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Research Article

REDUCED TIME AND TOXICITY WITH SIB IMRT IN CARCINOMA BREAST

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Abstract

Introduction: To reduce treatment duration, we are treating our carcinoma breast patients with simultaneous integrated boost radiotherapy after breast conservation surgery. Here we are presenting our experience at median follow up of three years. **Material and methods:** Patients having at least 6 months of follow up after completion of radiotherapy were evaluated .All patients were treated with intensity modulated image guided radiotherapy technique. Dose prescribed to clinical target volume breast was 50 Gy in 25 fractions and CTV boost was 60 Gy in 25 fractions. **Results:** Median age of our patients was 49 years. Five patients (10.2%) had acute grade 2 skin toxicity and all other (89.7%) grade 1.Grade 2 toxicity was noted in patients with pendulous and bulky breast. Average treatment duration was 34 days (range 32-56 days). Median follow up is three years after completion of radiotherapy. Twenty six (53.06 %) patients had late grade zero and twenty three (46.9%) grade 1 skin reactions. **Conclusion:** With simultaneous integrated boost in carcinoma breast patients, overall treatment time can be reduced without increasing early and late toxicities. Implementation is easy with decreased replanning workload. Henceforth SIB can be a feasible option for early breast cancer patients.

Keywords: Simultaneous integrated boost; treatment time reduction; breast conservation surgery

Introduction

Incidence of breast cancer is increasing like an epidemic in India and now it is the most common cancer among women in our country. Radiation therapy is a critical component of the multidisciplinary management of invasive breast cancer and has long been recognized as a key component of breast conserving therapy (Morrow *et al*., 2001; Clarke *et al*., 2005). Radiotherapy after breast conserving surgery takes about 6-7 weeks including whole breast radiotherapy for 5-51/2 weeks followed by boost to the cavity for 1-2 weeks. In radiotherapy such a long treatment duration is always worrisome for the patient and it also increases patient load to the machine. Among various reasons for defaulting from radiotherapy, long distance to radiation center and long treatment duration also play a role. (Nattinger *et al*., 2001). Several planning studies of simultaneous boost with whole breast irradiation. for post lumpectomy radiation by intensity modulated radiotherapy (IMRT) has been published.(Guerrero *et al*., 2001; Singla *et al*., 2006; Hurkmans *et al*., 2006; DeWyngaert *et al*., 2007) Guerrero et al estimated using the LQ model that a treatment course delivering 1.8 Gy × 25 treatments to the whole breast while delivering a simultaneous integrated boost (SIB) of 2.4 Gy × 25 treatments to the tumor bed was biologically equivalent to 45 Gy (1.8 Gy × 25) whole breast plus a sequential boost of 20 Gy (2 Gy × 10).(Guerrero et al ., 2001)

Henceforth we started treatment of our carcinoma breast patients with 50 Gy to the breast and simultaneously 60 Gy to the cavity by SIB IMRT and here we are presenting our experience at median follow up of three years.

Material and Methods

In our institute we are treating our carcinoma breast patients with simultaneous integrated boost radiotherapy after breast conservation surgery. Patients having at least 6 months of follow up after completion of radiotherapy were evaluated. Before surgery all patients underwent metastatic work up. After excluding metastases, patients underwent breast conservation surgery followed by chemotherapy according to standard guidelines. After completion of chemotherapy, patients were planned for adjuvant radiotherapy.

