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ORIGINAL ARTICLE

Evaluation of Inverse Planned and Forward Planned Intensity Modulated Radiotherapy Techniques in Breast Cancer

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Abstract

Introduction: The objective of this study is to compare the dosimetric parameters of radiation to the whole breast between the two intensity-modulated radiotherapy (IP IMRT) techniques, i.e. Inverse planned IMRT (IP IMRT) and Forward Planned IMRT (FP IMRT) with regard to target coverage (PTV) and irradiation of organs at risk (OAR). **Material and Methods**: Plain and Contrast enhanced computed tomography (CECT) datasets were created for 41 patients treated with whole breast radiation therapy. CT simulation and treatment is performed using deep inspiratory breath hold technique (DIBH). Radiotherapy treatment Planning is done using Eclipse Treatment Planning System (version 13.7) with a prescription dose of 40 Gy in 15#. The developed treatment plans were subjected to objective comparison of PTV and OARs using dose volume histograms (DVH). **Results:** IP IMRT plans provided better coverage (99.5% vs 97.6%), comparable though higher maximum dose (Dmax 45.0 VS 44.1 Gy), higher hot spot (PTV105% 49.2 vs 33), lower volumes receiving 20, 25, 30 Gy (V20, V25, V30) for heart, more homogeneous (homogeneity index 0.10 vs. 0.14) and conformal dose distribution (conformity Index 1.0 vs 0.98) compared to FP IMRT. Regarding OAR dosimetry it is observed that FP IMRT showed reduced mean dose to Coronary artery (LADCA), Contralateral Lung (CL), Contralateral breast (CB) along with reduction in low dose region (V5) to all OARs under study. It was also observed that Monitor units used and planning time were lower for FP IMRT. **Conclusion:** On weighing different dosimetric factors, both the techniques have displayed their own advantages and disadvantages. Choosing a planning technique needs to be customized taking into consideration various factors such as breast topography, size and volumes of breast, availability of expertise planning skills and resources.

Keywords: Breast cancer, Intensity-Modulated Radiation therapy, DIBH Method, Hypofractionation

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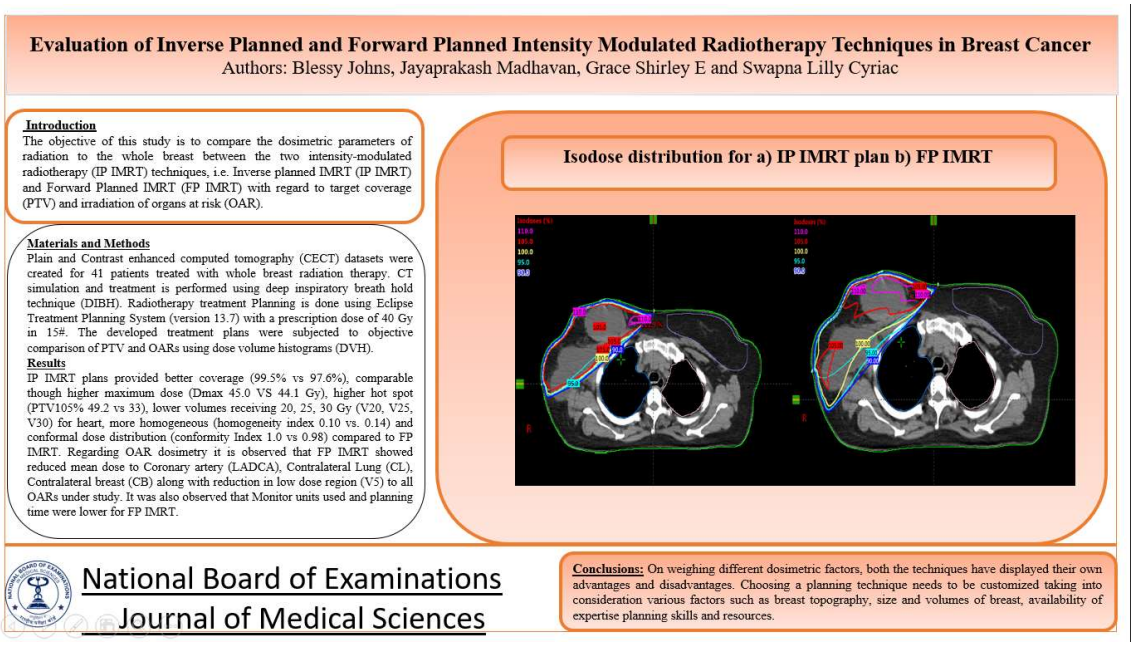
Graphical Abstract



Introduction

It has long been the standard of practice for women who have had Breast Conservation Surgery (BCS) to have their entire breast irradiated for Early Breast Cancer (EBC) [1]. The Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis demonstrated local control and survival gains which serves as the groundwork for this practice [2].

