Advanced Conformal Radiotherapy versus 3DCRT in Post-mastectomy Breast Cancer Patients: A Comparative Study on Skin Toxicities and Doses to Organs at Risk

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Abstract

Introduction: Radiotherapy is an essential modality of treatment after mastectomy. However, toxicities of post-mastectomy radiotherapy are still not well established. This study was aimed at comparing the acute skin toxicitiesand doses to the organs at risk between conventional and advanced conformal radiotherapy in post-mastectomy breast cancer patients.

Materials and Method: A quasi-experimental study was conducted on60 breast cancer patients after mastectomy from March 2021 to February 2022. Participants were distributed equally into two arms. Arm-A received radiotherapy in conventional conformal technique (3DCRT) andarm-B in advanced conformal techniques (IMRT or VMAT). Patients were evaluated before, during, and after the completion of the treatment.

Results: Among the 60 participants, 43% developed skin toxicities of which 18.3% were grade 2 or higher. IMRT and VMAT in comparison to 3DCRT had significantly lower mean dose and maximum dose for heart (4.92 Gy vs.7.74 Gy, p 0.005 ;30.95 Gy vs.45.40 Gy, p 0.0003) and ipsilateral lung (11.93 Gy vs.17.6 Gy, p 0.0001 ; 37.92 Gy vs.57.77 Gy, p 0.0001).V_5significantly increased for both. Maximum dose for opposite lung increased significantly (14.14 Gy vs. 7.05 Gy, p 0.001).Mean dose to esophagus was similar in both arms. In case of the spinal cord, mean dose increased in arm-B (3.64 Gy vs. 2.17 Gy, p 0.0004) while maximum dose decreased (15.83 Gy vs. 22.85 Gy, p 0.021).

Conclusion: For post-mastectomy patients, advanced conformal radiotherapy techniques are better for minimizing higher dose parameters of organs at risk. Low dose parameters are better in conventional technique. Neither is superior to prevent radiation induced acute skin toxicities.

Keywords: Post-mastectomy radiotherapy, Intensity-modulated radiotherapy, Radiation dosimetry, Three dimensional conformal radiotherapy

Introduction

Breast cancer is the fourth leading cause of cancer death worldwide, and the leading cause of cancer death among women.[1]Around 45% of new the cases occurred in Asia in 2020.[2]Although most patients in Western countries are diagnosed early, in less developed countries about 60% of patients have locally advanced or metastatic disease at the time of diagnosis.[3, 4]Modified radical mastectomy (MRM) is performed more often than breast conservative surgery (BCS) in Bangladesh. To decrease locoregional recurrence the majority of these patients undergo post-mastectomy radiotherapy (PMRT).[5]

Radiotherapy techniques include two-dimensional (2D) therapy, three-dimensional conformal radiotherapy (3DCRT), advanced conformal radiotherapy (intensity modulated radiotherapy, IMRT or volumetric modulated arc therapy, VMAT).But none of these are accepted as standard method for PMRT.[6]Despite the fact that 3DCRT has improved local control, normal tissue toxicities, particularly those of the underlying lung and heart, continue to be a concern.[7]IMRT and VMAT have been proved to be superior to 3DCRT in various sites like head and neck, central nervous system, lung, prostate etc. However, this can't be said regarding PMRT yet.[8]

Radiation-induced skin toxicities (radiation dermatitis)is the most common and symptomatic side effects of radiotherapy for breast cancer.[9]Those toxicities include skin redness, edema, and dry and moist desquamations. These often influence a patient's or physician's decisions regarding treatment negatively.[10]However, in the case of PMRT, these are not well defined because most Western research are conducted on whole breast irradiation following breast conserving surgery.[5, 11]Among major organs at risk heart and lungs are the most important. This is especially important due to the use of other cardiotoxic drugs like anthracyclines, taxanes and trastuzumab.[5] Other important considerations are doses to esophagus, and spinal cord.

This study aims at assessing the skin toxicities as well as comparing radiation doses to the critical organs with 3DCRT and advanced conformal radiotherapy (IMRT/VMAT) techniques.

