

Research Article

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Hypofractionated IMRT Breast Treatment with Simultaneous Versus Sequential Boost Techniques

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Abstract

Purpose: Whole breast irradiation is part of breast conservative management for early breast cancer; addition of boost dose to tumor bed improves local recurrence rates and is currently the standard of care. Randomized trials reported low a/b ratio for breast cancer that predict a radiobiological advantage for hypofractionation. Simultaneous boost radiation as a method of hypofractionation proved safe and effective for head and neck tumors. In this study we attempt to compare and analyze the dosimetric aspects of adding Simultaneous Integrated Boost (SIB) over Sequential Boost (SB) to a hypofractionated treatment schedule in breast cancer patients after BCS.

Materials and methods: CT simulation data sets for 23 patients were selected for this planning study; Targets and OAR were delineated as per RTOG guidelines. Multiple dynamic field IMRT plans were generated for each patient. The prescribed dose was 40 Gy/15 fractions to whole breast (2.67 Gy/fraction) and 48 Gy/15fractions to lumpectomy cavity (3.2 Gy/fraction) for SIB, and 40 Gy/15 fractions followed by 10Gy/5 fractions for SB. Generated Treatment plans were evaluated by experienced radiation oncologist, and the best plan was selected for the dosimetric analysis.

Results: The pre specified target coverage criteria were met for the lumpectomy cavity as well as whole breast in all plans. All quality indices for PTV coverage showed to be significantly improved with SIB for both whole breast and tumor bed volumes. SB technique showed more dose spillage outside the boost volume. SIB-IMRT was better in sparing OAR ,the volume of the ipsilateral lung V20 Gy was 19.8 % compared to 22.8 % (p = 0.04), maximum dose to LAD was 17.6 Gy Vs. 21.6 (p= 0.01) and contralateral breast mean dose was 0.36 Gy Vs. 1.27 Gy (p = 0.01) for SIB and SB respectively.

Conclusions: Hypofractionated breast SIB is feasible with better PTV coverage and OAR. Along with further reduction of the overall period which may increase patient convenience and resource utilization benefit.

Keywords: Hypofractionation; Simultaneous Integrated Boost (SIB); Intensity Modulated Radiotherapy (IMRT); Sequential Boost (SB); Left Anterior Descending Artery (LAD)

Introduction

Breast cancer is the leading cause of cancer related deaths in women worldwide [1]. The main treatment is surgery, conservative breast surgery (BCS) followed by radiotherapy offers equivalent survival as modified radical mastectomy with better cosmetic outcomes. Whole breast Radiation therapy is the current standard of care after BCS. Tumor bed boost was associated with improved local recurrence rate 6.2 % compared to 10.2% without boost [2,3].

Adjuvant radiotherapy significantly improves the overall survival of breast cancer patients. This result can be augmented with further decreasing the dose to normal tissues such as heart, lung and use of IMRT and use of optimal fractionation schedules. Van de Steene et al. reported that under optimal conditions the odds of death reduction and observed 10 year mortality reduction due to adjuvant radiotherapy can be expected to be at least 20% [4].

Multiple randomized studies reported low a/b value in the range of 3–4 for breast cancer that predict a potential radiobiological advantage for hypofractionated radiotherapy, furthermore, it can improve patient's convenience and utilization health care facilities [5,6]. The investigators from Standardization of Breast Radiotherapy (START) trials assessed local control rate and patient's quality of life after hypofractionated radiotherapy, there was no significant difference in loco-regional control, mild and marked breast appearance in patients who received 50 Gy in 25 fractions versus 41.6 in 13 fractions Gy [5].

J Nucl Med Radiat Ther ISSN:2155-9619 JNMRT an open access journal Introduction of Intensity Modulated Radiotherapy (IMRT) to breast cancer treatment further improved conformity and doses to normal tissue. IMRT not only improves dose homogeneity but might reduce the dose to the normal structures compared to conventional wedged fields [7,8].

