ORIGINAL RESEARCH PAPER

Volume-8 | Issue-8 | August - 2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PATTERNS OF FAILURE IN LOCALLY ADVANCED BREAST CANCER TREATED WITH OR WITHOUT RADIOTHERAPY

Oncology

Dr. Samip M. Pansora Assistant Professor, Radiation Oncology Saurashtra Cancer Care & Research Institute (sccri), Rajkot-360005, Gujarat, India

Dr. Meena Shah* Professor & Head, Radiation Oncology Saurashtra Cancer Care & Research Institute (sccri), Rajkot-360005, Gujarat, India *Corresponding Author

Dr Nimisha Gajera Medical Officer Saurashtra Cancer Care & Research Institute (sccri), Rajkot-360005, Gujarat, India

ABSTRACT

Background: The purpose of this study was to test the role of radiotherapy following modified radical mastectomy and adjuvant systemic therapy in the management of operable locally advanced breast carcinoma.

Materials and Method: After undergoing mastectomy and axillary dissection, 70 patients with locally advanced breast carcinoma were registered for study. All patients were then treated with full course of chemotherapy. After being restaged, all patients remaining without recurrence were offered postmastectomy radiotherapy. Though radiotherapy was offered to all patients, nearly half of the patients refused for radiotherapy and preferred observation. For ER positive patients, adjuvant endocrine therapy was advised for 5 years.

Results: Of 70 patients, 30 were deemed ineligible, leaving 40 cases eligible and analyzable. All the patients received planned adjuvant systemic chemotherapy. Out of these, 22 patients received Radiotherapy and 18 patients preferred Observation. Median follow-up period was 4 years. The loco-regional recurrence rate was 4.5% in radiation arm and 11% in observation arm. Of those in RT arm, 36.4% failed distantly with a median time to failure of 2 year. Of those in observation arm, 22.2% failed distantly, with a median time to failure of 3 years. When all sites at first failure were considered, there were fewer loco-regional recurrences in the RT arm but more of the RT patients had failed at 1 or more distant sites.

Conclusion: Radiotherapy for locally advanced breast carcinoma, following mastectomy, axillary dissection, and adjuvant systemic therapy, results in fewer locoregional but more distant recurrences at first failure. No significant advantage was seen for postmastectomy radiotherapy over observation in terms of either time to failure or survival. However, meaningful conclusions can't be drawn as our study has limitations because of its retrospective character and small number of patients.

KEYWORDS

Locally advanced Breast cancer (LABC), post mastectomy Radiotherapy (PMRT), Observation, Systemic chemotherapy, Failure

INTRODUCTION

Worldwide, breast cancer accounts for approximately 25% of all cancers diagnosed in women, and almost 15% of all cancer deaths. It is one of the most common malignancies in the Western world with the highest incidence in North America.[1] In India breast cancer is the most common cancer in women. In India 1,62,468 new breast cancer cases were diagnosed in 2018 and 87,090 died.[2] Locally advanced breast cancer (LABC) encompasses a broad spectrum of cancers with a wide variation in biologic behavior. Patients with locally advanced breast carcinoma (LABC) have no clinical, chemical, or radiographic evidence of distant tumor, yet most have occult systemic metastases. A multimodality treatment approach is usually required for achieving optimal control of local, regional, and distant disease. Combination of surgery and radiotherapy has resulted in better locoregional control than the use of either modality alone.[3, 4]The necessity of attacking occult distant metastases became obvious as early studies reported substantial gains in both local control and disease free survival when chemotherapy was combined with surgery and/or radiation in the management of both operable and nonresectable LABC.[4 5 6] Prognosis of breast cancer depends on a number of factors. The most significant prognostic factor is the axillary lymph node status, followed by tumor size, histologic grade, and age of the patient. The most significant prognostic factor for overall survival (OS) in patients with breast cancer is the presence or absence of axillary lymph node involvement. Furthermore, there is a direct relationship between the number of involved axillary nodes and the risk for distant recurrence.[7 8] More than three decades ago Fisher *et al*. reported that the 5-year OS for patients with node-negative disease was 82.8% compared with 73% for 1–3 positive nodes, 45.7% for 4–12 positive nodes, and 28.4% for ≥13 positive nodes.[9]