Materials and Methods

This quasi-experimental study was conducted from March 2021 to February 2022. Participants were recruited from the Department of Clinical Oncology, Bangabandu Sheikh Mujib Medical University and Labaid Cancer Hospital and Super Speciality Center, Dhaka. Ethical permission was obtained from the Institutional Review Board (IRB) of BSMMU and Ethical Committee of the Labaid Cancer Hospital.

Sixty previously untreated female breast cancer patients with histologically confirmed infiltrating ductal carcinoma after modified radical mastectomy (post-MRM) without evidence of distant metastasis or second malignancy were enrolled following their informed written consent. They were distributed equally into two arms by purposive sampling.

Patients in arm-A (the control arm) and arm-B (the experimental arm) received standard radiotherapy fractionation in conventional conformal technique (3DCRT) and advanced conformal technique (IMRT or VMAT), respectively. IMRT and VMAT were used for 19 and 11 participants respectively. Among the participants, 22 had left sided breast cancer and the rest 8 had right sided disease in each arm.

For dose calculation purposes, targets and OARs were delineated using RTOG guidelines. Doses to organs at risk, namely heart, lungs, esophagus, and spinal cord were calculated using Monaco®HD or Eclipse® treatment planning systems' predictive dose calculation algorithms and recorded during treatment planning. Mean dose, maximum dose and volumes receiving specific doses or higher were calculated for the heart, ipsilateral lung, contralateral lung, esophagus, and spinal cord.

All the patients were evaluated at the start of radiotherapy and weekly thereafter during treatment period for skin (radiation dermatitis) and other toxicities. Follow ups were done at week 7, 9, and 13after completion of treatment. 'Common Terminology Criteria for Adverse Events or CTCAE, v.5.0' published in 2017 was usedto assess toxicities.[12]

Data were analyzed using the SPSS software program (North Castle, NY, USA) for Windows, version 25.A p value of <0.05 was considered as statistically significant.

Results

Table-1 summarizes the baseline characteristics of patients in the two arms. There were no statistically significant differences between the two arms in terms of age, age at menarche, age at first pregnancy, T stage, N stage, or performance status. As per inclusion criteria no patients with metastasis (M1) or ECOG performance status 3 was included in the study.

Table 1: Baseline characteristics of the patients

	Arm A (3DCRT) (n = 30)	**Arm B (advanced RT)** (n = 30)	**Total** (n = 60)	**p* value**
Age(years)				
Mean (±SD)	45.23 (±8.49)	50.83 (±10.2)	49.53 (±10.27)	0.071
Range	37 (67-30)	44 (78-34)	48 (78-30)	
Age at menarche(years)				
Mean (±SD)	12.8 (±0.92)	13.12 (±1.16)	12.96 (±1.24)	0.24
Range	5 (15-10)	5 (16-11)	6 (16-10)	
Age at first pregnancy(years)				
Mean (±SD)	19.8 (±1.6)	20.6 (±2.1)	20.2 (±2.5)	0.1
Range	11 (28-17)	11 (31-20)	14 (31-17)	
T stage				
T1	2 (6.67%)	5 (16.67%)	7 (11.67%)	0.31
T2	8 (26.67%)	12 (40%)	20 (33.33%)	
T3	14 (46.67%)	9 (30%)	23 (38.33%)	
T4	6 (20%)	4 (13.33%)	10 (16.67%)	
N stage				
N1	17 (46.67%)	21 (70%)	38 (63.34%)	0.35
N2	11 (36.67%)	6 (20%)	17 (28.33%)	
N3	2 (6.66%)	3 (10%)	5 (8.33%)	
Performance status				
ECOG 0	22 (73.33%)	23 (76.67%)	45 (75%)	0.584
EGOG 1	8 (26.67%)	6 (20%)	14 (23.33%)	
ECOG 2	0 (0%)	1 (3.33%)	1 (1.67%)	

* Calculated using Student's t test or chi-square (χ^2) test

SD= Standard deviation

Skin toxicities among study arms are shown in table-2 and 3. More than half patients (56.67%) didn't develop any skin toxicities from radiation treatment. Grade 1 toxicity was more than grades 2 or 3. Overall only 3 (5%) patients had developed grade 3 radiation dermatitis. Whereas 53% of arm-A patients developed skin toxicities it was 33% in arm B. But this difference was not found to be significant (p = 0.118). Occurrence of severe dermatitis (grade 2 or above) was 23.33% and 13.33% in arm A and arm B respectively. But this difference was not significant either (p = 0.477).