Evolution of radiotherapy (RT) from Conventional 2D Wedge technique to three dimensional conformal radiotherapy (3D CRT) over the years is based on improving clinical outcome by maximizing therapeutic ratio ie maximum tumor control with minimal normal tissue complications. 3D CRT has the disadvantage of inhomogenous dose distribution, resulting in hotspots and normal tissue toxicity despite having good local control [3]. Hence novel radiation therapy technologies have been developed to address these issues, which lead to advances including Intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), lately electronic tissue compensation (Ecomp) [4].

IMRT is a technique that lowers normal tissue toxicity while delivering highly conformal radiation with better dose homogeneity. Treatment intensification is possible using IMRT since IMRT permits selective dose escalation within gross tumor volumes with acceptable toxicity (simultaneous integrated boost) [5]. The two common descriptors for IMRT are forward planning "fields in field" IMRT (FP IMRT) and inverse planning IMRT (IP IMRT). The parameters of beams with respect to number, direction, aperture, and weights in IP IMRT are determined by inverse planning optimization to meet adequate target coverage while meeting OAR dose constraints goals. The FP IMRT planning technique create subfields in open field by placing MLC (Multileaf Collimator) to hot

areas at the same time making sure target coverage is achieved by viewing isodose distribution in beams eye view (BEV) projection.

Another advancement in breast cancer RT technology is Respiratory gating (RG) techniques, including deep inspiration breath hold (DIBH) which has led to decreased incidence of RT induced Cardiovascular disease [6]. The purpose of using radiation during a deep breath hold is based on the observation that during a deep breath diaphragm flattening and lung expansion cause the distance between the breast and chest wall to reach its maximum. Timing radiation in DIBH has shown reduction in radiation dose to heart, ipsilateral lung and LADCA (Left anterior descending coronary artery) compared to free breathing in several studies [7].

In this study, radiation dose to breast which is PTV and adjacent normal tissue (OAR) are compared between IP IMRT and FP IMRT techniques incorporating DIBH prescribed for hypofractionation schedule which is the current standard of care in practise.

Materials and Methods

Patient Selection

This study was a prospective observational research project done from September 2018 to June 2019 conducted at KIMS Cancer centre, Trivandrum post Institutional human ethics committee (IHEC) approval. Females less than 70 years who have undergone BCS for early breast cancer with ECOG Performance Status 0-1 and comfortable breath hold lasting for 15 seconds were included. Twenty cases of the left sided and twenty one cases of the right sided breast cancer, with different breast volumes and separations were chosen.

Immobilization and CT simulation

Whole breast and post-operative surgical scars were marked with radio-opaque wire. Patients were counseled regarding the process of acquiring breath hold and trained prior to the planning CT scan. Patients were immobilised in supine position using vacuum cushion (vaclok), with head turned to the opposite side and both arms lifted above the shoulders.

On the day of simulation, patient's ability to hold their breath without any discomfort in treatment position was assessed. Free breathing scans followed by DIBH planning scans both plain and contrast enhanced CT scans (CECT) of slice thicknesses of 3 mm were obtained. The vertical displacement of chest wall during respiratory movement is measured to set the threshold. The reproducibility of breath hold threshold is verified by taking CBCT images during entire breathhold and compared with threshold obtained at simulation. Treatment was done by placing a block with reflective markers on the chest wall below the xiphoid process. The camera system linked to linear accelerator is automatically set to hold beam when patient's breathing fall outside of the acceptable threshold. This ensures patient is treated in deep inspiration.

Target Volumes

CT images is transferred to a planning system with an Eclipse External Beam Planning software. Image registration and delineation of gross tumour volume (GTV), PTV and OARs are carried out according to the RTOG Consensus guidelines for delineating target and normal structures for breast cancer in plain CT images [8].

Breast CTV consists of the apparent glandular breast tissue seen by

CT, as well as the palpable breast tissue marked with radio-opaque markers during CT simulation and the Lumpectomy CTV. The intact breast PTVs were restricted to 5mm under the skin surface, to exclude the buildup region from the PTV. The contralateral breast PTV consists of apparent CT glandular breast tissue seen by CT. Lung volumes were contoured with auto segmentation with manual verification. The heart was contoured from below the level where the pulmonary trunk divides into the left and right pulmonary arteries to its lower limit near the diaphragm [9]. The Liver was delineated slice by slice based on RTOG upper abdomen contouring guidelines [10]. Contouring of Left anterior descending branch of coronary artery (LADCA) was done according to heart atlas by Feng et al. [9].

