cumulative histograms, or maximum total score is 11. For HI, instead, the best total score is 0.

For PTV1 and PTV2 all the techniques have a good cumulative target coverage TC (10.5 - 11.0), whereas the cumulative CI for FIF is significantly lower than in the three IMRT. These results are confirmed looking the cumulative CN, here is evidenced the equivalence of the three IMRT techniques for the PTV1, but not for the PTV2, where 5F-IMRT is better than 4F-IMRT and this, in turn, is better than H-IMRT. As regards the homogeneity, we find the best value of cumulative HI in the 4F and 5F-IMRT for PTV1 and in the FIF for PTV2.

Table 1: Comparison of mean doses (Mean ± SD) to PTV1 (breast-boost) and PTV2 (boost) for FIF, H-IMRT, 4F-IMRT and 5F-IMRT planning techniques; prescription dose: 45 Gy to PTV1 and 50 Gy to PTV2.

Target	Parameter	FIF mean ± SD	H-IMRT mean ± SD	4F-IMRT mean ± SD	5F-IMRT mean ± SD
PTV1	D_{mean} (Gy)	47.33 ± 0.69	47.32 ± 2.73	46.31 ± 0.56†	46.07 ± 0.41†
	$V_{100\%}$ (%)	87.90 ± 6.11	81.88 ± 7.95	77.24 ± 8.80†	72.84 ± 7.96†
	$D_{95\%}$ (Gy)	44.33 ± 0.43	44.25 ± 2.60	43.25 ± 0.62†	43.33 ± 0.31†
	$D_{2\%}$ (Gy)	51.55 ± 0.91	50.51 ± 2.73	49.03 ± 0.67	49.07 ± 0.65
PTV2	D_{mean} (Gy)	51.13 ± 0.64	52.09 ± 2.60	50.37 ± 1.48	51.47 ± 0.73
	$V_{100\%}$ (%)	79.41 ± 11.48	81.90 ± 8.84	62.43 ± 19.61†	79.04 ± 11.78
	$D_{95\%}$ (%)	48.97 ± 0.67	49.68 ± 2.60	47.97 ± 1.55	48.84 ± 0.53
	$D_{2\%}$ (Gy)	53.15 ± 0.83	54.42 ± 3.16	53.10 ± 1.04	53.76 ± 0.90

SD = standard deviation; $D_{x\%}$ = lowest dose received by at least x% of the volume.
$V_{x\%}$=percentage of the volume receiving x% or more of prescription dose;
†= statistically significant difference with FIF technique ($p < 0.05$).

