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Breast-conserving radiotherapy with simultaneous integrated boost; field-in-field three-dimensional conformal radiotherapy versus inverse intensity-modulated radiotherapy – A dosimetric comparison: Do we need intensity-modulated radiotherapy?

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Abstract

Background and Purpose: To examine the feasibility of improving breast-conserving radiotherapy with simultaneous integrated boost (SIB) and analyzing the efficiency of forward versus inverse intensity-modulated radiotherapy (IMRT) techniques in providing the same. **Materials and Methods:** Three-dimensional conformal radiotherapy (3DCRT) field-in-field (FIF) plans with simultaneous and sequential boost and IMRT SIB plans were generated for the datasets of 20 patients who had undergone breast-conserving surgery. The 3 plans were compared dosimetrically for efficiency in terms of planning target volume (PTV) coverage (PTV 95%), homogeneity and conformity, dose delivered to ipsilateral/contralateral lungs (I/L: V10, V20, C/L: Vmean, V5), heart and contralateral breast (Vmean, V30 for heart and Vmean, V1, V5 for C/L breast). **Results:** The FIF 3DCRT plan with SIB (PLAN B) was more homogeneous than the classical technique with sequential boost (PLAN A). There were less hot spots in terms of Dmax (63.7 ± 1.3) versus Dmax (68.9 ± 1), $P < 0.001$ and boost V107%, B (0.3 ± 0.7) versus A (3.5 ± 5.99), $P = 0.001$. The IMRT SIB (PLAN C) did not provide any significant dosimetric advantage over the 3DCRT SIB technique. IMRT SIB plan C was associated with increased dose to contralateral lung in-terms of V5 (10.35 +/- 18.23) vs. (1.13 +/- 4.24), $P = 0.04$ and Vmean (2.12 ± 2.18) versus Vmean (0.595 ± 0.89), $P = 0.008$. There was 3-fold greater exposure in terms of Monitor Unit (MU) (1024.9 ± 298.32 versus 281.05 ± 20.23, $P < 0.001$) and treatment delivery time. **Conclusions:** FIF 3DCRT SIB provides a dosimetrically acceptable and technically feasible alternative to the classical 3DCRT plan with sequential boost for breast-conserving radiotherapy. It reduces treatment time by 2 weeks. IMRT SIB does not appear to have any dosimetric advantage; it is associated with significantly higher doses to contralateral lung and heart and radiation exposure in terms of MU.

Key words: Field-in-field three-dimensional conformal radiotherapy breast, intensity-modulated radiotherapy breast, simultaneous integrated boost

Introduction

The current standard of care for early breast cancer is breast-conserving therapy with a boost to the tumor bed. A recent meta-analysis supports the local control benefit and gain in survival associated with this treatment.[1] The added benefit of a sequential boost in terms of local control is also well supported by randomized trials.[2,3] The first component of breast-conserving radiotherapy that is whole breast irradiation (WBI) can be delivered with several conventional, conformal, and intensity-modulated techniques. In the current era of advanced technology, field-in-field three-dimensional conformal radiotherapy (FIF-3DCRT) and intensity-modulated radiotherapy (IMRT) appear to be more efficient in providing superior tumor coverage and sparing of heart and lung.[4-6] However, the optimal dose, fractionation, and delivery of the boost remain a gray area. The use of simultaneous integrated boost (SIB) of 10–16 Gy is gaining popularity because of the advantage provided in reducing overall treatment time by 2–3 weeks. The available data relating to the delivery of an integrated boost are mainly using IMRT.[7] Very few studies have addressed the feasibility of SIB integrated into FIF-3DCRT plan.[8] The advantages of this method of boost delivery would include an easier practical delivery, reduced treatment time, and cost-effectiveness. This would also be a more ideal alternative for countries where the availability of IMRT, image guidance, and gating are limited and may not be accessible to the majority of patients.

In our study, we have attempted to evaluate the dosimetric equivalence of an integrated boost delivered simultaneously with FIF-3DCRT versus the same delivered sequentially. We have then evaluated IMRT-SIB plans for the same patient dataset to see if there is any significant difference/advantage in terms of efficacy or sparing of normal tissues. As a secondary objective, we tried to evaluate if there are any patient-specific factors that may predict a better benefit with IMRT-SIB.

Materials and Methods

The current study has been conducted using image datasets from 20 patients with early breast cancer who had undergone breast-conserving radiotherapy during 2015–2017. Nine patients with left-sided lesions and eleven patients with right-sided breast cancer were included.