Treatment planning

For each dataset, two distinct IMRT plans (IP IMRT and FP IMRT) were generated and compared against each other independent of original plan used for treatment to minimise variability in contouring and planning and to make more suitable for comparability. For consistency all planning was done with same physicist. The planning was done by hypofractionation schedule of 40 Gy in 15# so as to meet the planning objective shown in Table 1.

Table 1. Dose-Volume Constraints for Planning Whole Breast Hypofractionated Radiotherapy

Structure	Criteria
Breast CTV	PTV 95% ≥ 95% D_{max} ≤ 46Gy
Heart	V20Gy ≤ 5% (L), V20 <0%(R) V10Gy ≤ 30% (L), V10Gy ≤ 10% (R) Dmean ≤ 4 Gy
LADCA	Dmax ≤ 30Gy Dmean ≤ 6Gy
Lung (IL)	V20Gy ≤ 15% V10Gy ≤ 35% V5Gy ≤ 50%
Contralateral lung (CL)	V5Gy ≤ 10%
Contralateral breast (CB)	Dmax ≤ 310 cGy D5% ≤ 186Gy
Liver	Dmean <20 Gy

CTV = clinical target volume, D% = dose that receives the % the volume, VGy = volume that receives the dose in Gy, D_{mean} = mean dose D_{max}, = maximum dose, LADCA- Left Anterior Descending branch of Coronary artery, L-Left sided breast cancer, R-Right sided Breast cancer

Inverse planning IMRT (IP IMRT)

Technique

IP IMRT optimized plans were generated using 7 different photon beam direction at an interval of approx 20 degree so as to achieve optimal target coverage keeping exit and entry dose to OAR minimal (Figure 1). Further the planner proceeds for refinements by manual fluence editing for expanding PTV coverage, bring down OAR doses or scaling down/eliminate hotspot.

Forward planning IMRT (FP IMRT)

Two open tangential fields of equal weights were created with the "isocentre" of the treatment machine placed at the centre of the midline joining two opposing fields (Figure 2). Subfields were generated by manually placing MLC to hot areas without compromising PTV coverage by viewing isodose on BEV projection using 95% dose cloud. The hot areas are kept in check by aided visualization of 110% dose cloud in BEV Projection.

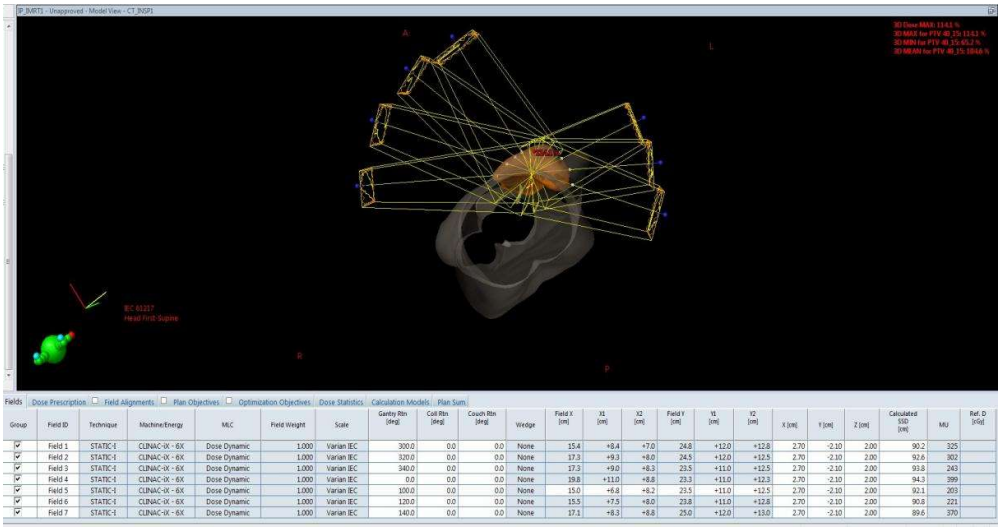


Figure 1. Beam Arrangements for IP IMRT.