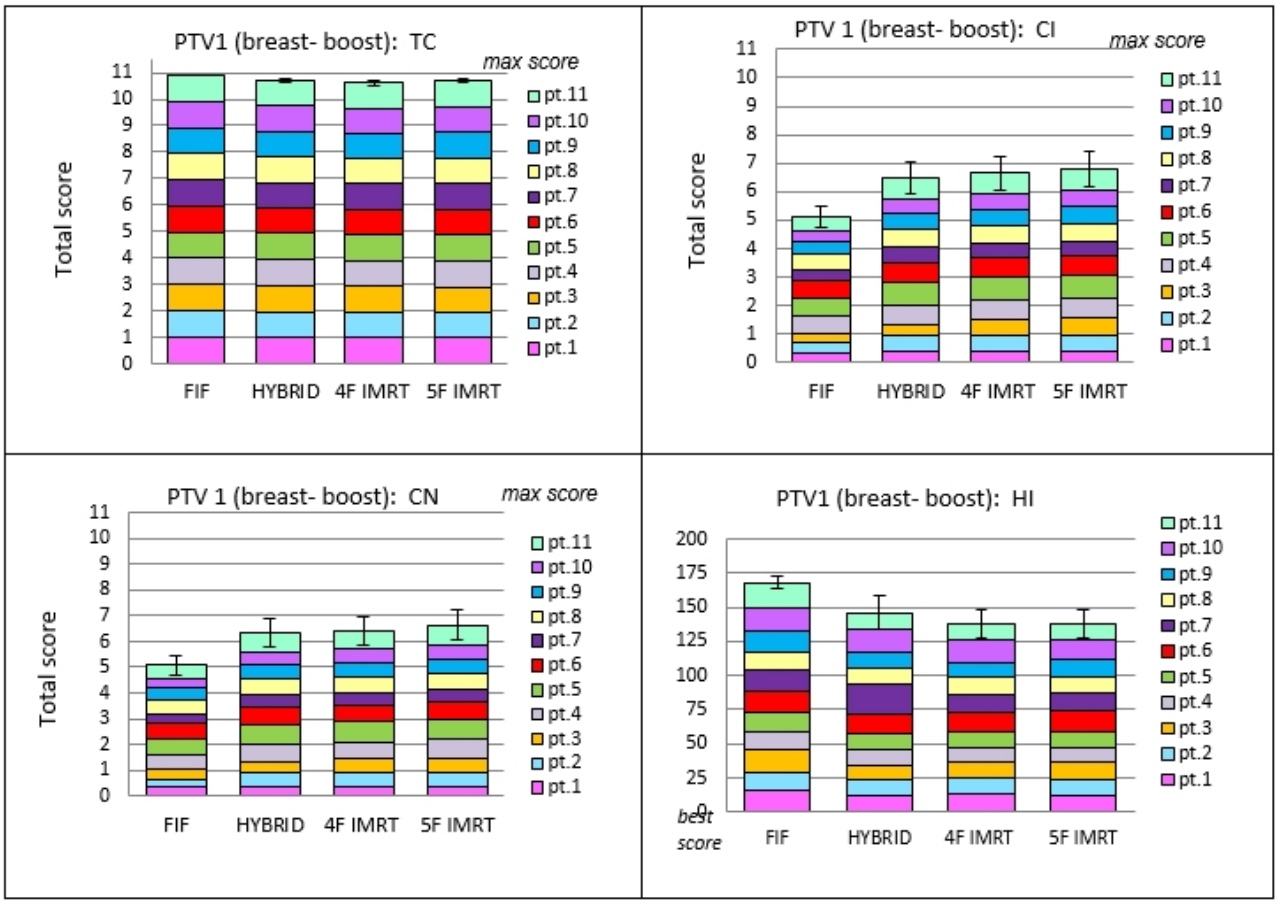

Figure 3: Comparison of PTV1 (breast-boost) cumulative index scoring for the four irradiation techniques.

