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Original Research

Feasibility and Toxicity of Hypofractionated Radiation Therapy in Patients Undergoing Post Mastectomy Radiation Therapy

Kanmani Velarasan Department of Radiation Oncology, Tirunelveli Medical College Hospital, Tirunelveli, India.
Deivanayagam Ramasundaram Department of Radiation Oncology, Tirunelveli Medical College Hospital, Tirunelveli, India.
Gopi Prasad Department of Radiation Oncology, Tirunelveli Medical College Hospital, Tirunelveli, India.

Introduction: Post mastectomy radiation (PMRT) plays major role in breast cancer treatment. Hypofractionated radiation is a relatively newer modality. Hypofractionation is more commonly used after breast conservation surgery. Landmark trials that studied hypofractionation had fewer PMRT subjects. Here we report our study on feasibility and toxicity profile of hypofractionated PMRT.

Aim: To describe the clinical and toxicity profile of patients undergoing hypofractionated 3D conformal radiation therapy in breast cancer patients.

Materials & Methods: This study included patients who are eligible for post mastectomy radiation therapy above 18 years planned for adjuvant PMRT (40.05Gy in 15 fractions delivered over 3 weeks in 3D conformal radiation) to the chest wall and supraclavicular nodes between April 2021 to October 2022., active lung infection, patient preference for conventional fractionation. Dosimetric parameters to target & organs at risk were analyzed. Toxicities including hematologic, dermatitis, pharyngitis & other were monitored.

Results: Of 71 patients, 70 patients were female and 1 is male. Majority (46%) of patients belonged to 46-55 years age group. Age ranged from 34 to 85 years. Mean age is 52 years. Clinical Stage IIIA was the most common stage with 29.5% patients followed by Stage IIB with 25.3% patients. Majority received adjuvant chemotherapy (52%). Mean treatment time is 21 days. All patients completed treatment without any major complications. Follow up ranged from 17 months to 27 months. Out of 71 patients, 1 patient expired on follow up after 4 months of radiation therapy due to non cancer related cause (Chronic pancreatitis). On follow up, 3 patients had distant metastasis alone (lung, bone metastasis, brain metastases) and 1 patient had both local disease and distant metastasis. 3 patients who progressed had stage IIIC disease & 1 had stage IIIB disease. The V90 to the Planned Target volume (PTV) ranged from 90.4% to 99% to right sided disease, 90.3% to 96.5% to left sided disease. Heart V17Gy ranged from 1.27% to 12.5% & heart V35Gy was 0.16% to 7.2%. Dermatitis was the most common adverse effect in this study. 31 patients (43.6%) developed fatigue during treatment. They continued their daily activities without any limitations. 35 patients (49.2%) had throat pain, of which 2 patients had it in 1st week, 21 patients had it in 2nd week and 12 patients had it in 3rd week. They were treated with non opioid analgesics. Shoulder pain was observed in 10 patients (14%) during treatment. Blood parameters were monitored weekly during treatment. No changes were observed.

Conclusion: Hypofractionated post mastectomy radiation therapy is well tolerated in our study group. None of them developed any major acute reactions during and post treatment in the follow up period. Patients completed their treatment without any breaks during treatment. Respiratory motion management especially left sided disease patients should be used for

achieving dose constraints.

Introduction

Breast cancer is one of the leading causes of death in both developing and developed countries. Improving life expectancies has lead to increasing incidences in cancer [1]. Incidence rates are increasing irrespective of urban and rural status [2]. In India, majority of patients present with locally advanced stages. Treatment involves neoadjuvant chemotherapy, modified radical mastectomy and post mastectomy radiation therapy. Treatment of breast cancer continues to keep evolving over time.

Radiation therapy evolved to have a major role in treatment of breast cancer. In 2005, EBCTCG meta-analysis, radiation therapy to the chest wall and regional lymphatics reduced 5-year LRR by 17% [3]. EBCTCG also showed radiation therapy after breast conservation surgery conferred similar results [4]. Breast cancer management needs multidisciplinary care. Major management of breast cancer often spans over 3 months to 9 months. Radiation therapy usually contributes to about 5-6 weeks. So time factor plays a important concern. The need of radiation therapy in breast cancer is increasing all over the world & studying the biology of breast cancers also has lead to usage of small fractions with higher doses throughout the world.