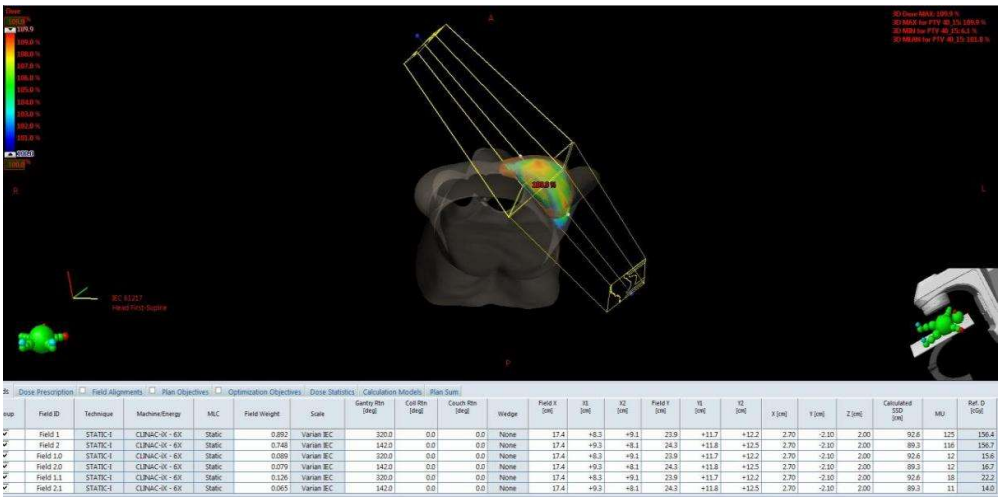


Figure 2. Beam arrangement for FP IMRT plan

Plan comparison and statistical analysis

PTV and OARs were compared objectively using DVH. The parameters were analysed using student's t-test with p value significance testing.

Evaluation parameter for PTV

The parameters listed in Table 2 were utilized to compare the plans with respect to PTV and OAR.

Table 2. Plan Evaluation parameters of PTV and OARs

Plan Evaluation Parameters	
PTV	PTV coverage of 95% with prescription isodose line of 95% (PTV95%) Maximum dose delivered to the target volume (D_{max}) Target Volume receiving 90%, 99% and 105% of dose ($V_{90\%}$, $V_{99\%}$, $V_{105\%}$) Homogeneity index (HI) Conformity index (CI)
Heart	Mean dose to the Heart (D_{mean}) Volume of Heart receiving 5Gy,20Gy,25Gy,30Gy (V_5, V_{20}, V_{25}, V_{30})
LADCA	Maximum dose(D_{max}) Mean dose (D_{mean})
Lung(IL)	Mean dose to the lung (D_{mean}) Volume of Lung receiving 5Gy and 20 Gy (V_5 and V_{20})
Contra lateral Breast(CB)	Mean dose to the contralateral Breast(D_{mean}) Volume of contralateral breast receiving 5Gy (V_5)
Contra lateral Lung(CL)	Mean dose to the contralateral lung(D_{mean}) Volume of Contralateral lung receiving 5Gy (V_5)
Liver	Mean dose to Liver(D_{mean})
Monitor units	MU

Homogeneity index (HI) in PTV is defined as per ICRU 83 as HI = (D2%–D98%)/D50%. D2%, D50% and D98% are the doses of 2%, 50% and 98% volume of the PTV, where D2% represents the dose corresponding to 2% target volume and is taken as the maximum dose; D98% represents the dose corresponding to 98% target volume in DVH, and is considered as the minimum dose and D50% represent the prescribed dose. Idea HI is 0. A lower HI is suggestive of more homogeneous dose distribution across the PTV. Conformity index (CI): CI as defined by ICRU 83 is CI=Volume of PTV covered by 95% isodose curve/Volume of PTV.CI of 1 is ideal.

Results

The dosimetric parameters of PTV and OAR with respect to IP IMRT and FP IMRT is tabulated below (Table 3).

Table 3. Comparison of dosimetric parameters for PTV

Radiation dose parameters	IP IMRT	FP IMRT	P value
PTV 95%	99.5	97.6	0.000
Dmax	45.0	44.1	0.000
V90%	99.9	99.6	0.000
V99%	98.3	84.1	0.000
V105%	49.2	33.0	0.000
Homogeneity index	0.10	0.14	0.000
Conformity index	1.00	0.98	0.000

Significant at 0.01 level

PTV Dosimetry

Comparable good dose coverage was achieved by both FP IMRT and IP IMRT, delivering more than 95% of recommended dose to greater than 95% of the breast PTV. Comparison between groups showed PTV receiving atleast 95% of prescribed dose (PTV 95%) was significantly higher with IP IMRT (99.5%) compared to FP IMRT (97.6%). In addition, volume of Breast receiving 90% of dose V90% (99.9% vs 99.6%) and 99% of dose V99%(98.3% vs 84.1%) was significantly better with IP IMRT compared to FP IMRT (Table 3). The FP IMRT plan produced a much reduced hot spot (V105%) within the breast volume than IP IMRT (49.2% vs 33%). It can be seen that the IP IMRT plans had Dmax in the range 111-113% (mean 112%). For the FP IMRT plan, Dmax ranged from 109-111% (mean 110%).

