Section: Radiation Oncology

Original Research Article

TO EVALUATE THE ROLE OF AXILLARY IRRADIATION IN CASE OF CARCINOMA BREAST POST MODIFIED RADICAL MASTECTOMY IN PATIENT WITH T3 WITH 1-3 NODE POSITIVE WITHOUT PERINODAL EXTENSION

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ABSTRACT

Background: In stage pT3N1 without perinodal extension role of axillary irradiation after axillary dissection remains controversial. If after modified radical mastectomy, axillary irradiation is not given then axillary recurrence is main issue and if we irradiate the axilla then side effects like arm edema and shoulder stiffness are bothersome. As survival increase due to modern radiotherapy technique, chemotherapy and targeted therapy, quality of life is a major concern in these subset of patients. **Materials and Methods:** In order to evaluate role of axillary irradiation in stage pT3N1 without PNE patients, Prospective trial was undertaken in the Department of Radiotherapy. A total of 50 patients attending the radiotherapy department for post-mastectomy radiotherapy were enrolled in the study. This study had two arms, with 25 patients in each of the arms. All the patients had 1-3 pathologically positive axillary nodes without extra-nodal extension. **Study Arm:** Patients received axillary, supraclavicular fossa and chest wall RT with dose of 45Gy in 20 fractions. **Control Arm:** Patients received only supraclavicular fossa and chest wall RT with dose of 45Gy in 20 fractions. **Conclusion:** 14 out of 25 (56%) patients in the study arm developed arm edema while the occurrence of the same was noted in 4 out of 25 (16%) patients of the control arm.10 out of 25 (40%) patients in study arm and 5 out of 25 (20%) patients in control arm developed significant shoulder stiffness. Irradiation of axilla in a patient of carcinoma breast with adequate axillary nodal dissection and histopathological report suggestive of a pT3N1 tumor without perinodal extension can be avoided without compromising the local and regional control. Avoiding axillary irradiation in such selective patients can reduce side effects like shoulder stiffness and arm edema to a significant extent which ultimately translates into a better quality of life.

INTRODUCTION

Over the years radiotherapy is gaining more and more important role in the management of breast cancers. More and more patients are having their treatment plans supplemented with radiotherapy.

The role of post mastectomy radiotherapy has been proven by many trials Danish 82b, 82c, 83b, 83c, British Columbia trial and two meta-analysis by Oxford 2005 and 2014. Since then post mastectomy radiotherapy to breast cancer patients in 1 to 3 axillary node positive and pT3 or more is standard of care.[1,2]

Radiotherapy techniques used in the primary treatment of breast cancers are of two basic types: Those intended to irradiate the breast/ chest-wall alone (Local treatment) and those intended to irradiate the breast/ chest wall with regional Lymph nodes (loco regional treatment). Each of these techniques inevitably causes some of underlying lung and heart to be irradiated particularly, if the regional lymphatics are included with the treatment volume.

The optimization of treatment planning for tangential breast fields involve reducing dose In-homogeneity within the treated breast volume and minimizing the dose to the normal adjacent structures such as lungs,

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heart and the opposite normal breast. The incidence of the axillary irradiation side effects like arm edema and shoulder stiffness is seen after three to six months of radiotherapy treatment. In view of the relatively long and increasing overall survival of breast cancer patients over the years, quality of life become important parameter to be considered during the treatment planning.

In stage pT3N1 without perinodal extension role of axillary irradiation after axillary dissection remains controversial. If after modified radical mastectomy, axillary irradiation is not given then axillary recurrence is main issue and if we irradiate the axilla then side effects like arm edema and shoulder stiffness are bothersome. As survival increase due to modern radiotherapy technique, chemotherapy and targeted therapy, quality of life is a major concern in these subset of patients.

Aims & Objectives

The purpose of this Study to evaluate the role of axillary irradiation in stage T3 N1 without perinodal extension in breast cancer with primary aim for loco-regional control and secondary aim to comparing side effects.