Planning process for all the patients was same that has been described in our previous paper.(Rashi et al .,2013)Target volumes and organ at risk both were contoured by radiation oncologist. All the organs at risk were contoured according to RTOG guidelines. Breast clinical target volume (CTV) included all glandular breast tissue that is included in the CT scan and also the clinical breast volume marked by radio opaque markers. Breast CTV excluded skin, pectoralis muscles, chest wall muscles and ribs. For planning target volume 0.5 cm margin anteroposterior, mediolateral and 0.8 cm margin craniocaudal were taken and this was limited to 5mm within skin surface .Cavity boost volume was delineated with the help of surgical clips seroma, surgery

induced changes and preoperative radiological findings. For clinical target volume boost three dimensional margin of one cm around cavity boost was taken. This volume was kept 5mm inside skin surface and was not encroaching in lung and not outside the breast PTV. Node positive patients also received radiation to supraclavicular region. Right lung, left lung and whole lung were auto contoured. Contralateral breast was contoured similar to opposite breast clinical target volume. Heart was contoured from apex to pulmonary artery also involved pericardium. Esophagus, trachea, ipsilateral humeral head were also contoured.

All patients were treated with intensity modulated image guided radiotherapy by seven to nine beams in between medial and lateral tangential fields. Skin flash tool was used during planning. Dose prescribed to clinical target volume breast was 50 Gy in 25 fractions and CTV boost was 60 Gy in 25 fractions. DVH constraints for ipsilateral lung were set at less than 20% of lung volume to be treated over 20Gy and less than 5 % over 40 Gy. For contra lateral lung V10 Gy should be less than 3 % and for contralateral breast V 5 Gy less than 5 %. For left breast, heart constraints were set at less than 10 % of heart volume to be treated over 25 Gy and less than 5 % over 40 Gy.

According to dose prescription and organ at risk constraints various radiotherapy plans were generated. Plans were evaluated by radiation oncologist. During treatment, weekly review of each patient was done to monitor treatment related toxicities. Acute and late toxicities were scored according to the Radiation Therapy Oncology Group (RTOG) morbidity scoring scale. Acute toxicity was defined as an occurrence of toxicity during or within three months of completion of treatment. Patients were followed three monthly for first two years then six monthly till five years and thereafter yearly.

Results

Forty nine patients were treated between November 2009 and May 2014. Demographic characteristics of patients are presented in Table 1. Median age of our patients was 49 years. All patients had Karnofsky performance score 90 or more. Pathological T stage was either T1 or T2. Histopathology of all our patients was invasive ductal carcinoma. Most of our patients had either N0 or N1 status.

All patients received five fractions per week. Volume of cavity ranged from 10.96cc to 204.4 cc and clinical target volume for cavity ranged from 34.81cc to 369.8cc. Clinical target volume for breast ranged from 450.8cc to 2414.1cc. Volume of target, organ at risk and dose achieved by organ at risk are described in Table 2 and 3 respectively. Acute skin toxicity was evaluated according to RTOG acute skin radiation morbidity scoring criteria. Five patients (10.2%) had acute grade 2 skin toxicity and all other (89.7%) grade 1.Grade 2 toxicity was noted in patients with pendulous and bulky breast during last week of treatment (Table 4).

Table 1: Demographic Characteristics of patients

Age(years)	
Median	49
Range	29-75
Pathological T Stage	
T1	15(30.6%)
T2	34 (69.3%)
Pathological N Stage	
N0	30 (61.2%)
N1a	16(32.6%)
N2a	1(2%)
N3a	2(4%)
Receptor Status	
ER Positive	24(48.9%)
PR Positive	19(38.7%)
Her2 Neu Positive	12(24.4%)

Average treatment duration was 34 days (range 32-56 days). Due to grade 2 reaction over folds in bulky patients, treatment was delayed in two patients. 81% patients completed their treatment within five weeks (up to 35 days) as shown in Table 5. Median follow up is three years after completion of radiotherapy. Twenty six (53.06 %) patients had late grade zero and twenty three (46.9%) grade 1 skin reactions. One patient expired due to natural causes after two years and seven months and one patient developed local recurrence along with lung and nodal metastases. All other patients are in regular follow up. Neither of our patients has experienced cardiac or pulmonary toxicity nor has developed second malignancy till January 2015.