Conformity Index was significantly better for IP IMRT where ideal CI of 1 was achieved compared to FP IMRT (0.98). Comparison between groups showed a better Homogeneity Index for IP IMRT (0.10) compared to FP IMRT (0.14). Figure 3a shows homogenous isodose distribution and more hot dose regions within PTV for IP IMRT compared with FP IMRT (Figure 3b).

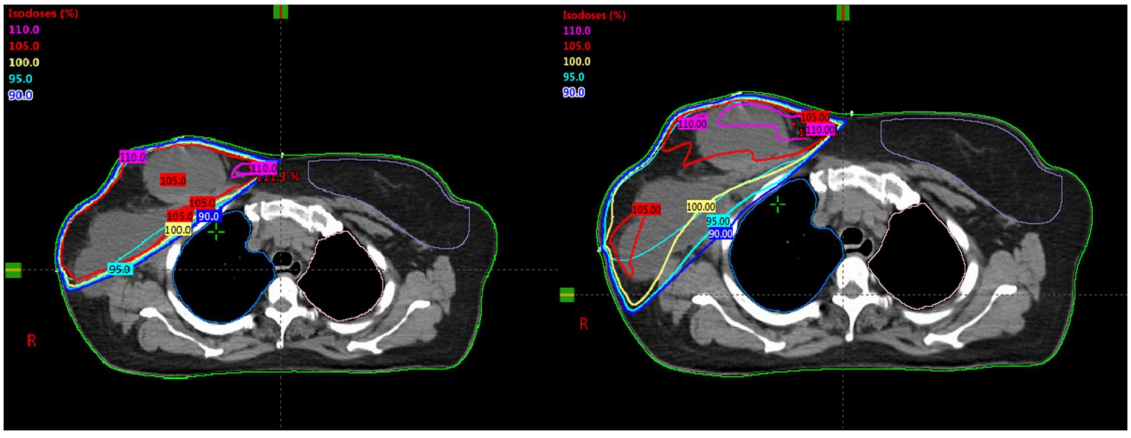


Figure 3. Isodose distribution for a) IP IMRT plan b) FP IMRT

OAR Dosimetry parameters

Table 4 presents a comparison of the dosimetric parameters for OARs for the two techniques of planning.

There is significant increase in Mean heart doses for left (4.08 vs 2.12) and right (2.02 vs 0.55) breast when comparing for IP IMRT with respect to FP IMRT. The low dose of heart i.e. volume of heart receiving 5 Gy (V5) was higher for IP IMRT for both left (28.1 vs 7.13) and right breast cancer (9.01 vs 0.02) with respect to FP MRT as shown in Figure 4. However, in-terms of Heart V20,V25,V30 it was observed that FP IMRT was higher than IP IMRT for right and left side of breast ($p<0.01$) as shown in Table 4. In addition, mean dose and maximum dose to LADCA for left and right breast irradiation when compared between two techniques has shown an edge for FP IMRT (Dmean 5.18 (L), 1.20 (R) vs 2.08 (L), 0.30 (R)), Dmax (7.99(L), 1.99 (R) vs 5.11 (L), 0.52 (R)).

Table 4. Comparison of dosimetric characteristics for OAR

OAR		IP IMRT(L)	IP IMRT(R)	FP IMRT(L)	FP IMRT(R)	P value
Heart	Dmean	4.08	2.02	2.12	0.55	0.000**
	V5	28.1	9.01	7.13	0.02	0.000**
	V20	0.72	0.00	2.45	0.00	0.010 (L)*,-
	V25	0.31	0.00	1.97	0.00	0.005 (L)**
	V30	0.10	0.00	1.51	0.00	0.005 (L)**,-
LADCA	Dmean	5.18	1.20	2.08	0.30	0.000**
	Dmax	7.99	1.99	5.11	0.52	0.043* (L), 0.00** (R)
Ipsilateral lung (IL)	Dmean	7.1		6.8		0.363**
	V5	43.5		27.9		0.000**
	V20	9.1		13.6		0.000**
Contralateral Breast (CB)	Dmean	0.69		0.15		0.000**
	V5	0.79		0.13		0.000**
Contralateral lung (CL)	Dmean	0.69		0.14		0.000**
	V5	0.06		0.00		0.002**
Liver	Dmean	1.57		1.30		0.500*
Monitor Units (MU)		1685.2		308.8		0.000**