MATERIALS AND METHODS

In order to evaluate role of axillary irradiation in stage pT3N1 without PNE patients, Prospective trial was undertaken in the Department of Radiotherapy The study design was presented before and approved by the Ethics committee of our institution. A total of 50 patients attending the radiotherapy department for post-mastectomy radiotherapy were enrolled in the study. This study had two arms, with 25 patients in each of the arms. All the patients had 1-3 pathologically positive axillary nodes without extra-nodal extension.

Study Arm: Patients received axillary, supraclavicular fossa and chest wall RT with dose of 45Gy in 20 fractions.

Control Arm: Patients received only supraclavicular fossa and chest wall RT with dose of 45Gy in 20 fractions.

Inclusion Criteria

- Age >20 to <60 years
- Post Modified radical mastectomy
- Invasive ductal carcinoma histology
- Non metastatic disease
- Stage pT3
- Axillary node 1 to 3 positive without PNE
- K.P. score > 70

Exclusion Criteria

- Age <20 and >60 years
- Other than modified radical mastectomy surgery
- Other than invasive ductal carcinoma histology
- Metastatic disease
- Stage pT1,pT2,c/pT4
- Node pN0, pN2-3 or PNE positive
- K.P. score < 70
- Neo-adjuvant chemotherapy

General examination was conducted followed by a careful chest wall, supraclavicular area and axillary area examination. Thorough examination was done for both affected side and normal side. An informed consent was taken from each patient. Detailed history was taken. Complete blood count, Blood chemistry profile, Chest x-ray, USG abdomen pelvis, bilateral Mammo sonography and CT scan was done as required.

All patients underwent a baseline recording of both arm circumference and any other abnormality prior to treatment. Arm circumference was measured of each patient at every follow up, arm circumference was measured at midpoint of shoulder joint to elbow joint of both arm and compare the difference between them. Lymphedema was stated if difference between two arm circumferences is 2 cm or more.[8,9,10]

NCI grading system for lymphedema

Grade 1	5-10% difference between the affected and unaffected arm in volume or circumference, at the point of greatest visible difference.
Grade 2	More than a 10-30% difference between the affected and unaffected arm in volume or circumference, at the point of greatest visible difference.
Grade 3	More than a 30% difference in volume between the two arms. Leaking of lymph through the surface of the skin (called lymphorrhea)
Grade 4	Disabling; diagnosis of lymphangiosarcoma

Shoulder stiffness was assessed by abduction, external rotation of shoulder with comparing it with opposite side. Physiotherapy of arm and shoulder is carried out before planning of radiotherapy to achieve adequate arm abduction.

All of the patients were treated on linear accelerator with 6 MV Photon energy with either simulator /CT based 2D plan /3D CRT.

RESULTS

This study comprises of two groups with 25 patients in each.

Table 1: Age Wise Distribution of the Patients

Years	21-30	31-40	41-50	51-60	Total
Case arm	2	6	8	9	25
Control arm	3	10	8	4	25

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In case arm maximum 36% of patients are between 51 to 60 years of age group. In control arm maximum 40% of patients are between 31 to 40 years of age group.

Axillary Node Dissected

Table 2

Lymph node	0 to 5	6 to 10	11 to 15	16 to 20	21 to 25	26 to 30
Case arm	0	6	14	3	2	0
Control arm	0	2	11	8	2	2

76% of patients in case arm and 92% of patients in control arm had more than 10 axillary lymph- node dissected.

Table 3

	Luminal A	Luminal B	Luminal C	Luminal D
Case arm	10	3	8	4
Control arm	10	2	10	3

ARM EDEMA

Arm edema was measured using measure tap

Table 4

Arm circumference	0-0.5	0.6 – 1	1.1-1.5	1.6 -2	2.1-2.5	2.5-3
Case arm	6	4	1	9	4	1
Control arm	17	4	0	3	1	0

Difference in circumference between of two arm more than or equal to 2 cm at the midpoint of shoulder and elbow joint is consider as a significant arm edema.

At 1.5yrs follow up, 14 out of 25 (56%) patients in the study arm developed arm edema while the incidence of the same was noted in 4 out of 25 (16%) patients of the control arm.