Table 2: Volume of target and organ at risk

Target /Organ at risk	**Mean Volume (cc)**	**Median Volume (cc)**
Ipsilateral lung	881.34	832.2
Contra lateral lung	912.7	897.4
Contra lateral breast	804.23	718.14
Cavity volume	61.95	43.92
CTV cavity (boost)	140.15	119.16
CTV breast	1057.8	977.61

Table 3: Dose achieved by organs at risk

Organs at risk		V20 Gy (%)	V40 Gy (%)	Mean Dose (Gy)
Ipsilateral Left lung	Mean	23.7	5.7	15.1
	Median	23.4	5.5	15.3
		V10 Gy (%)	**Mean Dose (Gy)**	
Opposite right lung	Mean	4.3	4.7	
	Median	2.8	4.7	
		V25 Gy (%)	**V40 Gy (%)**	
Heart	Mean	10.0	2.7	
	Median	10.7	1.6	
		V5 Gy (%)	**Mean Dose (Gy)**	
Contra lateral breast	Mean	4.3	3.6	
	Median	3.2	3.7	

Table 4: Acute and late skin toxicities

	Grade 0	Grade 1	Grade2
Acute skin toxicity	0.0%	89.7%	10.2%
Late skin toxicity	46.9%	53.06%	0.0%

Table 5: Treatment duration

Time duration (days)	35	36-40	>40
No of patients	40	7	2
Percentage (%)	81.6	14.2	4

Discussion

As described earlier by Gurrero et al our cavity boost 60 Gy in 25 fractions is equivalent to 50 Gy in 25 fractions followed by 20 Gy in 10 fractions.The use of boost after whole breast irradiation has been recommended by two prospective randomized studies in invasive breast cancer. (Bartelink *et al*., 2007; Romestaing *et al*., 1997) Recently several trials over hypofractionation has been published with their long term results but their status regarding boost is not clear. In START A and B trial boost has been used in non-randomized manner.(Haviland *et al*., 2013) With the use of boost, treatment is prolonged by one or two weeks and the purpose of hypofractionation is lost.(Freedman *et al*., 2013) Phase III randomized trials of hypofractionated whole breast irradiation comparing sequential boost to concurrent boost in early stage breast cancer are going on (RTOG 1005, IMPORT HIGH and IMRT MC2).

With the development of Intensity modulated radiotherapy, it was thought about simultaneous delivery of two different fractnation schedule. Hurkmans *et al.* developed simultaneously integrated boost (SIB) technique for a phase 3 trial. The intended normalized total dose was produced by 31 fractions of 1.66 Gy to the whole breast and 2.38 Gy to the boost volume. SIB resulted in a more conformal irradiation of the boost volume with similar mean lung and heart dose. In a clinical prospective trial Freedman et al treated their 75 patients with a whole breast dose of 2.25 Gy per day for 20 fractions and an incorporated tumor bed boost 2.8 Gy per fraction for a total of 56 Gy .(Freedman *et al*., 2009) We are treating our breast patients with 60 Gy and 50 Gy dose by SIB IMRT technique from November 2009 and also reported a preliminary study on left breast cancer patients. (Agrawal and Singh, 2013).

Tumor bed can be boosted by electrons also and this was our old trend. A planning study between photon and electron has been published for deep seated tumors. Skin sparing was worst and mean dose to heart and ipsilateral lung was greater with electrons. With photons these effects can be avoided (Toscas *et al.*, 2010) With SIB radiotherapy planning is done in single sitting .While for electrons, after whole breast treatment with photons replanning is done.

By simultaneous boost, dose to normal tissues (contralateral breast) remain almost similar or significantly decreased (lungs and heart) in comparison to sequential treatment. The mean heart dose and mean lung dose were both

reduced by approximately 10% (van der Laan *et al*., 2007).