Total treatment period can be further reduced with the use of SIB that proved safe and effective in other disease sites like head and neck, lung and prostate. In breast there are increasing clinical evidences suggesting similar advantages of SIB [9-13].

The objective of this study is to analyze the quality of PTV coverage and doses to the organs at risk (OAR) associated with hypofractionated whole breast irradiation with simultaneous integrated boost (SIB) compared to sequential boost (SB) using dynamic field IMRT technique.

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Received March 30, 2012; Accepted May 21, 2012; Published May 24, 2012

Citation: Moorthy S, Elhateer H, Das Majumdar SK, Shubber, Zainab, et al. (2012) Hypofractionated IMRT Breast Treatment with Simultaneous Versus Sequential Boost Techniques. J Nucl Med Radiat Ther 3:130. doi:10.4172/2155-9619.1000130

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Materials and Methods

The CT simulation data of previously treated 23 patients with early stage breast cancer T1-T2 node negative (12 left sides and 11 right sides) were used for our retrospective planning study. These patients were treated by conventional fractionation with SIB-IMRT. The same CT data sets, target volumes and Organ at risk volumes were used for this study.

Simulation

All patients were simulated using Four Dimensional Computed Tomography (4DCT) (Philips Medical Systems-6 slice CT SIM) with Whole body Vaclok (Civco Medical Solutions, USA) immobilization system. Patients were trained before simulation for Breath hold technique. Patients were positioned in wide bore CT-SIM couch with the help of lasers where both arms raised above the head. Radio opaque markers were placed during the procedure to guide the isocenter shift. CT scan images were obtained from mandible to upper abdomen area with IV contrast. CT scan slice thickness of 5 mm was used for planning.

Organ motion during the IMRT treatment has been accounted for using real-time position management (RPM Varian, Palo Alto, USA). The reflective markers placed at the position of the xyphoid process and respiration data registered. During treatment the system supports automatic on and off triggering of radiation beam during breath hold. The marker position approximates identical and in-phase alignment of breast and marker motion.

Target delineation

After Planning CT Scan is done, the DICOM images were transferred to Eclipse treatment planning system (version 10.0.34, Varian Medical Systems, USA). Then Planning Target Volume (PTV) and Organ at Risk Volumes were delineated. The lumpectomy gross tumor volume (L-GTV) was contoured using all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips. CTV2 was created by 1 cm 3D expansion L-GTV and was limited posteriorly at anterior surface of the pectoralis major and antero-laterally 3 mm from skin, PTV2 was created by 7 mm 3D expansion of CTV2.

CTV 1 included the palpable breast tissue demarcated with radioopaque markers at CT simulation. The apparent CT glandular breast tissue visualized by CT, consensus definitions of anatomical borders, and the Lumpectomy CTV from the RTOG breast cancer atlas .The breast CTV is limited anteriorly within 3 mm from the skin and posteriorly to the anterior surface of the pectoralis, serratous anterior muscle excluding chest wall. Breast PTV (PTV1) was created by 3D expansion of CTV1 by 7 mm. The normal structures were contoured as Ipsilateral Lung, Contra lateral Lung, Contra lateral Breast, Heart, LAD (Left Anterior Descending Artery), Spinal cord, Esophagus, Trachea, humerus head and Liver.

Planning details and dose prescription

Multiple IMRT plans were created for Clinac 600CD Linear Accelerator (Varian Medical Systems, USA) which is integrated with 120 leaves Millennium MLC. Treatment fields were almost evenly spaced within an arc of 180 degree on the side of the tumor. Gantry angles ranged from 330 to150 (clockwise) for left side tumors and from 50 to 200 (counterclockwise) for right side tumors. All IMRT plans were created in Eclipse with inverse plan optimization algorithm DVO (Dose Volume Optimizer Version 10.0.28). For the dose calculation PBC (Pencil Beam Convolution Version 10.0.28) algorithm was used and leaf motions were calculated with LMC (Leaf Motion Calculator Version 10.0.28) algorithm.