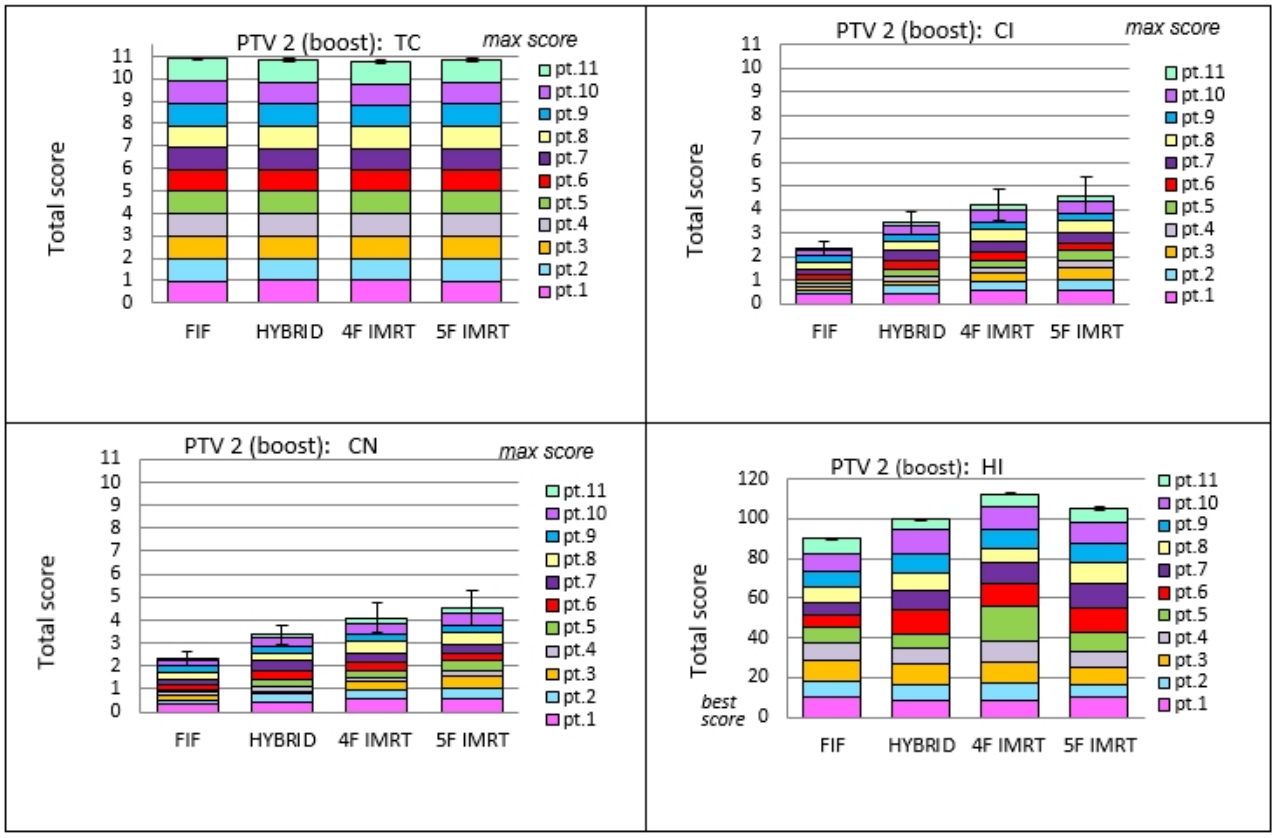

Figure 4: Comparison of PTV2 (boost) cumulative index scoring for the four irradiation techniques.

3.2. Organs at risk

The organs at risk data were analyzed according to plan objectives. Mean dose volume and standard deviations for the heart, LAD artery, lungs, contralateral breast and for all healthy tissue body-(PTV1 + PTV2) are showed in Table 3. The dose constraints were respected for all plans.

For the heart, when left breast irradiation is taken into account, by analyzing the p-value, only V_{40Gy} and V_{5Gy} have significant differences among the three IMRT planning and FIF technique. As expected, the volume of the heart receiving high doses is lower for IMRT planning compared to the FIF due to beam directions, whereas the opposite happens with low doses (Table 3).

For the LAD artery, the dose does not present statistically significant difference between IMRT and FIF ($p > 0.05$).

In both lungs the 5F-IMRT plan exhibits the highest mean dose, however, in the ipsilateral, the three IMRT techniques exhibit the V_{40Gy} and V_{30Gy} lowest than the FIF case, while, V_{20Gy} is substantially equivalent in all the four techniques.

A particular organ at risk, for the second cancer induction, is the contralateral (CTRL) breast. In Table 3 we can see as the mean dose and the V_{5Gy} volumes are low in all the cases, respectively < 1Gy (2% of the prescribed dose) and < 0.3 Gy (0.6% of the prescribed dose). As is intuitive, the volume percentage of contralateral breast receiving 2 Gy (V_{2Gy}) is lower using the FIF technique compared to IMRT cases, whereas the highest mean dose is given by the 5F-IMRT. In the remainder of this work, the risk of radiation-induced cancer to this organ will be assessed.

Regarding the dose distribution to healthy tissue (body-whole breast) significant differences among dose-volume parameters of IMRT and FIF plans can be observed. Figure 5 shows the curves obtained fitting with a polynomial the data in Table 3 (volume versus the dose received at the healthy tissue). We can see as, in the low dose range (less to about 15 Gy), the technique FIF gives less dose to healthy tissue than the three IMRT techniques. Among these, the 5F-IMRT presents the highest volume contoured by low dose (V_{5Gy} = 24.21%). The situation is reversed for doses greater than about 15 Gy, indeed, in this range the healthy tissue receives the highest dose from the FIF plan.

Table 2: Doses (mean ± SD) to organs at risk for FIF, H-IMRT, 4F-IMRT and 5F-IMRT planning techniques; prescription dose: 45Gy to PTV1 and 50 Gy to PTV2.

