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ORIGINAL ARTICLE

Assessment of acute toxicities and early local recurrences in post mastectomy breast cancer patients by accelerated hypofractionated radiotherapy; a single arm clinical trial

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Summary

Purpose: *Hypofractionated post mastectomy radiotherapy (PMRT) is commonly given using conventional radiotherapy technique. Volumetric modulated arc therapy (VMAT) and Intensity modulated radiation therapy (IMRT) are better sparing heart and lungs. This study was conducted to assess the toxicity profile and dosimetry outcomes of patients receiving PMRT using IMRT or VMAT.*

Methods: *67 biopsy-proven patients with carcinoma of the breast who had undergone modified radical mastectomy (MRM) were included in the study. They were treated using VMAT or IMRT to a dose of 42.56 Gy in 16 fractions. Acute and late toxicities were graded using RTOG toxicity grading scale. Toxicities and recurrences were summarized as proportions with 95% confidence intervals. Spearman's correlation was used to find association between the dose received by the organs at risk (OARs) and the grade of toxicities.*

Results: *The mean age of the study population was 48±9.5 years. The incidence of acute grade 2 and above radiation dermatitis and pneumonitis were 11.9% and 7.5 % respectively. The incidence of acute esophagitis was 46.3%. With a median follow up of 9 months there were no significant late toxicities. There was only one local recurrence and three progressed to distant metastases but without local recurrence. Twenty-four patients were treated by IMRT, 43 patients were treated by VMAT. Dosimetrically VMAT and IMRT were comparable in planning target volume (PTV) coverage and OAR doses, but VMAT had less number of monitor units and shorter treatment time.*

Conclusion: *Hypofractionated post mastectomy radiotherapy using IMRT and VMAT is feasible with less acute toxicities.*

Key words: *hypofractionation. postmastectomy radiotherapy. VMAT. IMRT. toxicities*

Introduction

Radiobiological models predicted that the α/β ratio of breast cancer to be 4 which behaves like a late responding tissue [1]. These late responding tissues are sensitive to high dose per fraction. Four landmark trials in the 1990s proved the non-inferiority of hypofractionated radiotherapy over conventional fractionation without increasing the toxicities [2-5]. Though hypofractionated radiotherapy has become the standard of treatment in whole breast radiotherapy, in the postmastectomy setting prospective studies are limited. Hypofractionation can cause increased late toxicities compared to conventional fractionation which can be reduced using VMAT and IMRT. So we conducted this study to assess the toxicity profile and dosimetry outcomes and local recurrences of patients receiving hypofractionated PMRT using IMRT or VMAT technique.

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Methods

Study design and participants

This was a single arm clinical trial done at the Department of Radiation Oncology JIPMER, India. Biopsy-proven breast cancer patients who had undergone Modified Radical Mastectomy (MRM) were included in the study. Patient with ischemic heart disease or other cardiac problems, history of past irradiation to the chest wall, metastatic disease and ECOG performance status ≥3 were excluded. All patients provided written informed consent. The study was done in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and was approved by the institutional ethics committee on 16 February 2017 (JIP/IEC/2016/1116). The study was registered in Clinical Trial Registry of India (Reg. no CTRI/2017/08/009197).

Study procedure

Contouring was done as per RTOG (Radiation Therapy Oncology Group) breast cancer atlas. The chest wall with pectoralis muscle, serratus anterior, ribs, and the intercostal muscles were included in the clinical target volume (CTV). When there was no tumor invasion of the overlying skin, the contour was cropped by 3 mm from the skin surface. In cases with pathological skin involvement, the contour included the skin. A 5 mm margin was given in medial, lateral, anterior and posterior direction, 1 cm margin was given in cranio-caudal direction to generate the planning treatment volume (PTV). Axilla level II and I were irradiated only if there was extra nodal extension or inadequate axillary lymph node clearance. Supraclavicular fossa, axilla and chest wall were treated as a single PTV. Internal mammary nodes were not irradiated. Brachial plexus was contoured according to Radiation Therapy Oncology Group (RTOG)-endorsed guidelines delineation [6].