Postmastectomy radiotherapy (RT) in high-risk breast cancer (BC) patients can reduce locoregional recurrences (LRR) and improve disease-free and overall survival.[10 11] But in addition to proven benefits, radiation therapy (RT) also has its known side effects like skin changes, secondary tumours and lately highly reported cardio-toxic effects.[12 13 14] Present study highlights the pattern of failure in operable locally advanced breast cancer treated with or without radiotherapy after MRM and systemic chemotherapy.

METHODS AND MATERIALS:

This is a retrospective analysis of patients with locally advanced breast cancer treated at Saurashtra Cancer Care& Research Institute, Rajkot from January 2013 to January 2017. The study cohort in the present study was selected consecutively and the data of all patients are prospectively maintained in our database.

Inclusion Criteria:

- Non-inflammatory, technically resectable LABC (any T4, N0-3 lesion except T4d; T3 lesions with N1-3 and T1 or T2 lesions having N2-3 lymph node disease)
- Histologically proven, infiltrating ductal carcinoma (IDC)
- Have undergone a MRM with grossly tumor– free margins
- Removal and examination of at least eight ipsilateral axillary lymph nodes
- No evidence of disease (NED) after MRM
- Age > 18 years and < 70 years

Exclusion Criteria:

- Very poor general condition (KPS<50)
- Inflammatory or bilateral breast carcinoma;
- Satellite skin metastases beyond the area of the ipsilateral breast that could not be removed by mastectomy;
- Edema of the ipsilateral arm or parasternal tumor indicative of internal mammary lymph node metastasis;
- Distant metastases
- Male breast cancer
- Prior or concurrent malignancy
- Prior treatment for the current breast carcinoma

All the eligible patients had undergone MRM after doing clinical and relevant investigations (Complete physical, hematologic, chemical, histopathological and radiological). Staging of the tumor was done as per the American Joint Committee on Cancer (AJCC) guidelines. Patients who underwent breast-conserving surgery, received neoadjuvant chemotherapy or who didn't turn up for follow up were not eligible for this study. All patients received planned chemotherapy, beginning as soon as possible after wound healing and not later than 6 weeks after MRM and continued until completion of planned drug

cycles (6-8) or treatment failure. Chemotherapy was administered only if hemoglobin was above 9.0 mg/dl, absolute neutrophil count was more than 1500/cu.mm and platelet count was more than 100000/cu.mm. ECG and 2D ECHO were done prior to start adjuvant chemotherapy. Those patients without any uncontrolled co morbidity and with adequate hematological, renal and hepatic reserve parameters were included in study. Chemotherapy regimens used were taxane based (AC f/b Taxane / EC f/b Taxane / TAC) and non taxane based (FAC/FEC). Drug dosages were based on the body surface area, which was calculated from the lesser of the patient's ideal and actual body weights. All drugs were given on day 1 and the drug cycles were to be repeated at 21−day intervals. Details of dosing schedules are given in Table-1.

Table 1: Chemotherapy Dosing Schedules [15]

Regimen	Drugs (mg/m^2)
TAC	Docetaxel 75 Adriamycin 50 × 6 Cyclophosphamide 500
FAC	5 Flurouracil 500 Adriamycin 50 × 6 Cyclophosphamide 500
FEC	5 Flurouracil 500 Epirubicin 100 × 6 Cyclophosphamide 500
AC f/b Taxane	Adriamycin 60 × 4 Cyclophosphamide 600 f/b Docetaxel 100 or Paclitaxel 175 × 4
EC f/b Taxane	Epirubicin 100 × 4 Cyclophosphamide 600 f/b Docetaxel 100 or Paclitaxel 175 × 4