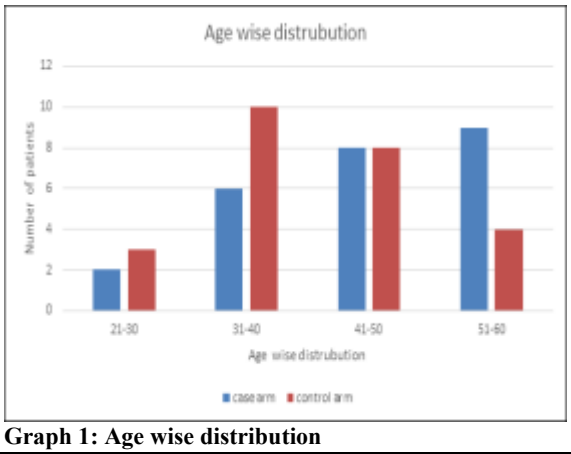
SHOULDER STIFFNESS

Shoulder stiffness was accessed by comparing, shoulder mobility with opposite side shoulder mobility like external rotation, abduction and arm elevation.

Table 5: Distribution of patients according to late radiation toxicity in control arm and test arm

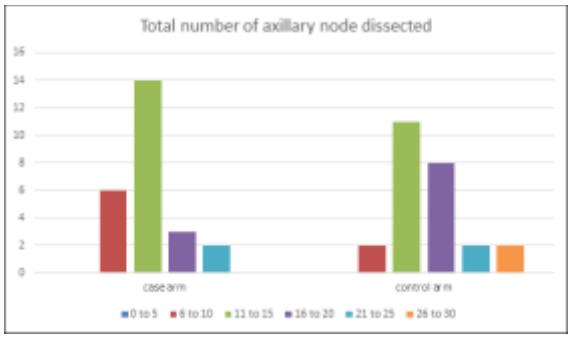
	Shoulder stiffness present	Shoulder stiffness absent
Case arm	10	15
Control arm	5	20

At median follow-up of 1.5 years, 10 out of 25 (40%) patients in case arm and 5 out of 25 (20%) patients in control arm developed significant shoulder stiffness.



Graph 1: Age wise distribution

In this study total number of axillary node dissected in each group is shown in the following table.



Graph 2: Number of Axillary node dissected

Hormonal Status

According to luminal classification, hormonal status of patients is as following.

Luminal A-ER and /or PR positive, Her2 receptor negative

Luminal B –ER and /Or PR positive, Her 2 receptor positive

Luminal C- ER, PR and HER 2 receptor negative

Luminal D- ER and PR negative, Her 2 receptor positive

In case arm, Depicted of patients according to luminal classification in each arm in the present study is shown in the table and pie chart below;

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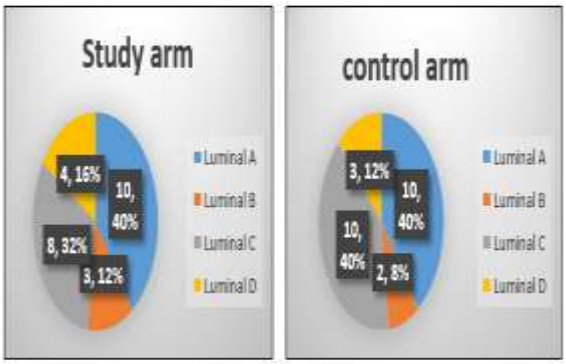
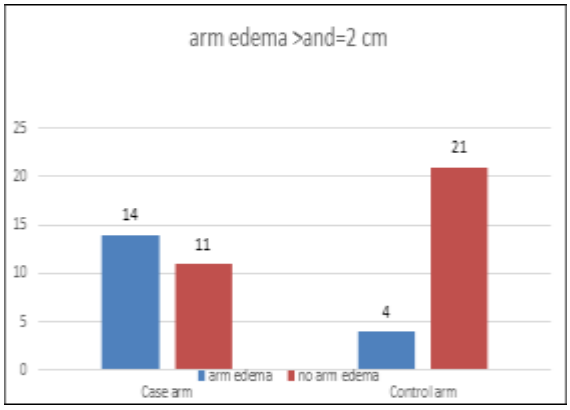
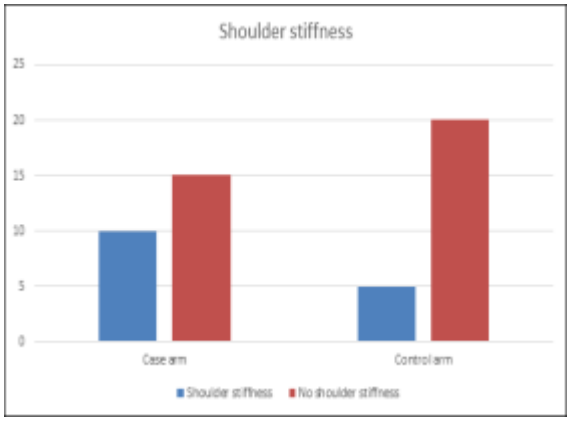