All patients had been immobilized in the supine position, and image datasets with 3-mm slices were available. The ipsilateral whole breast (clinical target volume [CTV]-T) was delineated as the mammary tissue extending from pectoralis muscle to skin. The boost volume (CTV-B) was identified from preclinical imaging, operative clips, and postoperative seroma. A 5-mm margin was added to the cavity when seroma was present, and additional 5 mm expansion was used to create the planning target volume (PTV) boost volume. The organs at risk (OAR) volumes included the ipsilateral lung, contralateral lung, bilateral lungs, contralateral breast, and heart.

Treatment planning and evaluation

Three separate radiotherapy plans were generated for each patient dataset.

- PLAN A: FIF-3DCRT with 45 Gy/25 fr to PTV-T followed by sequential boost of 20 Gy/10 fr to PTV-B

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- PLAN B: FIF-3DCRT with 45 Gy/25 fr to PTV-T with a SIB of 15 Gy to PTV-B
- PLAN C: Intensity-modulated plan with simultaneous boost of 60 Gy/25 fr delivered to PTV-B and 45 Gy/25 fr to PTV-T.

The FIF-3DCRT treatment plans were constructed with multileaf collimator (MLC) shielding and gantry angles of beams adjusted to provide optimal avoidance of OAR volumes. The PTV boost plans were similarly constructed, and manual optimization was performed by adjusting beam weight, wedge fractions, and MLC settings so as to encompass the 95% isodose and minimize hotspots of >107%. PLAN C was generated using dynamic field IMRT technique and created in Eclipse treatment planning system version 13.7. The IMRT plans were created for dual energy linear accelerators (Varian Medical Systems, USA) with integrated 120 leaf millennium MLC. Treatment fields were designed with gantry angles ranged from 330° to 150° for left-sided tumors and from 50° to 200° for right-sided targets.

The optimization objectives are given in Table 1.

Dose volume histograms were used for evaluation and dosimetric comparison of target volumes and OAR parameters. The efficacy of the plans was further evaluated with homogeneity and conformity parameters; conformity index and homogeneity index.

A subset analysis was performed to determine if patient-specific factors may direct optimal plan selection. The parameters evaluated were location of disease (right-sided breast vs. left-sided breast), size of the boost volume > or <100 cc, and overlap of heart within breast PTV > or <1.2 cm.

Statistical analysis

Paired sample statistics and Students *t*-test were used to evaluate planning goals/parameters and statistical difference between the dose-volume data. The reported *P* value was two-tailed and $P < 0.05$ was considered statistically significant.

Results

Dosimetric comparison for planning target volume coverage and organs at risk parameters PLAN A versus PLAN B

A comparison of FIF-3DCRT with sequential boost (PLAN A) versus FIF-3DCRT with concomitant boost (PLAN B) was done to compare the dosimetric equivalence [Table 2].

As observed from Table 2, PTV coverage of whole breast as well as boost was adequate in PLAN B. It was comparable to standard practice PLAN A, i.e., FIF-3DCRT with sequential boost in terms of efficacy of coverage and meeting normal tissue constraints of heart and lung. The FIF-3DCRT with SIB (PLAN B) had additional statistically significant benefit of reduced treatment delivery time and radiation exposure in terms of MU (281.1 ± 20.2 vs. 449.6 ± 21.8, $P < 0.001$). The hotspot V107 was also significantly less in FIF-3DCRT (SIB) plan 0.3 ± 0.7 versus 3.5 ± 5.99, $P = 0.001$.

Dosimetric comparison for planning target volume coverage and organs at risk parameters (PLAN B vs. PLAN C) field-in-field three-dimensional conformal radiotherapy (simultaneous integrated boost) versus intensity-modulated radiotherapy-simultaneous integrated boost

When FIF-3DCRT (SIB) was compared with IMRT-SIB [Table 3], it was shown to have several significant dosimetric advantages.

Table 1: Optimization objectives for intensity-modulated radiotherapy-simultaneous integrated boost

Optimization objectives for IMRT-SIB		
Target/organ	**Type**	**Constraint**
PTV-T	V95	>95%
	V107	<5%
PTV-B	V95	>95%
	V107	<5%
Ipsilateral lung	V20	<20%
Contralateral lung	V5	<10%
Heart	Mean dose	<15Gy
	V30	<15%
Contralateral breast	Mean dose	<1Gy

PTV=Planning target volume, IMRT-SIB=Intensity-modulated radiotherapy-simultaneous integrated boost

Table 2: Comparison of field-in-field three-dimensional conformal radiotherapy with sequential boost (PLAN A) versus field-in-field three-dimensional conformal radiotherapy with concomitant boost (PLAN B)