Concept of hypofractionation initially tried in the United Kingdom as early as 1986. Case series and cohort studies initially reported that these shorter schedules were acceptable in terms of both acute reactions and local control. So reducing the fraction from five weekly to three weekly schedules have proved to be feasible in terms of tumor control & toxicity. Since then several randomized studies have been conducted on this shorter fractionation regimens, the landmark trials being the START A and START B trials [5-7]. Hypofractionation studies on early breast cancer showed similar local tumor recurrence and late toxicity similar to conventional fractionation.

Concept of hypofractionation became the standard of care in patients with breast conservation surgery. Hypofractionation after mastectomy is slowly gaining support in India. But many studies are based on breast conservation patients & data towards post mastectomy radiation are fewer comparatively. In countries like India, hypofractionation is very helpful in reducing hospital stay thereby reducing infection rates, also particularly for economically less privileged patients & indirectly reduces cost of treatment. Indian breast cancer scenario will definitely benefit from this well established treatment regimen.

Aim of the study is to describe the clinical and toxicity profile of patients undergoing hypofractionated 3D conformal radiation therapy in breast cancer patients.

Materials and Methods

After getting approval from Institution scientific and ethics committee, patients were accrued for the study. All post mastectomy patients who presented to department of radiation oncology were screened for the study based on inclusion and exclusion criteria. Period of study is from April 2021 to October 2022, period of 18 months. Inclusion Criteria is any patient requiring post mastectomy radiation therapy, who are above 18 years were eligible. Exclusion criteria are age less than 18 years, patients planned for whole breast radiation therapy, Collagen vascular disease, Poor performance status (ECOG>3), Pregnancy & breastfeeding, Breast reconstructed patients, Axillary nodal involvement with extra nodal extension, Metastatic breast cancer, Prior history of radiation to chest, Myocardial infarction within 6 months, chronic heart condition, chronic lung condition, active lung infection, Patient preference for conventional fractionation.

3DCRT Procedure

All patients requiring post mastectomy radiation therapy were screened for the study based on inclusion and exclusion criteria after explaining the study and getting informed consent. Radiation therapy was started after healing of surgical wound or four weeks after chemotherapy. Metastatic workup is done for all patients. Echocardiogram was obtained before starting radiation therapy for left sided breast cancer patients.

CT Simulation

Patient immobilization was done using a breast board. Patient was positioned in supine position with arm abducted 90 degrees or greater. 5 mm cuts were used. Contrast was not used.

Contouring and Planning

Regions treated were chestwall and supraclavicular field in all patients. RTOG contouring guidelines were used to contour organs at risk, chest wall and supraclavicular field. Planned target volume (PTV) of 5mm is given for supraclavicular region. Bolus was not used for any patients.

Organs at Risk (OAR)

Lungs, Heart, Liver, Spinalcord, Contralateral breast, and Esophagus were contoured.

Dose Prescription

40.05 Gy in 15 fractions over 3 weeks.

Treatment Execution

After contouring and dose prescription, 3DCRT planning was done. Tangential beams were used for chestwall. Anterior beams were used for supraclavicular field. Planning was done in Eclipse planning software, Varian systems. 6 MV beams were commonly used. Plan evaluation was done using Dose Volume Histograms (DVH) and isodose distributions. Final plan was selected based on above parameters. Daily imaging (kV) was done for 3 days for treatment verification, followed by weekly imaging. CBCT was used whenever necessary.

Weekly Assessment and Followup

During treatment, patients regularly monitored. Patients symptoms if any were recorded. Weekly assessments were done. If any acute reactions were present, grading was done based on RTOG criteria .Patient followed up every 4-6 weeks. Radiation reactions were monitored for response. Disease progression if present were recorded.

Statistical Analysis

Baseline data like demographics, disease characteristics, comorbidities of the patient are recorded

in data entry sheet. Radiation therapy details like DVH parameters, date of starting and completion of radiation therapy are also recorded. Data was analyzed using SPSS 20.0 software. Data was represented graphically using appropriate diagrams. Frequencies and percentages were calculated for discrete variables like hormone status, grade, comorbidities etc. Mean, median and standard deviation were calculated for continuous variables like age. Correlation between variables were studied.