OAR	Parameter	FIF mean ± SD	Hybrid mean ± SD	4F-IMRT mean ± SD	5F-IMRT mean ± SD
HEART left breast irradiation	D_{mean} (Gy)	4.80 ± 2.08	4.51 ± 1.16	4.58 ± 1.02	5.28 ± 0.73
	V_{40Gy} (%)	3.88 ± 2.57	2.41 ± 1.34†	1.16 ± 0.93†	1.18 ± 0.90†
	V_{30Gy} (%)	6.44 ± 4.18	4.53 ± 2.34	3.70 ± 1.95	3.59 ± 2.12
	V_{20Gy} (%)	7.97 ± 4.82	6.32 ± 2.95	5.66 ± 2.70	5.50 ± 2.87
	V_{10Gy}(%)	10.06 ± 5.56	9.47 ± 3.69	9.37 ± 3.08	9.77 ± 2.21
	V_{5Gy} (%)	13.60 ± 6.52	16.95 ± 5.36†	19.16 ± 3.52†	23.44 ± 5.84†
LAD artery	V_{20Gy} (%)	53.31 ± 34.57	51.80 ± 34.62	42.10 ± 33.11	39.11 ± 33.39
	D_{max} (Gy)	30.97 ± 16.43	27.09 ± 14.33	26.01 ± 15.22	24.17 ± 13.15
IPSL LUNG	D_{mean} (Gy)	8.55 ± 8.43	8.78 ± 8.37	9.30 ± 8.72	11.13 ± 10.82†
	V_{40Gy} (%)	8.06 ± 4.02	3.92 ± 2.60†	3.49 ± 2.39†	2.81 ± 1.60†
	V_{30Gy} (%)	13.61 ± 5.12	10.92 ± 4.07	10.14 ± 3.69	10.32 ± 3.51†
	V_{20Gy} (%)	16.41 ± 5.32	16.09 ± 5.22	15.81 ± 4.84	16.96 ± 4.08
CTRL LUNG	D_{mean} (Gy)	0.37 ± 0.14	0.98 ± 1.84	0.43 ± 0.17	2.23 ± 1.25†
	V_{5Gy} (%)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.01	11.56 ± 19.58
	V_{2Gy} (%)	0.21 ± 0.32	0.40 ± 0.64	0.37 ± 0.67	35.36 ± 21.37
CTRL BREAST	D_{mean} (Gy)	0.55 ± 0.12	0.66 ± 0.13	0.58 ± 0.31	0.73 ± 0.14†
	V_{5Gy} (%)	0.11 ± 0.23	0.11 ± 0.17	0.29 ± 0.49	0.20 ± 0.28
	V_{2Gy} (%)	1.48 ± 1.33	2.43 ± 2.08	2.67 ± 3.06	2.71 ± 2.48
	$D_{2\%}$ (Gy)	9.54 ± 11.15	5.70 ± 3.61	4.88 ± 3.38	5.35 ± 2.78
HEALTY TISSUE	D_{mean} (Gy)	4.21 ± 2.73	4.36 ± 2.67	4.33 ± 2.58	4.78 ± 0.84
	V_{50Gy} (%)	0.21 ± 0.19	0.17 ± 0.48	0.02 ± 0.03†	0.02 ± 0.02†
	V_{45Gy} (%)	1.90 ± 1.03	0.77 ± 0.90†	0.49 ± 0.29†	0.42 ± 0.30†
	V_{30Gy} (%)	5.94 ± 1.93	5.03 ± 1.51	4.68 ± 1.11	4.54 ± 1.04†
	V_{20Gy} (%)	6.96 ± 2.06	6.63 ± 1.92	6.44 ± 1.65	6.50 ± 1.50
	V_{15Gy} (%)	7.58 ± 2.21	7.62 ± 2.33	7.56 ± 2.11	8.03 ± 1.82
	V_{10Gy} (%)	8.38 ± 2.39	9.42 ± 3.19	9.81 ± 3.05	11.42 ± 2.91†
	V_{5Gy} (%)	10.03 ± 2.73	14.91 ± 4.07†	15.73 ± 3.68†	24.21 ± 7.06†

SD = standard deviation; $V_{x\%}$=percentage of the volume receiving x% or more of prescription dose; $D_{x\%}$=lowest dose received by at least x% of the volume.

†= statistically significant difference with FIF technique ($p < 0.05$).

Table 4: Organ Equivalent Dose (OED) Gy and Excess Absolute Risk (EAR) for contralateral breast.

	FIF mean ± SD	Hybrid mean ± SD	4F-IMRT mean ± SD	5F-IMRT mean ± SD
OED (Gy)	0.6±0.3	0.8±0.3	0.9±0.4	0.7±0.1
EAR*	2.3±1.1	2.9±1.1	4.0±3.2	2.7±0.5

*per 10.000 women-years at age of 70 years after exposure at the age of 50 years.