Graph 3: Hormonal status Hormonal status according to luminal classification is as shown per bellow's pie graph



Graph 4: ARM Edema



Graph 5: Shoulder stiffness

None of the patients developed or observed other side effects like rib fracture, brachial plexopathy, Lhermitte's sign and match line fibrosis during my study period.

One of the patients of control arm died of brain metastasis (distant failure). Hormonal group status of patient was luminal C. This patient developed brain metastasis within 6 months of adjuvant radiotherapy to chest wall and supraclavicular fossa. Whole brain radiotherapy 30Gy/10# was given. But patient died within 1 month of WBRT at her residence.

Hence arm edema and shoulder stiffness in the study arm presented as a significant side-effect in contrast to the control arm without any difference in loco-regional outcome in the two groups.

DISCUSSION

Radiotherapy has been a part of standard treatment protocol in majority cases of breast cancer. In view of relatively long and increasing overall survival of breast cancer patients, due to chemotherapy and radiotherapy, the quality of life becomes an important parameter to be considered during the treatment planning.

In this study out of total 50 patients (25 in case arm and 25 in control arm) not a single patient developed loco-regional failure.

One patient in the control arm died due to distant metastasis.

14 out of 25 (56%) patients in the study arm developed arm edema while the occurrence of the same was noted in 4 out of 25 (16%) patients of the control arm.

10 out of 25 (40%) patients in case arm and 5 out of 25 (20%) patients in control arm developed significant shoulder stiffness.

Number of axillary node dissection, chemotherapy regimens and hormonal status are not correlate with local and regional recurrence in above study.

In this study, results showed that after axillary irradiation, no axillary recurrence were reported although many patients had side effects such as lymphedema of the arm and decreased shoulder movement thus decreasing the quality of life.

This study confirms the finding of previous studies addressing the same area.

Whelan et al, randomized patients for chest wall irradiation vs chest wall irradiation plus nodal irradiation (supraclavicular fossa, axilla, internal - mammary nodes). After median follow-up of 10 years he stated that there was no statistically significant loco-regional recurrence and disease free survival noted but after 10 years of follow-up lymphedema and pneumonitis was significant in nodal irradiated group. Here survival was 82.8% in nodal irradiation group vs 81.8% in control arm and lymph edema 8.4% in nodal irradiation arm vs 4.5% in control arm.

Poortman et al (EORTC Trial) reported that patients who received irradiation to whole breast or thoracic wall plus or minus nodal irradiation showed no significant difference in loco-regional recurrence after 10 years of follow-up and had overall survival range from 80.7% to 82.8%.

One meta-analysis done by Gustavo Nader Marta based on Whelan et al and Poortman et al also stated that no difference between local and regional control in nodal irradiation and control arm but side effect due to nodal irradiation is increase in post mastectomy 1 to 3 positive axillary node without PNE.

Loco-regional control in my study in both arms is 100% whereas in above mentioned studies it was 80.7% to 82.8% in case arm while 81.8% in control arm. But the major drawback is duration of follow-up being 1.5 years as compared to 10 years follow-up in

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the above mentioned studies. As far as side effects (lymphedema) of the treatment is concerned, it was only 8.4% in nodal irradiation arm in previous studies while in my study it was 56%.