Results

Patient Characteristics

Of 71 patients, 70 patients were female and 1 is male. Majority (46%) of patients belonged to 46-55 years age group. Age ranged from 34 to 85 years. Mean age is 52 years. 51% patients were ECOG performance status 1.

The study group had 49% patients with comorbidities, diabetes mellitus (54%) being the most common followed by hypertension (27%), hypothyroidism (14%). 4 patients had previous history of hysterectomy and 5 patients had family history of breast cancer (3 patients had second degree relative with cancer and 2 patients had first degree relative with cancer). Most patients have 2 children and mean breast feeding time of 10 months (Table 1).

S. No	Variable	Number
1	Sex	Female – 70
		Male – 1
2	Age	< 35 years – 2
		36-45 years – 12
		46-55 years – 33
		56-65 years – 17
		> 65 years - 7
3	Comorbidities (n = 35)	Type 2 Diabetes mellitus - 19
		Systemic hypertension - 10
		Hypothyroidism - 5
		Heart disease - 1
4	Laterality	Right sided – 37
		Left sided - 34
5	Clinical stage at presentation	I – 1
		IIA – 12
		IIB – 18
		IIIA – 21
		IIIB – 15
		IIIC - 4
6	Chemotherapy	Upfront Neoadjuvant chemotherapy – 12
		Adjuvant chemotherapy – 37
		Neoadjuvant and adjuvant chemotherapy - 22
7	Receptor status	Luminal A – 22
		Luminal B – 23
		Her 2 enriched – 8
		Triple negative - 18
8	Pathological stage	I – 1
		IIA – 14
		IIB – 20

		IIIA – 20
		IIIB – 7
		IIIC - 3

Table 1. Characteristics of Patients.

37 patients had right sided disease and 34 patients had left sided disease. Upper outer quadrant (46.4%, n=33) was the most involved site followed by central quadrant. Clinical Stage IIIA was the most common stage with 29.5% patients followed by Stage IIB with 25.3% patients. 97% patients have invasive ductal cancer- NOS type. Pathological stage IIIA (28.1%) and IIB (28.1%) were most common. Complete response was seen in 6 patients. 12 patients received upfront neoadjuvant chemotherapy, 37 % patients received adjuvant chemotherapy alone and 22 patients received both neoadjuvant and adjuvant chemotherapy. Adriamycin and Cyclophosphamide followed by Paclitaxel was the most common regimen followed in both neoadjuvant and adjuvant chemotherapy settings.

Mean treatment time is 21 days. Treatment time ranged from 19 to 26 days. All patients completed treatment without any major complications. Follow up ranged from 17 months to 27 months. Out of 71 patients, 1 patient expired on follow up after 4 months of radiation therapy. She expired due to non cancer related cause (Chronic pancreatitis). On followup, 3 patients had distant metastasis alone (lung metastasis, bone metastasis,brain metastases) and 1 patient had both local disease and distant metastasis. 3 patients who progressed had stage IIIC disease & 1 had stage IIIB disease. These patients are on systemic therapy and doing well. All other patients are disease free at the time of last follow up.

Acute Toxicities

Dermatitis

Dermatitis was the most common adverse effect in this study. None of the patients had grade III or IV dermatitis (Table 2).

Dermatitis	Week 1	Week 2	Week 3	Week 6
	(During RT)	(During RT)	(During RT)	(Post RT)
	n patients	n patients	n patients	n patients
Grade I	0	34	60	39
Grade II	0	0	7	32
Grade III	0	0	0	0
Grade IV	0	0	0	0

Table 2. Dermatitis Pattern in treated Patients.

Fatigue

31 patients (43.6%) developed fatigue during treatment. They continued their daily activities without any limitations.

Cough

Dry cough was observed in 18 patients (25.3%) during 3rd week of radiation therapy. No radiographic changes were observed.

Throat pain (Pharyngitis)

Throat pain was the next common adverse effect. 35 patients (49.2%) had throat pain, of which 2 patients had it in 1st week, 21 patients had it in 2nd week and 12 patients had it in 3rd week. They were treated with non opioid analgesics. None of the patients had complaints of pharyngitis at the time of follow-ups (Table 3).