After completion of systemic therapy, the patients were to be evaluated to rule out recurrence of the breast carcinoma during drug therapy, and those without any evidence of relapse were offered post operative radiotherapy. The treatment volumes typically included the chest wall and draining lymphatics (supraclavicular, infraclavicular, internal mammary (IMN) and/or axillary bed at risk). Dose prescription was 50 Gy in 25 fractions at 2 Gy per fraction by conventional two-dimensional planning on Cobalt 60 Teletherapy unit or by 3D conformal radiotherapy on Linear Accelerator. Though postoperative radiotherapy was offered to all patients, nearly half of the patients refused for radiotherapy and preferred observation. For ER/PR-positive patients, adjuvant endocrine therapy (Tamoxifen/Letrozole) was advised for 5 years. Toxicity assessment was done as per standard criteria.

Patient Evaluation

History and physical examination were performed every 3 months for 2 years and every 6 months thereafter. Blood counts and chemistries were carried out every 3 months for 1 year and every 6 months thereafter. Chest X−ray and USG abdomen were performed every 6 months for the 2 years, and annually thereafter. Contralateral mammography was to be performed every 12 months. Patients were to be followed for time to relapse and survival, the starting point being the date of registration for systemic chemotherapy. Loco-regional recurrence (LRR) was defined as disease recurrence in the ipsilateral breast or in the ipsilateral axillary, supraclavicular, infraclavicular or internal mammary lymph nodes.

OBSERVATION & RESULTS

We analyzed 70 stage III breast cancer patients who underwent modified radical mastectomy followed by chemotherapy with or without Radiotherapy at Saurashtra Cancer Care and Research Institute, Rajkot between January 2013 and Jan 2017. Of these, 30 were deemed ineligible, leaving 40 cases eligible and analyzable on the chemotherapy step of this study. All the patients received adjuvant systemic chemotherapy. Those patients who received postmastectomy radiotherapy (PMRT) were considered in arm I (PMRT arm- 22 patients) and those who refused radiotherapy were considered arm II (observation (OBS) arm- 18 patients). Table 2 lists the patient characteristics of eligible and analyzable patients. 36.4% & 33.3% of patients were above 50 yrs of age and 63.6% and 66.7% of patients were <= 50 years of age in arm I and arm II respectively. 77.5% of patients had clinically positive lymph nodes, 30% of patients were premenopausal and 70% were in menopause. According to AJCC− TNM system, 36.4% and 61% of the patients were

Table 2: Patient characteristics

Patient characteristics	Radiotherapy arm	Observation arm	Total
Age>50	8 (36.4%)	6 (33.3%)	14 (35%)
Age<=50	14 (63.6%)	12 (66.7%)	26 (65%)
Menopausal status			
Premenopausal	9 (40.9%)	3 (16.7%)	12 (30%)
Postmenopausal	13 (59.1%)	15 (83.3%)	28 (70%)
Estrogen receptor status			
Positive	17 (77.3%)	14 (77.8%)	31 (77.5%)
Negative	5 (22.7%)	4 (22.2%)	9 (22.5%)
Clinical T stage			
T1	1 (4.5%)	0 (0%)	1 (2.5%)
T2	4 (18.2%)	3 (16.7%)	7 (17.5%)
T3	8 (36.4%)	11 (61.1%)	19 (47.5%)
T4a	3 (13.6%)	1 (5.6%)	4 (10%)
T4b	6 (27.3%)	2 (11.1%)	8 (20%)
T4c	0 (0%)	1 (5.6%)	1 (1.5%)
Clinical N stage			
N0	2 (9.1%)	3 (16.7%)	5 (12.5%)
N1	5 (22.7%)	3 (16.7%)	8 (20%)
N2	11 (50%)	9 (50%)	20 (50%)
N3	4 (18.2%)	3 (16.7%)	7 (17.5%)
Pathological staging			
IIIA	8 (36.4%)	11 (61.1%)	19 (47.5%)
IIIB	9 (40.9%)	6 (33.3%)	15 (37.5%)
IIIC	5 (22.7%)	1 (5.6%)	6 (15%)
Median no. of LNs examined (range)	13 (8-22)	14 (6-21)	
Median no. of positive LNs	7	7	
Median pathologic tumor size in cm	6	6.5	