Table 1. Dose constraints

Organ	*Constraints*
Ipsilateral lung D_{mean}	≤18 Gy
Ipsilateral lung V_{27Gy}	≤ 15-20%
Ipsilateral lung V_{18Gy}	≤25-30%
Contralateral lung D_{mean}	≤ 3 Gy
Contralateral breast D_{mean}	≤ 3 Gy
Heart D_{mean} (right-sided disease)	≤ 3 Gy
Heart D_{mean} (left-sided disease)	≤13 Gy
Heart $V_{22.5Gy}$	≤10-15%
Heart V_{27Gy}	≤ 40-45 %
Spinal cord D_{max}	≤38 Gy
Brachial plexus D_{max}	≤ 48 Gy
Esophagus D_{mean}	≤ 31 Gy
Esophagus D_{max}	≤ 42.5 Gy

This Table gives the list of dose constraints of the OAR used for inverse planning

A total dose of 42.56 Gy in 16 fractions was prescribed to the PTV. The optimization objective was that the 95% isodose line should encompass 95% of the PTV. The dose constraints given in QUANTEC were modified according to dose per fraction based on Linear Quadratic BED equation. The α/β ratio for the lung and heart was taken as 4 and for brachial plexus and spinal cord it was taken as 3. The dose constraints used are shown in the Table 1.

The treatment planning system (TPS) (Eclipse 10.0) Varian was used to generate both plans. The TPS uses dose volume optimizer (DVO) for the calculation of IMRT plan and progressive resolution optimizer (PRO) for VMAT plans. The treatment was delivered using Varian Clinac iX with 6MV photon energy.

Outcomes

Primary outcome variable was grade 2 and above acute skin toxicity. Secondary outcome variables were other acute and late toxicities, local recurrence, distant recurrence, dosimetry outcomes for PTV coverage and OARs. Acute and late toxicities were graded using the RTOG toxicity grading scale. Assessment of toxicities was done weekly during the course of treatment, once during the end of the treatment and also during the first follow up after one month of completion of treatment. Subsequently, patients were followed 2-monthly for 1 year post treatment for assessing the late toxicities. Local recurrence was assessed clinically during every follow up visit. If any suspicious lesion was found in the irradiated area during clinical examination, FNAC/Biopsy of the lesion was be done to confirm the recurrence.

Statistics

Assuming confidence level of 95%, expected incidence of grade II and above dermatitis as 60 % [7]

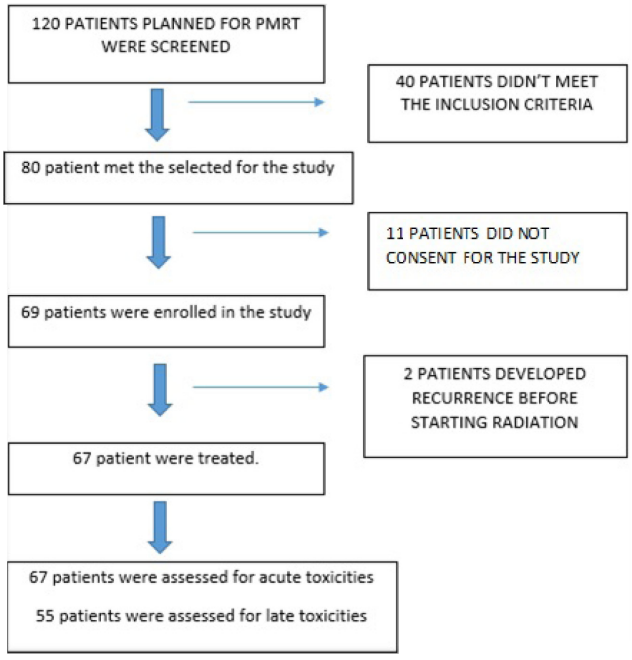

Figure 1. This Figure shows the details of patient selection, enrollment and their assessment in the study.

and absolute precision of 12% the required sample size was 65. Toxicities and recurrences were summarized as proportions with 95% confidence intervals. For dosimetry outcome variables, the comparison of parameters between VMAT and IMRT was performed using independent t-test or Mann-Whitney U test. Spearman's correlation was used to find association between the dose received by the OAR and the grade of toxicities. Data analysis was done using SPSS version 19.

Results

Between January 2017 and October 2018, we recruited 67 patients. Details of patient selection, enrolment, and assessment are presented in Figure 1.