Table 2: Skin toxicities among study arms (n = 60)

Radiation dermatitis	**Arm A (3DCRT) (n = 30)**		**Arm B (Advanced RT) (n = 30)**		**Total (n = 60)**	
	Frequency	%	Frequency	%	Frequency	%
Absent	14	46.67	20	66.67	34	56.67
Present	16	53.33	10	33.33	26	43.33

p = 0.118

Table 3: Grade wise skin toxicities among study arms

Radiation dermatitis	Arm A (conventional RT) (n = 30)			Arm B (advanced RT) (n = 30)		
	Frequency	%	Cumulative %	Frequency	%	Cumulative %
Grade 3	2	6.66	6.66	1	3.33	3.33
Grade 2	5	16.67	23.33	3	10.00	13.33
Grade 1	9	30.00	53.33	6	20.00	33.33
Grade 0	14	46.67	100	20	66.67	100
Total	30	100		30	100	

p = 0.477

Grade 0 for radiation dermatitis means no radiation induced skin toxicities occurred. Cumulative percentage of radiation dermatitis is shown within each study arm.

Table-4 summarizes the radiation exposure of the OARs namely heart, ipsilateral lung, contralateral lung, esophagus, and spinal cord. The mean and maximum dose to heart, ipsilateral lung, and also the maximum dose to spinal cord in arm-A were significantly higher ($p <0.05$) than arm-B. The V_{25} of heart and V_{20} of ipsilateral lung were also higher in arm-A but were not significant ($p >0.05$). On the other hand, mean and maximum dose to the contralateral lung, $V_5$to ipsilateral lung, and also the mean dose to spinal cord were significantly higher (p <0.05) in arm-B than the arm-A.

Table 4: OAR dose characteristics among study arms

Organs	Arm A n = 30	Arm B n = 30	Mean difference	p* value
Heart				
Mean dose (Gy)	7.74 ± 4.39	4.92 ± 2.98	2.81	**0.005**
Maximum dose (Gy)	45.40 ± 16.4	30.95 ± 12.3	14.45	**0.0003**
V_{25}(%)	10.76 ± 8.23	7.47 ± 4.51	3.3	0.06
V_5(%)	22.34 ± 14.57	30.86 ± 14.97	8.5	**0.03**
Ipsilateral lung				
Mean dose (Gy)	17.6 ± 2.55	11.93 ± 4.07	5.66	**0.0001**
Maximum dose (Gy)	57.77 ± 7.6	37.92 ± 11.14	19.84	**0.0001**
V_{20} (%)	33.8 ± 4.9	31.85 ± 6.95	1.94	0.2
V_5(%)	53.52 ± 6.26	61.4 ± 14.51	7.88	**0.01**
Contralateral lung				
Mean dose (Gy)	1.0 ± 0.16	2.89 ± 2.37	1.89	**0.0001**
Maximum dose (Gy)	7.05 ± 7.35	14.17 ± 8.62	7.12	**0.001**
Esophagus				
Mean dose (Gy)	6.36 ± 3.48	7.09 ± 3.73	0.73	0.4
Spinal cord				
Mean dose (Gy)	2.17 ± 1.02	3.64 ± 1.85	1.48	**0.0004**
Maximum dose (Gy)	22.85 ± 14.17	15.83 ± 7.65	7.02	**0.021**

* Independent sample t test was used

Values are presented as mean ± 1 standard deviation.