Stage IIIA, 40.9% and 33.3% were IIIB, and 22.7% and 5.5% were IIIC in RT arm and OBS arm respectively. Median no of positive lymph nodes in both arms were 7. Patients received two main regimens, including taxane-based regimens in 60% (68.2% in arm I and 50% in arm II) and non-taxane based regimens in 40% (31.8% in arm I and 50% in arm II). The detail of taxane and non taxane based chemotherapy is listed in Table 3. There were no significant differences in the distribution of adjuvant regimens between two groups. All the patients tolerated adjuvant systemic chemotherapy well with grade 1-2 immediate/acute toxicity only in most of patients. Grade 3 and 4 toxicities were not observed in any patient. 10 (25%) patients had grade 1 and 30 (75%) patients had grade 2 alopecia. Other side effects of chemotherapy seen were nausea, vomiting (>90%), oral mucositis (32.5%), neutropenia (65%) and neuropathy (47.5%). Acute side effects observed in RT arm were mostly skin reactions (grade-1in 4.5%, grade-2 in 77.3% and grade-3 in 18% patients) and late side effects of RT included arm edema and limited range of motion arm grade 1 in 27% and grade 2 in 9% of patients.

Table 3: Taxane based and Non taxane based chemotherapy

Chemotherapy	Radiotherapy arm	Observation arm	Total
Taxane	15 (68.2%)	9 (50%)	24 (60%)
Non taxane	7 (31.8%)	9 (50%)	16 (40%)
Taxane based			
AC f/b Taxane	13 (59%)	5 (27.8%)	18 (45%)
EC f/b Taxane	1 (4.5%)	2 (11.1%)	3 (7.5%)
TAC	1 (4.5%)	2 (11.1%)	3 (7.5%)
Non taxane based			
FAC	2 (9%)	5 (27.8%)	7 (17.5%)
FEC	5 (22.7%)	4 (22.2%)	9 (22.5%)

The median follow-up time from the date of registration for chemotherapy in outpatient department was 48 months (range 24-72 months). Of those in radiation arm, 1 patient (4.5%) failed loco-regionally (ipsilateral internal mammary lymph node) at 3 years and 9 months. 8 (36.4%) patients failed distantly with a median time to

failure of 2 years. The patient with IMN recurrence had T4bN2a ECE (extra capsular extension) positive disease and had 4 months delay in receiving postoperative RT. 20 patients (91%) in arm I were alive at last follow–up. Of those in observation arm, 2 patients (11%) relapsed locally at one year and 5 years. Distant failure occurred 4 (22.2%) patients with a median time to relapse of 3 years, and all were alive at last follow–up.Table 4 lists the sites of failure at the time of first recurrence for each treatment regimen. When all sites at first failure were considered, there were 6.6% more local recurrences in the OBS arm than in the PMRT arm, and 14% more distant relapses in the PMRT arm than in the OBS arm. Conversely there were fewer loco-regional recurrences in the PMRT arm but more of the PMRT patients had failed at 1 or more distant sites. Most common site of distant metastasis was liver (20%) followed by lungs (15%) , bone (10%) and (5%)% to brain.