The mean age of the study population was 48±9.5 years. Of the patients 67.2% had ECOG performance status 1. Thirty-four patients had left sided disease and 33 had right sided disease. Stage IIIA disease had 34.3% of the patients, IIB had 32.8% and 19.4% had stage IIIB disease. The most common location of the tumor was the upper outer quadrant and the most common histology was infiltrating ductal carcinoma. Of the patients 80% had adequate axillary lymph node dissection and 31 (46.3%) received neoadjuvant chemotherapy (NACT). The most commonly used chemotherapy regimen was anthracycline plus taxane (95.5%). Thirty-three patients received radiation using the breast board and the remaining 34 patients received radiation using the wing board. The median (IQR) time taken from surgery to the start of radiation was 155 days (123-226). The median (IQR) treatment duration was 23 days (22-27). Twenty-four patients were treated by IMRT and 43 were treated by VMAT.

The median (IQR) treatment time was 14.6 min (8.0-19.5). The median (IQR) Monitor Units was 858 (715-1575). The mean PTV D_{max} was 114±3.7%. The mean of V38.3Gy was 98.9±1.1%. The mean V40.4Gy was 96.8±1.85%. The median (IQR) value of V45.5Gy was 102 cc (17-403.7). The mean D2% was 46.5±1.3% Gy. The mean D50% was 44.3±0.9% Gy. The mean D98% was 39.3±1.7 % Gy. Figure 2 shows the comparison of Conformity index between VMAT and IMRT technique. The mean homogeneity index was 0.16±0.05. The mean conformity index was 1.17±0.08. Table 2 and 3 show the comparison of dosimetric outcomes and OAR between VMAT and IMRT techniques, respectively.

The incidence of grade 2 and above acute radiation dermatitis was 11.9 % (95% CI 6.1-21.8). Only one patient developed grade 3 skin reaction. The incidence of grade 2 and above acute esophagitis

Table 2. Comparison of dosimetric parameters between IMRT and VMAT

	Mean	*Minimum*	*Maximum*	*Median*	*p value*
Vmat $D_{2\%}$	46.72 (1.51)	42.55	48.95	46.8	0.08#
Imrt $D_{2\%}$	46.20 (0.87)	44.94	48.74	46.15	
Vmat $D_{50\%}$	44.6 (1.00)	41.2	46.24	44.53	**0.01#**
Imrt $D_{50\%}$	43.97 (0.76)	43.05	46.61	43.78	
Vmat $D_{98\%}$	39.75 (1.77)	34.13	43.20	39.94	**0.02#**
Imrt $D_{98\%}$	38.74 (1.61)	34.16	41.20	39.08	
Vmat 45.5 Gy	26.61 (24.06)	0.00	77.0	20.0	**0.04***
Imrt V45.5 Gy	8.29 (10.39)	0.11	39.60	4.85	
Vmat 40.4 Gy	97.1 (2.00)	92.00	99.99	97.7	**0.049#**
Imrt 40.4 Gy	96.31 (1.44)	93.00	99.00	96.00	
Vmat 38.3 Gy	99.05 (1.12)	95.00	99.99	99.50	**0.01***
Imrt 38.3 Gy	98.55 (1.01)	95.00	99.90	99.00	
Vmat HI	0.15 (0.05)	0.06	0.28	0.14	0.27*
Imrt HI	0.17 (0.04)	0.11	0.31	0.15	
Vmat CI	1.19 (0.08)	1.01	1.35	1.18	**0.01#**
Imrt CI	1.13 (0.76)	1.03	1.41	1.13	
Vmat MU	757 (117.9)	440	1064	746	**<0.001***
Imrt MU	1858 (501.4)	1171	3281	1805	
Vmat TT	10.2 (4.0)	4.2	16.6	9.3	**<0.001***
Imrt TT	24.2 (9.8)	12.25	54.5	22.0	

This Table shows the comparison of dosimetric outcomes between VMAT and IMRT Technique. For normally distributed variables Independent t Test (#) was used. For non-normally distributed variables Mann-Whitney U test (*) was used. HI: Homogeneity Index. CI: Conformity Index. MU: Monitor Units. TT: Treatment Time.
Bold numbers denote statistical significance