Group	Plan	*n*	Mean±SD	*P*
Dmax	A	20	68.9±1.0	<0.0001
	B	20	63.7±1.3	
Whole breast V95	A	20	91.6±4.0	0.850
	B	20	91.9±4.0	
Boost V95	A	20	95.2±6.4	0.2848
	B	20	94.1±4.8	
Boost V107	A	20	3.5±5.99	0.0013
	B	20	0.3±0.7	
HI	A	20	0.2±0.2	0.364
	B	20	0.1±0.1	
CI	A	20	0.2±0.1	0.438
	B	20	0.2±0.1	
Heart mean dose	A	20	7.8±8.1	0.997
	B	20	7.8±8.1	
Heart V30	A	20	11.5±18.3	0.998
	B	20	11.5±18.3	
I_L_ lung V10	A	20	36.8±8.9	0.982
	B	20	36.7±8.8	
I_L_ lung V20	A	20	30.5±8.5	0.583
	B	20	32.2±11.1	
C_L_lung V5	A	20	1.1±4.3	1.000
	B	20	1.1±4.2	
C_L lung mean	A	20	0.6±0.9	1.000
	B	20	0.6±0.9	
Combined lungs mean	A	20	8.0±2.2	0.960
	B	20	8.0±2.2	
Combined lungs V20	A	20	15.8±4.8	0.969
	B	20	15.9±5.0	
C_L breast V1	A	20	19.9±11.0	0.998
	B	20	19.9±11.0	
C_L breast V5	A	20	11±9	1.000
	B	20	11±8.9	
C_L_breast mean	A	20	2.7±2.5	0.84
	B	20	2.9±2.6	
MU	A	20	449.6±21.8	0.000
	B	20	281.1±20.2	

SD=Standard deviation, CI=Conformity index, HI=Homogeneity index, MU=Monitor unit

Table 3 describes the comparison of plan efficacy between PLAN B and C in terms of PTV primary, boost, and OAR parameters.

Table 3: Comparison of plan efficacy between PLAN B and C in terms of planning target volume primary, boost, and organs at risk parameters

Group	Plan	*n*	Mean±SD	*P*
Dmax	C	20	63.635±1.0664	0.804
	B	20	63.730±1.3207	
Whole breast V95	C	20	94.985±2.8863	0.008
	B	20	91.885±3.9931	
Boost V95	C	20	92.365±7.8878	0.365
	B	20	94.260±4.7581	
Boost V107	C	20	0.085±0.2323	0.282
	B	20	0.275±0.7355	
HI	C	20	0.115±0.0489	0.778
	B	20	0.120±0.0616	
CI	C	20	0.745±0.2605	0.001
	B	20	0.225±0.0851	
Heart mean dose	C	20	9.890±6.5241	0.383
	B	20	7.835±8.1199	
Heart V30	C	20	8.610±11.4323	0.556
	B	20	11.485±18.3199	
I_L lung V10	C	20	46.740±9.8099	0.002
	B	20	36.725±8.8402	
I_L lung V20	C	20	30.745±6.1034	0.608
	B	20	32.215±11.0969	
C_L lung V5	C	20	10.345±18.2278	0.039
	B	20	1.125±4.2380	
C_L lung mean	C	20	2.115±2.1840	0.008
	B	20	0.595±0.595	
Combined lungs mean	C	20	9.130±1.8308	0.084
	B	20	7.990±2.2064	
Combined lungs V20	C	20	15.390±4.1309	0.802
	B	20	15.075±3.7481	
C_L breast V1	C	20	43.490±23.6394	0.000
	B	20	20.725±10.1202	
C_L breast V5	C	20	17.720±8.7845	0.016
	B	20	10.695±8.7674	
C_L breast mean	C	20	3.370±1.7027	0.090
	B	20	2.390±1.8538	
MU	C	20	1024.900±298.3190	0.000
	B	20	281.050 ± 20.2315	

CI=Conformity index, HI=Homogeneity index, SD=Standard deviation, MU=Monitor unit

As seen from the data accrued, target coverage in both plans is comparable in terms of Dmax V107%, whole breast V95%, and boost V95%. The IMRT-SIB was more conformal, 0.75 ± 0.26 versus 0.23 ± 0.08 (P = 0.001). The FIF-3DCRT (SIB) technique appeared to have shorter treatment delivery time and exposure (281.05 ± 20.23 vs. 1024.9 ± 298.32, P < 0.001).

The FIF-3DCRT (SIB) plans appeared better in terms of several normal tissue parameters with less dose scatter to contralateral breast and lung. The dose received by the contralateral lung was significantly more in IMRT SIB as seen by the parameters: V5 10.35 ± 18.23 versus 1.13 ± 4.24 (P = 0.039) and Vmean 2.12 ± 2.18 versus 0.595 ± 0.89 (P = 0.008).

The dose received to contralateral breast in terms of V1 and V5 was higher for PLAN C, i.e., IMRT-SIB (V1: 43.49 ± 23.64 vs. 20.725 ± 10.1202, P < 0.001 and V5: 17.7 ± 8.78 vs. 10.69 ± 8.16, P = 0.016).