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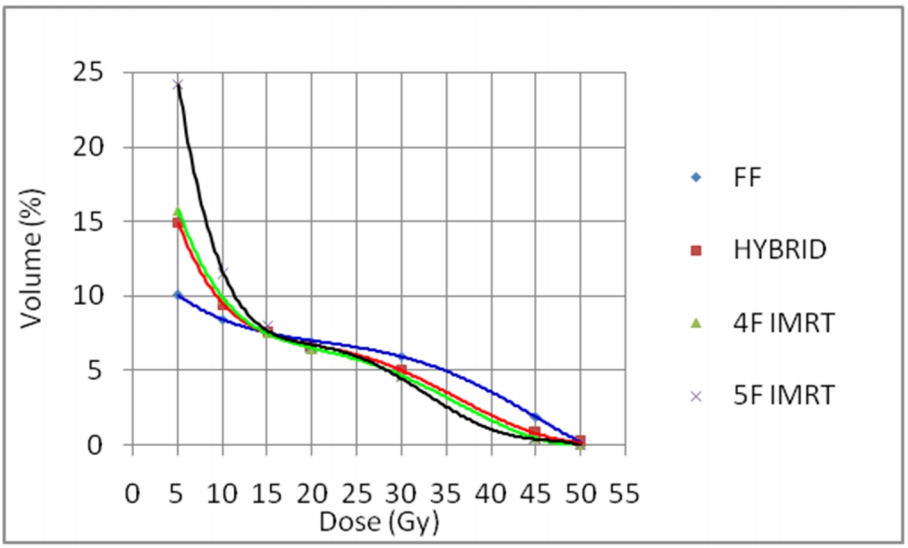

Figure 5: V% vs. dose for healthy tissue (body-whole breast) when 45 Gy was given to PTV1 and 50 Gy to PTV2.

3.3. The risk of second cancer induction

When an irradiation technique is applied to a large number of patients in clinic, it must be take into account not only the high dose to the OARs, in order to avoid deterministic damage, but also the low dose to healthy tissue in order to limit the stochastic risk of second cancer induction. In radiotherapy treatment, high doses of radiation are used to irradiate the tumor; therefore, the stochastic risk of radiation-induced cancer to neighboring healthy tissues affected by scattered or direct scattered radiation can assume non-negligible values. Looking at the results of our study, it is evident the advantage of the IMRT technique compared to FIF in the breast irradiation: the same dose coverage of the target but a better conformation of it and a spare of organs at risk from high dose. However, the volumes of OARs affected by low doses are larger with IMRT. This can be observed in Figure 6 where the dose distributions obtained with 5F-IMRT and FIF plans in the same CT slice are reported. To allow a better detail of the images the low doses range (0-200 cGy) has been emphasized.

The breast tissue is very sensitive to radiation, especially for young women, thus, to find an alternative technique to the FIF to be used clinically, we also evaluated the secondary cancer risk to contralateral breast due to radiation.

In our plans the mean secondary dose per 50 Gy treatment dose to this organ was less than 1 Gy: 0.55, 0.66, 0.58 and 0.73 Gy, respectively for FIF, H-IMRT, 4F-IMRT and 5F-IMRT plans. However, the dose distribution was highly inhomogeneous as shown, as example, in Figure 7 for two techniques used in this work, where a small part of its volume may receive 5 Gy or more. We calculated the risk of developing a solid second cancer after the radiotherapy using BEIR (Biological Effects of Ionizing Radiation) VII Phase 2 models.[15,16] The EAR at low dose per 10,000 persons-years was evaluated through the organ equivalent dose (OED) for the linear model based on the differential DVHs.[17,18] The EAR is the additional risk above the background absolute risk (in the absence of exposure), while OED, for any inhomogenous dose distribution in an organ, is the dose in Sv, which, when distributed uniformly across the organ, causes the same radiation induced cancer incidence. OED values are age independent and can be used to compare different treatment plans with regard to the organ- and plan-specific secondary cancer induction rate.

EAR= $EAR_0 \cdot$ OED (per 10,000 persons-years per Gy)

$$OED_{T,linear} = \frac{1}{V_T}\sum_i (DVH(D_i) \bullet D_i)$$

where, DVH (Di_j) is the volume of the voxel i of organ T receiving the dose D_i and V_T is the total organ volume.
EAR_0 (per 10,000 persons-years per Gy) is the excess absolute risk at low doses. For breast cancer induction in females at low doses EAR0 = 3.7 cases per 10,000 persons-years per Gy at age of 70 years after exposure at age of 50 years.[19]

Analyzing the DVH data we calculated the EAR values in contralateral breast for all the plans. The results are showed in Table 4.