All breast sizes and women treated with adjuvant chemotherapy before radiation were permitted on study by Freedman *et al.* The maximum acute skin toxicity by the end of treatment was grade 0 in 9 patients (12%), grade 1 in 49 (65%), and grade 2 in 17 (23%). There was no grade 3 or higher skin toxicity. After radiation, all grade 2 toxicities had resolved by 6 weeks. The 5-year local recurrence rate is 2.7%. None of our patients had acute grade 3 skin toxicity and grade 2 toxicity was noticed in 10.2% patients. This grade 2 toxicity was noted in patients with pendulous and bulky breast in skin fold areas not in the boost areas. According to RTOG late toxicity criteria twenty six (53.06 %) patients had late grade zero and twenty three (46.9%) grade 1 skin reactions (slight pigmentation). In all patients slight pigmentation resolved in 4 to 6 months. Mcdonald et al. treated their breast patients with SIB IMRT. (Mc Donald *et al.*, 2010) Grade 2 acute toxicity was noted in 43% patients and global breast cosmesis was good or excellent in 96.5% patients. IMRT has been shown to reduce rates of acute radiation dermatitis during whole breast radiation and is in wide spread use in many centers including our own institution.(Pignol *et al.*, 2008) Higher dose in boost region did not produce differential fibrosis or edema of breast.

In our study, mean ipsilateral lung volume is 881.34 cc while median volume of ipsilateral lung receiving 20 Gy or more was 23.4% and median volume of heart receiving 25 Gy or more was 10.7%.The RTOG and European Organization for Research and Treatment of Cancer constraints are in widespread use and normally accepted. Emami B published their updated data regarding normal tissue tolerance in year 2013.(Emami B et al.,2013) Our doses to normal tissues (ipsilateral and contralateral lung , heart, opposite breast) are within dosimetric limits. Sparse data is available in literature for comparison. In 2010 Mcdonald et al reported their 3 year outcomes of SIB - IMRT. The median ipsilateral lung volume receiving 20 Gy or more (V20) was 10.6% (range, 0– 27%). Analyzing left breast cases only (n = 168), the median volume of heart receiving 15 Gy or more (V15) was 2.9% (range, 0–17.4%).This difference may be due to difference in volume of organs at risk or body curvature.

Enja JB et al reported 5 year clinical outcomes of hypofractionated 3D conformal radiotherapy SIB for invasive cancer .The updated result showed excellent out comes. The unadjusted 5-year acturarial rate of local control was 98.9% and overall survival was 93.3%. 6% patients developed a secondary malignancy during follow up. Several factors can be attributed to the high local control rate. Better definition of target volume and high biologically effective dose may be among those factors.(Bantema-Joppe et al.,2013)

Conclusion

With simultaneous integrated boost in carcinoma breast patients, overall treatment time can be reduced without increasing early and late toxicities. Implementation is easy with decreased replanning workload. Henceforth SIB can be a feasible option for early breast cancer patients.

References

Bantema-Joppe EJ, Vredeveld EJ, de Bock GH and Busz DM, Woltman-van Iersel M, Dolsma WV *et al.* (2013) Five year outcomes of hypofractionated simultaneous integrated boost irradiation in breast conserving therapy; patterns of recurrence. *Radiother. Oncol*. **108**(2): 269-72. DOI: 10.1016/j.radonc.2013.08.037

Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Bogaert W Van den , Fourquet A and *et al.* (2007) Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881–10882 trial. *J. Clin. Oncol.* **25**: 3259–65. DOI: 10.1200/JCO.2007.11.4991

Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E and *et al.* (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* **366**: 2087–2106. DOI: 10.1016/S0140-6736(05)67887-7

De Wyngaert JK, Jozsef G, Mitchell J, Rosenstein B and Formenti SC (2007) Accelerated intensity- modulated radiotherapy to breast in prone position: Dosimetric results. *Int. J. Radiat. Oncol. Biol. Phys.* **68**: 1251–1259. DOI: 10.1016/j.ijrobp.2007.04.018

Emami B (2013) Tolerance of normal tissue to therapeutic irradiation. *Spring* **1**(1): 35-47.