Veronesi U et al, randomized 214 patients to breast conservation without axillary treatment and 221 patients to breast conservation plus axillary RT. After a median follow-up of 63 months, in no axillary treatment group in three cases (1.5%) axillary metastases were found. And in the axillary RT group one case (0.5%) axillary metastases was found. Rates of distant metastases and local failures were low, and 5-year disease free survival was 96.0% (95% confidence interval, 94.1%-97.9%) without significant differences between the two arms.

Louis-Sylvestre et al, 658 patients with a breast carcinoma clinically uninvolved lymph nodes were randomly assigned to axillary dissection or axillary radiotherapy. All patients underwent wide excision of the tumor and breast irradiation. At 10 and 15 years, survival rates were identical in both groups (73.8% v 75.5% at 15 years). Recurrences in the axillary node were less frequent in the axillary dissection group at 15 years (1% v 3%; P =.04). There was no difference in recurrence rates in the breast or supraclavicular and distant metastases between the two groups.

Mila Donker et al (AMAROS TRIAL) randomized patients between axillary radiotherapy vs axillary dissection in sentinel axillary node positive. In this study, axillary dissection was noted to be associated with more surgical morbidity in term of arm edema than axillary irradiation alone. And axillary recurrence in either of the arms was not significantly different, being is 0.43% in axillary dissection arm vs 1.19% in axillary radiation arm.

Giuliano ae et al divided patients to axillary dissection vs axillary sentinel lymph node dissection arms followed by adjuvant radiotherapy. They stated that Axillary lymph node dissection vs sentinel lymph node dissection has no overall survival or loco regional difference.

According to study by Yarnold et al, in patients with one to three positive nodes without extracapsular extension who undergo adequate axillary dissection, there does not appear to be a benefit to target full axilla. Also, after axillary dissection, axillary radiation was associated with lympho-edema and shoulder stiffness.

Hetelekidis et al, Evaluated 368 patients with T1 or T2 breast cancer and pathologically positive nodes treated with breast conserving surgery therapy. The median number of lymph node dissected were 10. 20% patients were treated with supraclavicular radiotherapy, 64% received both supraclavicular and axillary radiotherapy. 33% patients had ECE. There was no significant co-relation of either disease free survival or overall survival or local-regional nodal or distant failure rate with axillary irradiation.

Meek AG et al stated that either surgery alone or radiation alone to axilla is associated with low incidence of lymphedema. Combination of axillary RT with axillary dissection increase the risk of arm lymphedema from 2-10% to 13-18%.

Jin hee et al. Among 450 cases of breast cancer, 24·9% had developed lymph-edema. There were significantly increased risks of lymph-edema if women were with higher staging, had modified radical mastectomy, had axillary lymph node dissection, received axillary radiotherapy and were with body mass index greater than 25 kg/m2.

Kissin et al. reported that lymphedema (measured by limb volume) was present in 25% of the members of a cohort of 200 patients after a variety of surgical treatments for breast cancer overall and in 38% of patients receiving axillary node dissection plus radiation therapy.

Erickson et al, the overall incidence of reported arm edema was 26%, with a range from 0% with partial or total mastectomy and sentinel node biopsy to 56% 2 years after surgery (modified radical mastectomy or breast-conserving surgery with axillary radiation therapy) and axillary dissection.

Most of the studies done above addressed axillary dissection vs axillary RT, with similar outcomes stating loco-regional control in axilla to be better with surgical intervention than radiotherapy.

All the above mentioned studies included patients with adequate axillary dissection, that is, more than 10 nodes dissected. These patients did not benefit from addition of axillary irradiation but had greater incidence of arm edema. However, studies concerning patients of stage pT3N1 who do not have ECE are limited and is an area of active research.

CONCLUSION

- Irradiation of axilla in a patient of carcinoma breast with adequate axillary nodal dissection and histopathological report suggestive of a pT3N1 tumor without perinodal extension can be avoided without compromising the local and regional control.
- Avoiding axillary irradiation in such selective patients can reduce side effects like shoulder stiffness and arm edema to a significant extent which ultimately translates into a better quality of life.
- However, the present study has its drawbacks like a small number of sample size in both the arms and short median follow up duration and more conclusive results would hence require further evaluation.

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