(L)-left breast cancer,(R)-Right breast cancer

**: - Significant at 0.01 level, *: - Significant at 0.05 level

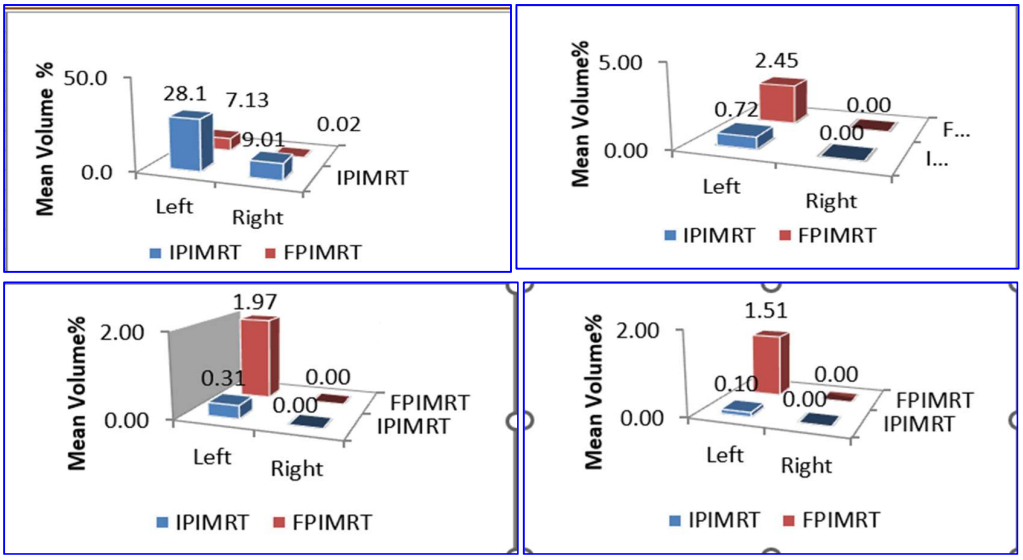


Figure 4. Comparison of Volume of heart [%] receiving 5Gy, 20 Gy, 25 Gy and 30 Gy for Left and right sided Breast Cancer

In terms of volumes of OAR receiving 5 Gy FP IMRT has shown significant lower value ie IL (43.5 vs 27.9), CL(0.06 vs 0.00) and CB (0.79 vs 0.13) for P<0.01) as shown in Table 4. With respect to V20 for the Ipsilateral lung, IP IMRT had an edge over FP IMRT technique (9.1 vs 13.6). Mean dose (Dmean) to CB (0.69 vs 0.15) and CL (0.69 vs 0.14) is better for FP IMRT. The mean dose to liver for right sided breast cancer did not show any significant difference (1.57 vs 1.3). Monitor units (MU) used for treatment was significantly more for IP IMRT (1685.2 vs 308.8). Figures 5 and 6 shows the DVH pattern display from which the dosimetric characteristics described above were obtained. DVH for OAR shows a concave dose distribution which amounts to better dosimetry with sparing of critical organs at risk adjacent to the target volume.