Freedman GM, Li T, Nicolaou N, Chen Y, Ma CC and Anderson PR. (2009) Breast intensity modulated radiation therapy reduces time spent with acute dermatitis for women of all breast sizes during radiation. *Int. J. Radiat. Oncol. Biol. Phys.* **74**: 689–694. DOI: 10.1016/j.ijrobp.2008.08.071

Freedman GM, White JR, Douglous WA, Li XA and Vinci FA. (2013) Accelerated fractionation with a concurrent boost for early stage breast cancer. *Radiotherapy and Oncology* **106**: 15–20. DOI: 10.1016/j.radonc.2012.12.001

Guerrero M, Li XA, Earl MA, Sarfaraz M and Kiggundu E (2004) Simultaneous integrated boost for breast cancer using IMRT: A radiobiological and treatment planning study. *Int. J. Radiat. Oncol. Biol. Phys.* **59**: 1513–1522. DOI: 10.1016/j.ijrobp.2004.04.007

Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ and *et al.* (2013) The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet. Oncol.* **14**: 1086–1094. DOI: 10.1016/S1470-2045(13)70386-3

Hurkmans CW, Meijer GJ, van Vliet-Vroegindeweij C and *et al.* (2006) High-dose simultaneously integrated breast boost using intensity- modulated radiotherapy and inverse optimization. *Int. J. Radiat. Oncol. Biol. Phys.* **66**: 923–930. DOI: 10.1016/j.ijrobp.2006.05.041

Mc Donald MW, Godette KD, Whitaker DJ, Davis LW and Johnstone PAS (2010) Three year outcomes of breast intensity modulated radiation therapy with simultaneous integrated boost. *Int. J. Radiat. Oncol. Biol. Phys*. **77**: 523–530. DOI: 10.1016/j.ijrobp.2009.05.042

Morrow M, White J, Moughan J, Owen J, Pajack T, Sylvester J *et al.* (2001) Factors predicting the use of breast conserving therapy in stage I and II breast carcinoma. *J. Clin. Oncol.* **19**: 2254–2262.

Nattinger AB, Kneusel RT, Hoffmann RG and Gilligan MA (2001) Relationship of distance from a radiotherapy facility and initial breast cancer treatment. *J. Natl. Cancer Inst.* **93**: 1344–1346. GOI: 10.1093/jnci/93.17.1344

Pignol JP, Olivotto I, Rakovitch E, Eileen Rakovitch, Sandra Gardner, Katharina Sixel, Wayne Beckham and *et al.* (2008) A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J. Clin. Oncol.* **26**: 2085–2092. DOI: 10.1200/JCO.2007.15.2488

Agrawal R and Singh D (2013) Simultaneous integrated boost by intensity modulated radiation therapy in carcinoma left breast after breast conservation surgery-A preliminary experience. *Int. J. Appl. Sci. Biotechnol* **1(**4): 197-201.

Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM and *et al.* (1997) Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J. Clin. Oncol.* **15**: 963–968.

Singla R, King S, Albuquerque K, Creech S and Dogan N (2006) Simultaneous- integrated boost intensity-modulated radiation therapy (SIB- IMRT) in the treatment of early-stage left-sided breast carcinoma. *Med. Dosim.* **31**: 190–196. DOI: 10.1016/j.meddos.2005.11.001

Toscas JI, Linero D, Rubio I, Hidalgo A, Arnalte R, Escudé L and *et al.* (2010) Boosting the tumor bed from deep-seated tumors in early-stage breast cancer: A planning study between electron, photon, and proton beams. Radiother Oncol. **96**(2): 192-198. DOI: 10.1016/j.radonc.2010.05.007

van der Laan HP, Dolsma WV, Maduro JH, Erik W Korevaar and Johannes A (2007) Three-dimensional conformal simultaneously integrated boost technique for breast-conserving radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys*. **68**: 1018–1023. DOI: 10.1016/j.ijrobp.2007.01.037