Using Beams Eye View (BEV) fields were set up to minimize the dose to heart, lung, contralateral breast and maximize the dose to target coverage. Two plans were created for Sequential plan. In plan 1, multiple coplanar beams were used to produce adequate dose coverage PTV1 and PTV2. New volume (PTV1-PTV2) is created by the name whole breast excluding boost volume by subtracting boost volume with 5 mm margin from whole breast volume. The excess dose spillages into breast volume and coverage effectiveness were analyzed using this volume.

The dose – volume constraints to the target and critical organs were mentioned in Table 1. Heterogeneity correction was done using Modified Batho method in Eclipse. Dose-Volume Histograms (DVH) was used to analyze the volume receiving 20 Gy, 30 Gy and 40 Gy, Mean, Maximum and Minimum doses.

The dose prescribed for SIB method was 40 Gy in 15 fractions (2.67 Gy/fraction) for PTV1 and 48 Gy in 15 fractions (3.2 Gy/fraction) for PTV2 in 5 fractions per week schedule. For SB method the dose prescribed was 40 Gy in 15 fractions (2.67 Gy/fraction) for PTV1 and 50 Gy in 20 fractions (2.5 Gy/fraction) for PTV2 in 5 fractions per week schedule.

The target dose uniformity and conformity are calculated and evaluated based on ICRU 83

The conformity index (CI) as defined in ICRU is

 $CI_{(ref)}$ = Volume covered by the reference dose / Volume of PTV

CI = 1.0 is ideal value

The Homogeneity Index (HI) as defined in ICRU is

 $HI = (D_{2\%} - D_{98\%}) / D_{50\%}$

HI = 0 (Zero) is ideal value

Туре	Target (Gy)	Volume (%)
V95	38	95
V110	44	20
V95	45.6	95
V110	52.8	10
V20	20	20
V10	10	40
	_	
V5	5	10
MEAN	<15	-
V25	25	<5
MEAN	<u><</u> 1	-
MAX	20	-
	Type V95 V110 V95 V110 V20 V10 V20 V10 V5 MEAN V25 MEAN MAX	Type Target (Gy) V95 38 V110 44 V95 45.6 V110 52.8 V20 20 V10 10 V5 5 MEAN <15

 Table 1: Optimization objectives for Hypo fractionated IMRT plans.

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Where

D $_{_{2\%}}$ D $_{_{98\%}}$ D $_{_{50\%}}$ is dose received by 2%, 98%, 50% volume

Statistical analysis

Statistical analysis was performed using Wilcoxon Signed Rank test. This matched pair t test was applied to determine the statistical difference between the doses –volume data. Values were reported in ranges. The reported p value is two tailed and p values of <0.05 are considered significant.

Results

The planning objectives were met in all cases with both techniques. Dose-Volume Histograms (DVH) describing the dose volume relationship of the Target as well as Normal tissues of the both techniques is presented in Table 2. DVH shows normal tissue sparing was better with SIB than SB.

Breast volume

Mean Breast volume was 1498.6 cm³ (range 913.5 cm³ to 2463.1 cm³). The normalized target coverage is presented in Table 2a. The coverage of PTV 1 was significantly improved in the SIB arm 98.22% of the prescribed dose compared to 96.8% in SB arm (p< 0.01).

Boost volume

Mean PTV2 volume was 190.3 cm³ (range 51.4 cm³ to 327.8 cm³). The normalized target coverage is presented in Table 2b. As for PTV1, SIB was associated with higher PTV 2 coverage 99.38 % versus 97.3 % SB (p = 0.01).