Table 3. Comparison of OAR doses between IMRT and VMAT

	IMRT	*VMAT*	*p value*
Ipsilateral lung D_{mean}	17.1 Gy	17.4 Gy	0.25#
Ipsilateral lung $V_{27\ Gy}$	19 %	20%	0.64#
Ipsilateral lung $V_{18\ Gy}$	32.9 %	32.6%	0.81#
Ipsilateral lung $V_{4.5Gy}$	99.5	98.0	0.18*
Heart D_{mean} (Left breast side cancer)	14.7 Gy	14.2 Gy	0.52#
Heart D_{mean} (Right breast side cancer)	7.7 Gy	5 Gy	**0.01***
Heart V_{18Gy}	27%	25.8%	0.56#
Heart $V_{22.5Gy}$	17.4%	17.1%	0.70#
Heart V_{27Gy}	12.6%	12.1%	0.61#
Heart V_{36Gy}	4.3%	5.2%	0.74#
Contralateral lung D_{mean}	4.5 Gy	4.6 Gy	0.91#
Contralateral breast D_{mean}	4.1 Gy	4.1 Gy	0.44#
Liver D_{mean} (Left breast side cancer)	5 Gy	3.7 Gy	0.09#
Liver D_{mean} (Right breast side cancer)	12.6 Gy	9.3 Gy	0.07*
Spinal cord D_{max}	25.9 Gy	26.1 Gy	0.34#
Brachial plexus D_{max}	44.8 Gy	46.0 Gy	**0.003#**
Esophagus Dmean	14.6 Gy	13.4 Gy	0.08#
Esophagus D_{max}	43.0 Gy	45.0 Gy	**0.001***
Skin D_{max}	48.1 Gy	46.8 Gy	**0.01***
Skin D_{mean}	23.3 Gy	22.7 Gy	0.2#
Skin V_{38Gy}	33.2	30.0	**0.02***
Skin $V_{42.6Gy}$	16.7	15.1	0.50#

This Table shows the comparison of the OAR doses between VMAT and IMRT Technique. For normally distributed variables independent t-test (#) was used. For non-normally distributed variables Mann-Whitney U test (*) was used.
Bold numbers denote statistical significance

was 46.3 % (95% CI 34.86-58.08). Only one patient developed grade 3 esophagitis. The incidence of grade 2 and above acute pneumonitis was 7.5% (95% CI 3.23-16.31). Only one patient developed grade 3 pneumonitis. One patient developed acute grade 3 cardiac toxicity in the form of reduced ejection fraction and acute mitral regurgitation.

A subset analysis was performed to detect any difference on the incidence of acute toxicities among patients who received radiation using breast board or wing board

With respect to acute pneumonitis and acute radiation dermatitis, there was an equal distribution of grade ≥2 as well as grade ≤1 toxicities between the two groups.

It was found that there was an increased incidence of grade ≥2 esophagitis in patients who received radiation using wing board. X^2 test was used to check the significance, but it was not statistically significant (p=0.17).

Except for esophagus D_{max} there was no significant correlation between the dose received by the OAR and the grade of toxicity. Esophagus D_{max} had a significant correlation with the maximum grade of esophagitis (p<0.001). All the patients who developed grade 2 and above toxicities had a D_{max} of esophagus more than 40 Gy. The incidence of grade 2 and above toxicity at D_{max} of more than 40 Gy was 43.6% which increased to 68 % if D_{max} was more than 45 Gy.

With a median follow up of 9 months, there were 4 recurrences and one death. One patient developed local recurrence and 3 patients developed metastatic disease. Among the metastatic disease cases, one patient developed brain metastases, one had spine metastasis and the other had multiple liver secondaries. There was no breast cancer related mortality. The patient who expired died of acute fulminant hepatitis unrelated to breast cancer.

Fifty-five patients were assessed for late toxicities. There were no grade 2 or above late skin toxicities. Of the patients 72.7 % did not have any skin toxicity. There were no grade 2 or above subcutaneous fibrosis. 82% did not have any subcutaneous fibrosis. The incidence of grade 2 and above late radiation pneumonitis was 5.5% (95 % CI 1.8 to 14.8). The incidence of grade 2 and above cardiac toxicity was 18% (95% CI 0.3 to 9.6). Three patients developed grade 1 and only one patient developed grade 2 brachial plexopathy. The incidence of grade

2 and above brachial plexopathy was 18% (95% CI 0.3 to 9.6). The incidence of grade 2 and above shoulder stiffness was 3.6% (95 % CI 1.0 to 12.32). The incidence of grade 2 and above lymphedema was 5.5% (95 % CI 1.8 to 14.8).

Discussion

Two main reasons for hypofractionation in breast cancer exist. The first is radiobiological superiority of hypofractionation for breast cancer and the second is the shorter treatment duration [1]. In our study the median (IQR) treatment duration was 23 days (22-27) as opposed to the conventional fractionation where the duration of treatment was 35 days. None of the patients had radiation treatment interruptions due to acute toxicities while on treatment. As a result, the compliance of the patients for treatment was improved.