Pharyngitis	Week 1	Week 2	Week 3	Week 6
	(During RT)	(During RT)	(During RT)	(Post RT)
	n patients	n patients	n patients	n patients
Grade I	2	21	12	0
Grade II	0	0	0	0
Grade III	0	0	0	0
Grade IV	0	0	0	0

Table 3. Pharyngitis Pattern.

Shoulder Pain

Shoulder pain was observed in 10 patients (14%) during treatment. All these patients had previous history of shoulder pain which developed after surgery. These patients had physiotherapy and their symptoms was relieved.

Blood Parameters

Blood parameters were monitored weekly during treatment. No changes were observed.

DVH Parameters (Table 4)

Parameter	Range	
	Right sided	Left sided
V90%	90.4% to 99%	90.3% to 96.5%
V95%	86% to 95.1%	84% to 93%
Global max	105% to 110%	107.3% to 110%
V105%	0.5% to 4.78%	1.8% to 5.3%
V107%	0% to 0.5%	0% to 0.6%

Table 4. Target Coverage.

OARS

Contralateral breast - All patients were within dose tolerance limits. Mean dose to contralateral breast is 104 cGy. Spinal cord tolerances were within normal limits (Table 5, 6 and 7).

Parameter V17Gy	Range	
	Right sided	Left sided
Ipsilateral lung	16.97% to 28.7%	12.64% to 22.92%

Table 5. Lung Dose.

Parameter	Range	
Heart	Right	Left
Mean dose	35.3 cGy to 152.6 cGy	135.7 cGy to 712 cGy

Table 6. Heart Mean Dose.

Parameter	Range
V17Gy	1.27% to 12.5%
V35Gy	0.16% to 7.2%

Table 7. Heart Parameters.

Discussion

Hypofractionated radiotherapy is an established regimen for treating breast cancers. But most studies are based on whole breast radiation therapy. Post mastectomy hypofractionated radiation therapy trials are fewer compared to whole breast radiation. In the landmark START trials, only 8% had post mastectomy radiation therapy [5-7].

Skin toxicity was minimal and well tolerated as seen as in other studies [8]. Dermatitis started from second week of radiation therapy. Majority of patients experienced dermatitis during third week. Odynophagia (Pharyngitis) was seen from second week of radiation therapy and required step 1 analgesics. It was well tolerated. None of them had grade 3 pharyngitis or required break in treatment.

This study was conducted during covid pandemic. Hypofractionation needed less hospital stay and hence less chance of transmission. Hypofractionation also reduced machine's workload. So more patients can be treated during similar time. This is particularly advantageous in developing countries like India. Cosmetic effects need to be studied for longer time.

Most women in our study were in the age group of 46 to 55 years (46.4%, n=33). Most of these women are working women and some are even sole earners for their family. So, conventional fractionation of 23 to 25 fractions leads to more work hours lost and thereby earnings for their family. Also costs during stay of treatment in hospital can lead to increased spending like food costs, room costs for their relatives etc.

Nearly 34 patients had children less than 15 years old and so care for them during treatment is difficult for the patient. Costs for travel and difficulty to travel during covid crisis complicated the treatment. So, hypofractionated treatment completing within 3 weeks is an advantageous treatment. In a study by Bekelman et al [9], hypofractionation permitted savings of 10% for health care expenditures. Yang et al showed significant reduction in cost in multiple countries [10]. Indian scenario also shows similar findings. Hypofractionation also permits savings for patient.

Limitations

This study is based on a single institution and was not a randomised study. Multi institutional randomized controlled trials are necessary to evaluate hypofractionation in Indian context. Respiratory motion management was not utilized in many patients, only 4 patients had motion management. Dose to Cardiac substructures like Left Anterior Descending Artery (LAD) were not studied. Patients were followed up for short duration (Mean follow up period was 22 months), so late effects of treatment were not known. Economic benefits of hypofractionation and Quality of Life assessment were not studied.

In conclusion, Hypofractionated post mastectomy radiation therapy is well tolerated in our study group. Patients completed their treatment without any breaks during treatment. Respiratory motion management especially left sided disease patients should be used for achieving dose constraints.

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