Dose homogeneity and conformity

There was a consistent improvement in conformity index for SIB for both PTV1 and PTV2. The conformity index for the boost dose was (0.97 for SIB Vs.0.94 SB) with resulting decreased spillage of the

Dosimetric Parameter	SIB	SB	P Value
Minimum Dose (Gy)	25.71	23.81	0.29
Maximum Dose (Gy)	45.48	49.87	<0.01
Mean Dose (Gy)	37.77	36.63	0.36
V95 (%)	98.22	96.87	<0.01
V100 (%)	95.87	92.05	0.02
V110 (%)	18.97	35.12	<0.01
Conformity Index	0.95	0.92	0.02
Homogeneity Index	0.12	0.18	0.02
(PTV1-PTV2) V45Gy (%)	13.09	21.71	<0.01

Table 2a: Comparison of Whole breast volume coverage parameter (Mean) for SIB boost and Sequential boost methods of intact breast cancer patients (Prescribed Dose 40 Gy).

Dosimetric Parameter	SIB	SB	P Value
Minimum Dose (Gy)	37.82	36.57	0.15
Maximum Dose (Gy)	53.55	56.08	<0.01
Mean Dose (Gy)	44.81	42.83	0.02
V95 (%)	99.38	97.3	0.01
V100 (%)	98.29	95.27	<0.01
V110 (%)	5.87	14.78	<0.01
Conformity Index	0.97	0.94	0.01
Homogeneity Index	0.09	0.14	0.01

 Table 2b: Comparison of boost volume coverage parameter (Mean) for SIB boost and Sequential boost methods of intact breast cancer patients (Prescribed Dose 48 Gy).



Figure 1: Sequential Breast (SB) plan sum of primary and boost which shows the spillage of dose into the breast volume from boost volume.



Figure 2: Simultaneous Integrated Boost (SIB) plan shows the non –spillage of dose into breast volume from boost volume.

high dose region in to surrounding breast tissue. Also the homogeneity index was significantly improved with SIB (p=0.01) (Figure 1 and 2).

OAR doses

Doses to OAR showed to be significantly improved with SIB, ipsilateral lung V20 Gy and mean doses were significantly lower with SIB (p=0.04 & 0.02). Also, contralateral breast dose was significantly reduced with SIB (p=0.01). The volume of the heart receiving 30 Gy was reduced significantly in SIB arm (1.0% Vs. 1.8 % for SB) with P value of 0.01.

SIB also was associated with significantly reduced maximum point dose to the LAD (17.59 Gy Vs. 21.61 Gy) with p value of 0.01. OAR results are presented in the Table 3.

Discussions

The concept hypofractionated radiation therapy for breast cancer has been addressed in multiple clinical trials for its potential radiobiologic advantages as breast cancer was shown to have low a/b ratio. Studies have confirmed that hypofractionated radiotherapy as effective as conventional fractionation schedules using 1.8–2 Gy per fraction with no significant compromise of the cosmetic outcomes [5,6,14,15]. This approach could be advantageous for patients at higher risk of local recurrence [16].

START- B trial reported no significant difference in cosmetic outcome after whole breast radiation dose of 40 Gy / 15 fractions

Parameter	SIB	SB	P Value
Ipsilateral Lung			
V20 Gy (%)	19.81	22.79	0.04
Mean (Gy)	12.91	13.26	0.02
Heart			
V30 Gy (%)	1.0	1.8	0.01
V25 Gy (%)	3.70	4.11	0.42
Mean (Gy)	9.36	9.57	0.21
Opposite Lung			
V 5 Gy (%)	5.98	8.85	0.76
Both Lung			
V20 Gy (%)	10.8	11.4	0.32
Mean (Gy)	7.35	7.7	0.06
Contralateral Breast			
V5 Gy (%)	0.84	3.69	0.06
Mean (Gy)	0.36	1.27	0.01
LAD			
Maximum Dose (Gy)	17.59	21.61	0.01

 Table 3: Comparison of Mean values of Normal tissue dose volume parameters for SIB boost and Sequential boost.

compared to conventional fractionation 50 Gy/25 fractions based on photographic and self assessment evaluation with similar local regional tumor control rates [6]. In START A trail the late effects were significantly less with 39 Gy in 13 fractions over 5 weeks compared to standard fractionation 50 Gy/25 fractions with no significant difference in local control rate. Moreover long term result of a Canadian trial on Hypofractionated radiotherapy for breast cancer has confirmed that hypofractionated whole-breast irradiation was not inferior to standard radiation treatment in terms of tumor control as well as cosmetic outcome [17].