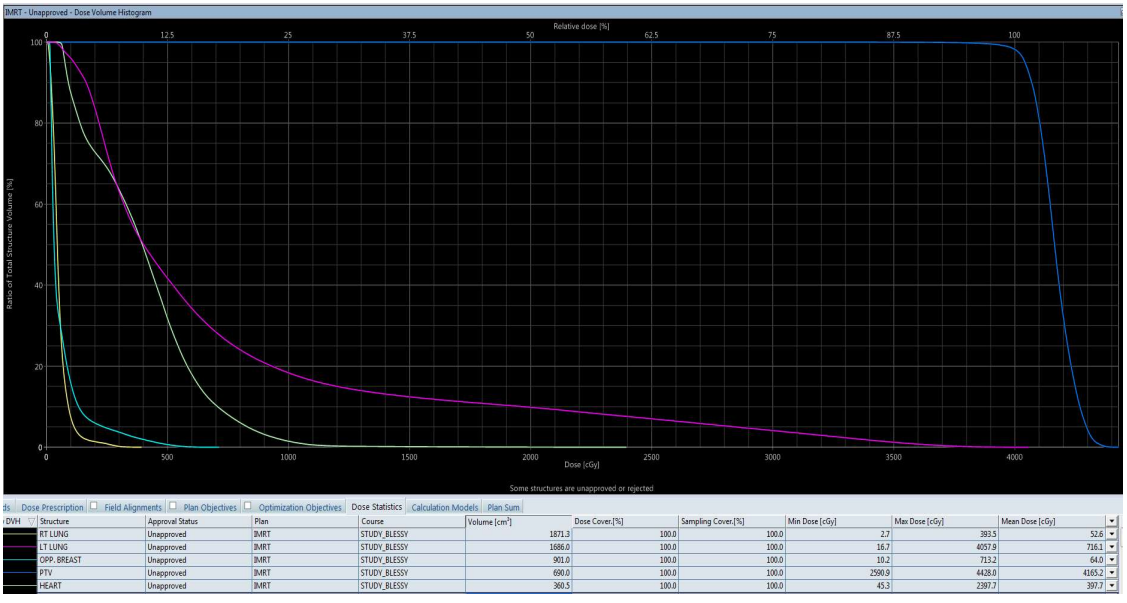
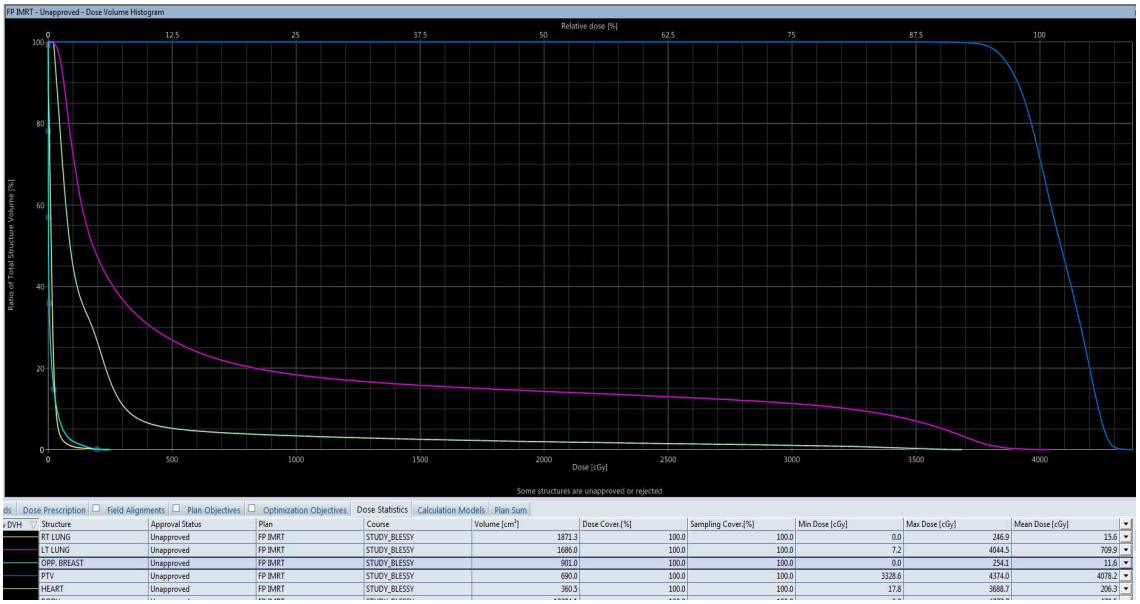


Figure 5. Dose Volume Histogram of IP IMRT plan



DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
	RT LUNG	Unapproved	FP IMRT	STUDY_BLESSY	1871.3	100.0	100.0	0.0	246.9	15.6
	LT LUNG	Unapproved	FP IMRT	STUDY_BLESSY	1686.0	100.0	100.0	7.2	4044.5	709.9
	OPP. BREAST	Unapproved	FP IMRT	STUDY_BLESSY	981.0	100.0	100.0	0.0	254.1	11.6
	PTV	Unapproved	FP IMRT	STUDY_BLESSY	690.0	100.0	100.0	3328.6	4374.0	4078.2
	HEART	Unapproved	FP IMRT	STUDY_BLESSY	360.5	100.0	100.0	17.8	3688.7	206.3

Figure 6. Dose volume Histogram of FP IMRT plan

Discussion

Concerning planning target volume, though FP IMRT and IP IMRT achieved target dose coverage delivering prescribed dose to PTV, coverage was better with IP IMRT technique. Figures 5 and 6 shows DVH for planning target volume for both the techniques. The maximum dose for IP IMRT plans exceeded 110% of the prescription dose. Therefore, FP IMRT technique produced a much smaller hotspot inside the breast volume (Figure 3b). Additionally, IP IMRT plan showed better homogeneity and conformity in comparison to FP IMRT. Figure 3a show more homogenous and conformal dose distribution within PTV for IP IMRT technique. DVH of PTV in Figure 5&6 exhibit a more steep drop off of dose at the PTV border for IP IMRT which means volume of normal tissues exposed to high dose is reduced significantly for IP IMRT. These results are close to other studies conducted by Al Rahbi et al. [11] and Elzawawy et al. [12].