Discussion

Among the sixty participants, 26(43.3%) developed skin toxicities of which 11 (18.3%) were grade 2 or higher. In contrast, Pignol et al.[11]and Macmillan et al.[13] reported presence of radiation toxicities in more than 50% study subjects. This may be due to improvements in treatment delivery and quality control with time. It may also be from demographic difference like race and ethnicity. Radiation tolerance is known to differ according to such parameters as described by Wright et al.[9]

Grade 1 toxicity was more than grades 2 or 3 in both arms. Only 3 (5%) patients developed grade 3 skin toxicity in this study. Overall skin toxicities were higher in arm-A (53.3% vs. 33.3%, p 0.118). Severe skin toxicities (grade 2 or higher) were also more in arm-A (23.3% vs. 13.3%, p 0.3). But these differences were not statistically significant. These findings match for overall moist desquamation with Pignol et al.[11]and Macmillan et al.[13] except for the grade 3 dermatitis. Pignol et al. found extensive moist desquamation in 28.4%of 257 patients and grade 3 skin toxicity was 32.7%. Macmillan et al. reported moist desquamationin 27% of breast cancer patients. Low incidence of grade 3 dermatitis was possibly related to better dose distribution and dose calculation algorithms in latest machines.

Advanced conformal radiotherapy (IMRT & VMAT) in comparison to 3DCRT significantly reduced the mean doses as well as the high dose volumes (e.g., maximum dose, V_{25}) to heart but not the low dose volumes such as V_5. IMRT & VMAT had lower mean dose (4.92 Gy vs.7.74 Gy, p 0.005)and maximum (30.95 Gy vs.45.4 Gy, p 0.0003) dose for heart. Reduction in V_{25} of heart was not significant. On the other hand, V_5 increased significantly (30.86% vs. 22.34%, p 0.03). These findings correspond to Rastogi et al.[5] They reported that IMRT significantly reduced the high-dose volume of heart V_{25}(4.59% vs. 9.19%, $p < 0.001$) and mean dose heart (4.57 vs. 8.96 Gy, $p < 0.001$)in comparison to 3DCRT.However V_5 of heart increased(31.02% vs. 23.27%, $p < 0.001$) in IMRT which was statistically significant. Similarly, Aras et al.[14] reported significant reduction in low dose volumes of heart (V_{10} 13.7 cm^3 vs. 10 cm^3, p 0.01) with 3DCRT in comparison with IMRT. They also found that there was no statistically significant difference between the two techniques at the maximum and average doses in the high dose regions like $V_{25}$and mean dose which don't match the outcome of this study.

There were similar findings in case of ipsilateral lung. Advanced conformal radiotherapy significantly reduced the mean dose and high dose volumes to the ipsilateral lung in comparison to 3DCRT but not V_5. IMRT & VMAT had lower mean dose and maximum dose (11.93 Gy vs. 17.6 Gy, p 0.0001; 37.92 Gy vs. 57.77 Gy, p 0.0001). The reduction in $V_{20}$was not significant but V_5 increased significantly (61.4% vs. 53.52%, p 0.01). These findings correspond to Rastogi et al too.[5] Aras et al.[14] also reported significant reduction in low dose volumes of ipsilateral lung with 3DCRT. But they found that there was no statistically significant difference between the two techniques at the meandose and average doses in the high dose regions.

The maximum dose for opposite lung increased in arm-B (14.14 Gy vs.7.05 Gy, p 0.001). Although the mean dose also increased significantly in arm-B it was minimal (mean difference 1.85 Gy). These findings match those found by Schubert et al.[7] They reported an increase in mean dose but a decrease in maximum dose in 3DCRT in comparison to IMRT.

Mean dose to esophagus was similar in both arms (6.36 Gy vs. 7.09 Gy, p 0.4). In case of the spinal cord, mean dose increased in arm-B (3.64 Gy vs. 2.17 Gy, p 0.0004) while maximum dose decreased (15.83 Gy vs. 22.85 Gy, p 0.021). This corresponds to the findings of Ma et al.[15]

Conclusion

As per this study, it can be concluded that for post-mastectomy patients advanced conformal radiotherapy techniques are better for minimizing higher dose parameters of organs at risk. But low dose parameters are better in 3DCRT technique. Neither is superior to prevent radiation induced acute skin toxicities. On the basis of these findings, we think that the advanced modalities of radio therapy are preferable to minimize dose to vital organs.

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