All the above mentioned studies were conducted prior to adoption of IMRT for treatment of breast cancer; IMRT might further decrease the risk of side-effects, consequently favoring the use of hypofractionated regimens. In fact, IMRT, due to improved conformity and homogeneity of dose distribution, reduces the dose to the OAR and it has been shown to reduce rates of acute radiation dermatitis during WBI. Currently, IMRT is in widespread use by many centers worldwide [18].

Hypofractionated WBI schedule for SB lasts 4 week's duration inclusive of boost radiation. In contrast SIB schedule delivers boost dose along with whole breast simultaneously, reduces the total treatment duration by 1 week. The radiobiologic data asserts that the shorter the overall period of treatment (especially for low a/b tumors) good tumor control probability. Also shorter overall treatment period would be more convenient for patients and for health care providers, as it would increase the utilizing radiation therapy facility.

In an analysis of late effects in patients treated in the UK FAST trial on hypofractionated whole breast radiotherapy with 3DCRT; Goldsmith et al reported that large breast size is associated with high risk for adverse effect; the mean breast volume in that trial was 1357 cc [19], in our study, the mean breast volume was 1498 cc. The use of IMRT allowed us to achieve adequate PTV coverage in both arms, with acceptable quality; SIB was associated with significantly improved dose homogeneity and dose to OAR over the SB. Also dose conformity measured by the RTOG CI was significantly improved with SIB that resulted in marked decrease of the boost dose spillage into the surrounding breast tissue.

Multiple dosimetric studies have reported improved homogeneity

of dose distribution with the use of IMRT which result in reduced dose to the heart and lungs, and contralateral breast [20-23]. A feasibility study on the use of Simultaneous Boost Radiotherapy with IMRT improved boost coverage and decreased OAR doses, compared with sequential boost [18]. Our institutional dose volume constraint for the lung in breast radiotherapy is to keep V20 at < 30% of the ipsilateral lung using conventional fractionation as the risk of radiation pneumonitis shown to be increased with increased both lungs V20 above 30% [24]. For the current study we have tried to keep V20 at 20 % with the lowest possible mean lung dose (MLD). SIB arm showed statistically significant improvement of the MLD as well as the ipsilateral lung V 20 Gy with an average of 12.9 Gy (p=0.04) and 19.8% (p=0.02) respectively. These results are in line with the results from Chen et al who reported average ipsilateral lung V20 of 20.9 % using the same dose schedule [25].

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Dose to heart and LAD was also reduced significantly with the use of SIB, the mean V30 Gy was 1% compared to 1.8 % for SB (p=0.01), the maximum point dose to LAD was 17.6 with SIB versus 21.6 for SB (p=0.01). Heart dose higher than 30 Gy is associated with increased incidence of coronary arterial disease (CAD) [26]. The advances in the treatment techniques including IMRT reduced cardiac exposure so that steady decline of Radiation Risk is being noticed [27].

Overall, SIB seems to be superior in terms of dosimetry planning. This optimized result could be attributed to optimization of inverse planning done for both primary as well as boost plans simultaneously. Since single plan, we had better control of optimization techniques than sum of optimized plans as in SB. Also SB planning and treatment is time consuming than SIB. As on today, limited studies are available for breast hypofractionation with SIB IMRT for further comparison.

Conclusion

This feasibility study of concomitant boost radiotherapy using IMRT demonstrates excellent dosimetric coverage of the boost volume, with better sparing of normal tissue, compared to Sequential Boost Technique. The overall treatment course was reduced by 1 week which may lead to patient convenience. Clinical studies will conclude the long term toxicity and efficacy.

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