Long term complication of concern in breast radiotherapy is RT induced cardiovascular damage. The risk is linearly increased as a function of mean heart dose (MHD) with an estimated risk of 7.4% with every 1 Gy increase in MHD [13]. Regarding dosimetry of Heart in our study, FP IMRT has shown a notable decrease in MHD for both right and left sided breast cancer. The volume of tissue receiving low-dose i.e. atleast 5 Gy was significantly reduced with FP IMRT technique for both right and left sided breast cancer. The relative volume of Heart receiving high dose 20 Gy, 25 Gy and 30 Gy was higher for FP IMRT.

Coronary arteries is similar to spinal cord in terms of structural organization of subunits both deemed as “serial subunit” organ. In other words, damage to any part of the artery might have potentially fatal consequences even if the entire coronary artery is not exposed to radiation. As a result, DVH factors which are helpful in estimating CAD risk is maximum and mean dose as demonstrated

by Taylor et al. [14]. It is concluded in several studies the importance of reducing dose to LAD branch of coronary artery have been demonstrated to reduce incidence of RT induced cardiac events. It is observed in our study that the mean dose and maximum dose for coronary artery were higher for left and right sided breast cancer for IP IMRT technique.

Meta analysis showed RT for breast cancer dramatically increased the risk of non breast cancers with a RR of 1.22 [15]. The risk remained high even after 5 years with a RR of 1.22 [15]. Regarding lung toxicity, incidental radiation exposure to ipsilateral lung has shown to increase radiation pneumonitis and lung fibrosis. Study demonstrated late toxicity when more than 40% of lung volume received at least 10 Gy and more than 20% of lung received at least 20 Gy [16]. In our study mean dose to the ipsilateral lung did not show significant difference between both techniques. Volume of ipsilateral lung receiving 5 Gy was lower for FP IMRT compared to IP IMRT. Volume of ipsilateral lung receiving 20 Gy was lower for IP IMRT technique with two techniques showing an advantage of V20 less than 20Gy. With respect to dose contralateral lung, mean dose to CL and volume of CL receiving 5 Gy was significantly low for FP IMRT technique.

Long-term risk of developing a second primary breast cancer on the opposite side was shown in earlier studies which was inversely related to age at exposure and was dose dependent. One study showed increased risk in women under 40 who received >1 Gy to CB. Recent treatment techniques like IMRT has led to lower CB doses, hence less risk of developing breast cancer in unirradiated breast. Mean dose to the contralateral breast was less than 1 Gy for both the techniques with significantly low dose for FP IMRT. Volume receiving atleast 5 Gy is more for IP IMRT technique compared to FP IMRT. Dose to liver was studied in 21 patients with right sided breast cancer. Regarding dose to the Liver, the mean dose to the Liver was not significant between forward and inverse planned IMRT techniques.

Regarding monitor units various studies demonstrated FP IMRT techniques did not require as many MUs as IP IMRT techniques [11]. IP IMRT plans were shown to increase overall MUs, which is shown to increase volume exposed to low dose with respect to normal tissues. In our study monitor unit used was significantly lower for FP IMRT technique. IP IMRT used 5 times more monitor units compared to FP IMRT.

Limitations

There are certain limitations our study. Our study used dose measured from treatment planning system. More accurate measurements are obtained if independent dose verification of phantom were incorporated. In addition dosimetry of boost was not done for PTV to keep study simple with less complex planning skills to save time and expertise. Besides our study did not take into account clinical outcome with respect to treatment.

Conclusion

Our study showed IP IMRT provides better target coverage, conformity and homogeneity, as well as low high dose volumes to heart and lung compared to FP IMRT radiation planning technique. However, this superior target coverage comes at the expense of increase

in hot regions with in the PTV and increase in low dose exposure to OARs. This along with increased monitor units is a concern with respect to increase incidence of RT induced second malignancy. FP IMRT also has shown an optimal target coverage with reduction in hotspot within breast and reduction in low dose volumes to OARs. Reduction in MU and shorter planning and treatment times and need for less QA procedures are added advantages which increases throughput of patients through Linear Accelerator in case of FP IMRT.

Resource limitation is a concern that hinders adoption of IP IMRT in developing countries. In this context adjuvant breast radiotherapy with FP IMRT technique can be adopted as simple and equally efficient planning technique for whole breast irradiation in patients with Breast cancer.

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Conflict of Interest

The authors declares that they do not have conflict of interest.

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