In a study done at our institute, 3DCRT and VMAT were compared in left-sided breast cancer in terms of PTV coverage and dose avoidance to the heart and the lung. This study showed that VMAT could achieve equivalent PTV coverage and better sparing of heart and lung compared to 3DCRT [8]. The dosimetric advantages which IMRT and VMAT offer over 3DCRT may broaden the use of hypofractionation in PMRT. This formed the basis for using VMAT and IMRT in our study.

PTV coverage was given first priority in our study. The mean $V_{95\%}$ was 96.8±1.85% which was similar to the coverage seen in a study done by Orecchia et al, where the mean $V_{95\%}$ was 94.0±4.5% [9].

For left-sided disease, the mean Dmean of the heart was 14.2±2.1%. This is comparable to the mean dose achieved in a study conducted by Swamy et al where the average Dmean of the heart using VMAT technique was 13.02 Gy [10].

The mean ipsilateral lung Dmean was 17.3±1.3 Gy. The median (IQR) value of V27Gy was 20% (18-21). The mean value of V18Gy was 32.7±3.7%. These results are similar to study done by Changchung et al, where the V20Gy was 34.08±7.16% for VMAT plans [11].

VMAT provided a better coverage to the PTV over IMRT but the latter is more conformal. The main difference between the VMAT and IMRT is that the number of Monitor units required and the treatment time is less for VMAT. It is advantageous for in high-volume centres where the number of patients treated with VMAT could be more when compared to IMRT.

The other advantages of decreasing the treatment include lesser integral dose, minimizing the intrafraction motion error and better patient compliance.

The incidence of acute grade ≥2 dermatitis was 11.9%. The maximum grade of toxicity happened one week after completion of radiation therapy, i.e., around four weeks after starting radiation. This could possibly be explained by the fact that the skin replacement over time is also around four weeks.

We observed an unexpected increase in the incidence of acute esophagitis. One possible explanation for the increased incidence of esophagitis in our study could be the technique of radiation (IMRT and VMAT). In conventional technique we use 10-15 degrees of gantry tilt so that the esophagus moves out of the field. But in case of IMRT and tomotherapy dose spillage occurs and moreover the cervical esophagus lies in close proximity to the SCF field and is irradiated [12].

The incidence of symptomatic radiation pneumonitis after 45-50Gy of PMRT using conventional techniques ranges from 1- 7% which was similar to what was observed in our study [13].

The Danish Breast Cancer Cooperative Group recommends the D_{max} of brachial plexus should not exceed 54 Gy [14]. In our study using the D_{max} was kept at 48 Gy considering the α/β ratio of brachial plexus as 3 such that the EQD2 was 54 Gy. The mean value of brachial plexus D_{max} was 45.5±1.4 Gy. Patients can develop brachial plexopathy even 15 to 20 years after radiation therapy. So, a longer duration of follow up is required to find out the incidence of brachial plexopathy [15].

Only one patient developed local recurrence and 3 patients developed metastatic disease without local recurrence. During follow up it was found that, among the 3 patients who developed metastatic disease, 2 had disease progression and the third patient had partial response after neoadjuvant chemotherapy. Radiotherapy controlled the local disease but the tumour was not responsive to chemotherapy, hence resulted in a distant metastasis. This opens up new avenues in the response assessment to neoadjuvant chemotherapy. A patient who does not respond after 2-3 cycles should be considered for 2nd line chemotherapy in the neoadjuvant setting.

Breast cancer is the leading cancer among women in our country. In our centre, it is the second most common cancer after all head and neck subsites grouped together. If we use hypofractionation (16 fractions) instead of conventional fractionation (25 fractions) we can save 900 treatment session per 100 patients treated (2500-1600=900). In these 900 sessions we can further treat 56 patients. So in a high-volume centre hypofractionation is an ideal regimen.

To conclude, hypofractionated radiotherapy

is feasible in post mastectomy radiation therapy. Dosimetrically VMAT and IMRT achieved similar PTV coverage and OAR doses.

Despite having high incidence of acute esophagitis, there were no late grade 2 or more esophagitis cases which probably gives us a picture that the dysphagia could be transient. A longer follow up period is required to comment about the late toxicities and the local control rates.

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Conflict of interests

The authors declare no conflict of interests.

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