Table 4: Sites of first Failure

Site of Failure	Radiotherapy arm	Observation arm	Total
Loco-regional	1 (4.5%)	2 (11.1%)	3 (7.5%)
Distant	8 (36.4%)	4 (22.2%)	12 (30%)
Loco-regional + Distant (both)	0	1 (5.6%) subsequent	1 (2.5%)
Total	9 (40.9%)	5 (27.8%)	14 (35%)

DISCUSSION

There is no doubt that patients who have undergone MRM for LABC have fewer locoregional first recurrences when treated with adjuvant systemic therapy followed by XRT than by systemic therapy alone. [16] British Columbia trial randomized 318 premenopausal breast cancer patients for PMRT versus observation arm. All patients received adjuvant chemotherapy. The 20-year Local Recurrence (LR) rates were 13% in PMRT arm versus 39% in observation arm which favored adjuvant RT. The 20-year overall survival rates were 47% in PMRT arm versus 37% in OBS arm which favored PMRT.[17] DBCG (Danish Breast Cancer Cooperative Group) 82b trial randomized 1,708 premenopausal patients with stage II and III breast cancer to PMRT versus observation. All patients received adjuvant chemotherapy. The 10-year local recurrence rates were 9% in PMRT arm versus 32% in OBS arm, favored adjuvant RT. The 10-year overall Survival rates were 45% in observation arm versus 54% in PMRT arm, favored adjuvant RT.[10] DBCG(Danish Breast Cancer Cooperative Group) 82c trial randomized 1,375 postmenopausal patients with stage II and III breast cancer to PMRT versus observationAll patients received hormonal therapy with tamoxifen. The 10-year LR rates were 8% in PMRT arm versus 35% in OBS arm, favored PMRT ($p < 0.0001$). The 10-year OS were 45% in PMRT arm versus 36% in Observation arm, favored adjuvant RT. [10]

No significant benefit was seen in overall time to relapse or survival in EORTC trial[18] when consolidation irradiation was administered following surgery and adjuvant chemo-hormonal therapy. Effective systemic therapy alone following mastectomy in lymph node positive patients has been shown to decrease loco-regional recurrences by 40% and 50%, respectively, as reported from an NSABP trial and a review of the results from five sequential International Breast Cancer Study Group trials. [19 20] Further, 50% of first locoregional recurrences in patients who had not received postoperative adjuvant XRT can be controlled. An even greater proportion of the recurrences may be controlled if they are small, can be completely excised, and first recurrence after a long disease free interval following mastectomy.[20-24] Although postoperative XRT, when used alone as an adjuvant therapy, clearly has proven value in local control and possibly in overall survival, its role in the context of effective adjuvant systemic therapy has not been defined.

In our analysis, there were 6.5% fewer loco-regional recurrences at the time of the first failure in the PMRT patients than in the OBS patients (4.5% vs. 11%) at median follow–up of 4 years. Patients who received PMRT experienced higher incidence of distant failure at first recurrence than the OBS group (36.4% vs. 22.2%). The predictors of LRR included higher T stage, the number of positive nodes, dissection of <10 nodes, extracapsular extension , skin/nipple involvement, and estrogen receptor-negative disease, post mastectomy RT refusal and delay in post mastectomy RT. Higher T stage (T4) and higher N stage (N2-3) were associated with higher rate of local as well as distant metastasis. Further ECE was also associated with lower distant disease free survival (DFS). Similarly distant DFS was significantly higher in patients who were given hormonal therapy (ER positive) as compared to those who were not on hormonal therapy (ER negative). PMRT to the chest wall and peripheral lymphatics and adjuvant systemic therapy for resectable LABC decreased loco-regional recurrences (LRR) but PMRT had shown no impact on overall survival.

It is still not clear which patients will benefit sufficiently to justify the inconvenience, potential morbidity, and expense of additional XRT. Therefore, one can question whether the benefit of this small difference in uncontrolled disease justifies prophylactic irradiation for all LABC patients, many of whom are not destined to develop loco-regional disease at first recurrence following mastectomy, axillary dissection, and adjuvant chemotherapy.

CONCLUSION:

Present study demonstrated that PMRT and adjuvant systemic therapy resulted in fewer loco regional but more distant recurrences at first failure than was seen in patients who preferred OBS over RT. No significant advantage was found for PMRT over OBS with respect to overall time to relapse or survival. It is important to define and refine the role of PMRT in the care of LABC so that those most likely to develop locoregional recurrence can be selectively irradiated, while those least likely to fail locally can avoid unnecessary treatment. However, meaningful conclusions can't be drawn as our study has limitations because of its retrospective character, small number of patients and furthermore patients received different chemotherapy regimens.