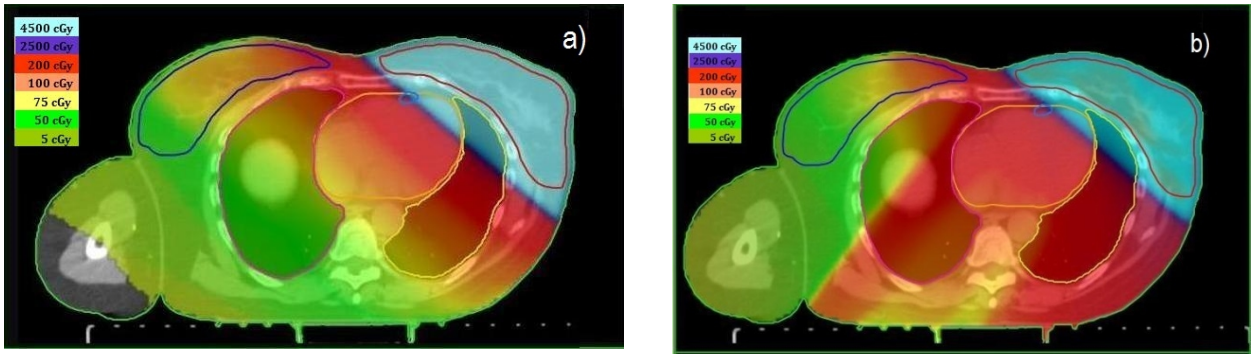

Figure 6: Dose distribution in a transverse plane of the patient due to FIF technique (a) and 5F-IMRT (b).

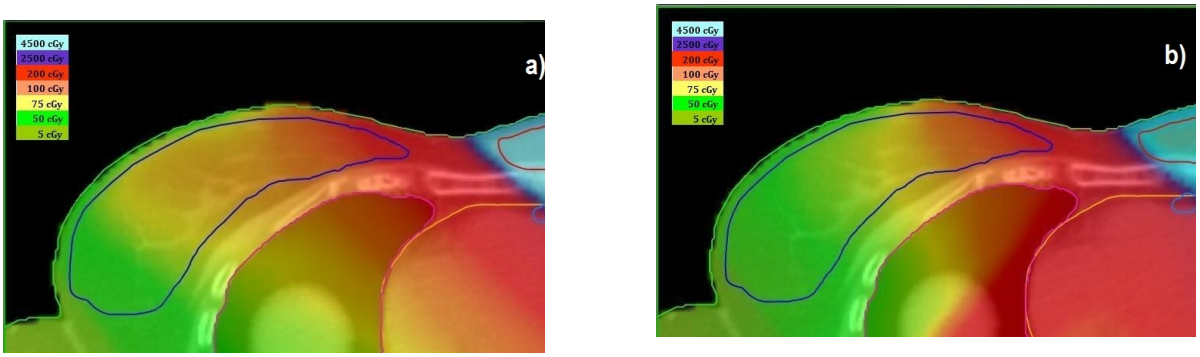

Figure 7: Dose distribution to the contralateral breast in a transverse plane due to FIF technique (a) and 5F-IMRT (b).

As expected, the associated risk is higher in IMRT plans respect to FIF mainly due to multiple beam angles used and to scatter dose. The highest value is in the 4F-IMRT plan and not in 5F-IMRT because in the latter the added anterior beam discharge the dose to the contralateral breast, but the penalty is an increased dose to the heart and lungs as shown in Figure 6b). Thus, in the case of younger patients (<45 years) the 4F-IMRT and 5F-IMRT techniques should be avoided as they increase the risk of radio-induced cancer to the breast the first and to heart and lungs the second.

4. Conclusion

The IMRT step and shot technique was implemented in our hospital for those cases in which the standard tangential fields technique or its variant field-in-field, not allowed to obtain good conformation and uniformity of the dose to the targets or sparing of OARs.

In this study we investigated three different IMRT techniques for 11 patients, in terms of delivered dose to targets (PTV breast and PTV boost) and estimated risks of secondary cancer for normal organs. The results were compared to those obtained with the FIF. We found that all the techniques achieved approximately the same coverage of the two targets, but the three IMRT provided an improved conformation. The homogeneity was better with IMRT for PTV1 but for PTV2 it was better with the FIF. All the three IMRT techniques reduced volumes of the OARs, as lungs, heart and contralateral breast, which received doses greater than about 15 Gy, but the low dose (less than about 15 Gy) to the same normal tissues, was increased. Respect to FIF, the larger volume irradiated to low dose increased the risk of radiation induced cancer, so these treatments should not be used extensively, but limited only to those cases in which 3DCRT techniques are unable to achieve optimal results. Regarding the treatment delivery time of the IMRT techniques it was not too longer than the field-in-field (20 min vs. 15 min) but the pre-treatment steps (contouring of organs, planning and pre-treatment verification) were time expensive for physicist and physician staff, a further reason to reduce the application of these techniques only to selected cases.

Conflict of Interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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