A previous study by Van der Laan *et al*.[8] had established that the overlap between heart and breast PTV (OHB) >1.4cm as a significant parameter for patients who may benefit with IMRT SIB over FIF 3DCRT (SIB). We did a similar evaluation analyzing any left-sided lesions that may benefit. We analyzed two different cutoff values of 1.2 cm and 1.4 cm. There was a benefit in terms of lung sparing V10 and V20 (P = 0.05) for patients with OHB >1.2 cm. However, limited number of left-sided lesions dilutes the statistical significance.

Discussion

The current era of adjuvant radiotherapy following breast-conserving surgery is focused on taking advantage of radiobiological rationale and clinical evidence of equivalence to reduce overall treatment time. Four prospective randomized clinical trials have shown promising evidence of hypofractionated schedules.[9-12] However, in the Asian population, we have majority of patients with a less favorable clinical profile that does not fit into recommended safe guideline for selection (ASTRO evidence based guidelines for hypofractionation in whole breast irradiation 2011).[13] We see a younger population of breast cancer patients who will require intensive often cardiotoxic chemotherapy.

A reasonable alternative for providing the radiobiological benefit of reduced treatment time would be integrating the sequential boost component of the standard whole breast radiotherapy schedule. The applicability of SIB has been proven feasible with several radiotherapy techniques: 3DCRT and electron boost, 3DCRT-FIF, and IMRT-SIB.[14-16] IMRT has been the most favored technique of integrating simultaneous higher doses to smaller volumes in both head and neck and breast radiotherapy.

Several trials have supporting evidence to suggest that IMRT provides reduced side effects in terms of acute reactions, improved homogeneity, and relative sparing of normal OAR.[17] However, the limitations of this approach include increased dose and exposure to opposite lung and breast, with a potential of elevating the risk of second malignancies. The availability of IMRT facilities as well as gating is limited. In most institutions, this technique is 30%–50% more expensive, requires trained personal and dedicated quality assurance. Forward planned 3D conformal breast radiotherapy is the standard of care after breast-conserving surgery. In most centres with the faciltity of 3DCRT, integrating the boost component into the primary whole breast irradiation plan would solve several of the aforementioned issues with IMRT SIB. However is this technique adequate in terms of PTV dose coverage? Does it provide comparable sparing normal tissues? These are the issues the authors have tried to evaluate with the current study.

In the first set of data analysis, FIF-3DCRT (SIB) (PLAN B) was compared with the most commonly practiced schedule of FIF-3DCRT with sequential boost (PLAN A). The FIF 3DCRT (SIB) technique provided a more homogeneous dose distribution and reduced hotspot when compared to the classical technique in terms of Dmax PLAN B (63.7 ± 1.3) versus PLAN A (68.9 ± 1), $P \leq 0.0001$ and boost V107 PLAN B (0.3 ± 0.7) versus PLAN A (3.5 ± 5.99), P = 0.0013. All other parameters of dose coverage and normal tissue sparing were comparable in both plans with no statistically significant difference. Van de Laan *et al*. had observed similar results in an earlier study.[14] We may infer that the FIF-3DCRT (SIB) technique provides the benefit of a better dose distribution and a reduction of treatment time by 2 weeks. This benefit would be at no additional cost to the patient or technical investment to the institute.

The second set of data analysis was designed to evaluate if these results could be improved on by intensity modulation of beam delivery. The results of our study did not identify any statistical significant advantage of IMRT-SIB (PLAN C) over FIF-3DCRT (SIB) (PLAN B). In fact, they suggested that FIF-3DCRT (SIB) plan provided significantly better sparing of contralateral lung ($P = 0.008$) as well as contralateral breast ($P < 0.001$). The exposure in terms of MU and treatment delivery time was 70% less than with IMRT-SIB (281.5MU ± 20.2 vs. 1024.9 ± 298.3, $P < 0.001$).

An earlier study by van der Laan *et al*.[8] had identified few patient predictive factors that defined a subset of patients who would benefit from IMRT. These were OHB >1.4 cm and boost volume >125 cc. Our subset analysis did not elicit any significant difference; however, the numbers were probably too small. An IMRT-SIB plan would also involve a 20%–30% higher treatment cost to the patient, requires technical expertise, and facilities for image guidance and gating.

Conclusions

FIF-3DCRT (SIB) provides a dosimetrically acceptable and technically feasible alternative to the classical 3DCRT plan with sequential boost for WBI. It reduces treatment time for the patient by 2 weeks with the potential of improving compliance without increased toxicity. IMRT-SIB does not appear to convey any additional dosimetric advantage over 3DCRT SIB and may increase the risk of second malignancies on account of greater dose delivered to contralateral breast and lung.

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Conflicts of interest

There are no conflicts of interest.

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