REFERENCES

1. http://www.who.int/news-room/fect-sheets/detail/cancer, worldwide breast cancer data reporting.
2. http://cancerindia.org.in/breast-cancer/ burden of breast in India in year 2018.
3. Montague ED. Radiation management of advanced breast cancer. Int J Radiat Oncol Biol Phys1978; 4: 305-7.
4. Bruckman JE, Harris JR et al. Results of treating stage III carcinoma of the breast by primary radiation therapy. Cancer 1979; 49:985-93.
5. DeLena M, Zucali R, et al. Combined chemotherapy-radiotherapy approach in locally advanced (T3b-T4) breast cancer. Cancer Chemother Pharmacol 1978; 1:53-9.
6. Buzdar AU, Gutterman JU, et al. Intensive postoperative chemoimmunotherapy for patients with stage II and stage III breast cancer. Cancer 1978; 41:1064-75.
7. Saez RA, McGuire WL, Clark GM et al. Prognostic factors in breast cancer. Semin Surg Oncol 1989; 5:102-10
8. Nemoto T, Natarajan N, et al. Breast cancer in the medical half. Results of 1978 National Survey of the American of surgeons. Cancer 1983; 51: 1333-8.
9. Fisher B. Bauer M, Wickerham DL, et al. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. Cancer 1983; 52:1551-7.
10. Nielsen HM, Overgaard M, Grau C, Jensen A R, et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b randomized study. J Clin Oncol 2006; 24: 2268-75.
11. Overgaard M, Jensen MB, Overgaard J, et al: Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 353:1641-1648, 1999
12. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol 2005; 6: 557-65.
13. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013; 368: 987-98.
14. Marinko T, Borstnar S, et al. Early cardiotoxicity after adjuvant concomitant treatment with radiotherapy and trastuzumab in patients with breast cancer. Radiol Oncol 2018; 52 : 204-212.
15. NCCN (National comprehensive cancer Network) guidelines version 1.2019 principles of systemic therapy.
16. Kennedy, MJ, Abeloff, MD et al. Management of locally recurrent breast cancer. Cancer 1993; 71:2395-409
17. Ragaz J, Olivotto IA, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 2005; 97:116-26.
18. Donna Neuberg Sc D, Kishan J. Pandya M.D et al. The role of radiotherapy in the management of operable locally advanced breast carcinoma Results of a randomized trial by the Eastern Cooperative Oncology Group. Cancer 1997; 79(6):1061-1268.
19. Fisher B, Fisher ER, Redmond C et al. Ten year results from the NSABP clinical trial evaluating the use of 1-phenylalanine mustard (L-PAM) in the management of primary breast cancer. J Clin Oncol 1986; 4: 929-41
20. Goldhirsch A, Gelber RD, Price KN et al. Effect of systemic adjuvant treatment on first sites of breast cancer relapse. Lancet 1994; 343: 377-81.
21. Halverson KJ, Perez CA, et al. Survival following locoregional recurrence of breast cancer: Univariate and multivariate analysis. Int J Radiat Oncol Biol Phys 1992; 23: 285-91.
22. Fowble B, Gray R, et al. Identification of a subgroup of patients with breast cancer and histologically positive axillary nodes receiving adjuvant chemotherapy who may benefit from postoperative radiotherapy. J Clin Oncol 1988; 6: 1107-17.
23. Schwaibold F, Fowble B, et al. The result of radiation therapy for isolated local regional recurrence after mastectomy. Int J Radiat Oncol Biol phys 1991; 21 : 299-310.
24. Tennvall-Nittby, Tengrup I, Landberg, T et al. The total incidence of locoregional recurrence in a randomized trial of breast cancer TNM stage II. The south Sweden breast cancer Trial. Acta Oncol 1993; 32: 641-6.