



Retrospective Comparison of Adjuvant Radiotherapy in Early Stage Breast Cancer and Impact of Delayed PMRT

Authors

Dr Sanjal Kumar.V, Dr S.N. Jagadesh Kumar, Dr Sanjitha, Dr Harishkumar.P

Corresponding Author

Dr Sanjal Kumar.V

Email: sanjal.bmc@gmail.com

Abstract

Objectives: To retrospectively evaluate the importance of post mastectomy radiotherapy in early stage breast cancer and impact of timing of starting radiotherapy in terms of local control and disease free survival.

Methodology: This retrospective descriptive study was based on a database of 765 patients who were diagnosed and treated from 2006 to 2012 with 5 years minimum follow up. Patients were divided into three arms

1. ARM I – Patients with T1/2 N0 M0 with no classical indication of PMRT-No PMRT given
2. ARM II – Patients with T1/2 N0 M0 with no classical Indication of PMRT who received PMRT
3. ARM III - – Patients with T3/4 N+ M0 or with classical

Indication of PMRT who received PMRT

ARM III was subdivided as follows

III A – Patients who received Adjuvant radiotherapy within 6 months of completing surgery

III B – Patients who received Adjuvant radiotherapy after 6 months of completing surgery

Case sheets were scrutinised and data regarding stage, Neoadjuvant chemo, surgery dates, timing of starting radiotherapy ,completion of radiotherapy and toxicity , regular follow ups and if any disease progression the timing of metastasis etc. were collected.

The Kaplan–Meier method was used for calculation and Plotting of the LRFS and DMFS curves of the patient groups, and the Log-rank test was used for the comparison of the survival curves. The results were investigated using the Cox proportional hazards model

Results: ARM I – 92, ARM II – 85, ARM III – 588, III A – 330/588 (56.1%)

III B – 258/588 (43.9%)

Local Recurrence - 17 patients in arm I ,6 patients in arm II and 47 patients in arm IIIB had chest wall recurrence. Regional nodal recurrence was not seen in any of the arms

Distant Metastases- 15 patients in arm I, 11 patients in arm II and 70 patients in arm III (23 patients in arm IIIA and 47 patients in arm IIIB) had distant metastases.

Disease Free Survival - DFS in arm I was at an average of 10.14 and median DFS was at 10, DFS in arm II was at an average of 13.39 and median DFS was at 14, in arm IIIA was at an average of 9.3 years and median DFS at 9 years, In arm IIIB was at an average of 8.5 years and median DFS at 9 years, In the whole study, ARM II was significant $<p=0.541>$ in comparison with ARM I and ARM IIIA and IIIB. When you compare ARM IIIA and IIIB, there is no significant difference $<p<0.103>$.

Conclusions: DFS was significantly better in patients receiving RT compared with those not receiving RT when compared with ARM I and ARM II. Thus signifying some beneficial role in T1-2N0M0. Timing of initiating pmrt did not affect the disease free survival or overall survival. This is a single institution study further meta-analysis is needed to opine regarding timing of starting Radiotherapy and role of PMRT in early stage breast cancer.

Keywords: adjuvant radiotherapy in breast, post mastectomy radiotherapy, early stage breast cancer, PMRT.

Introduction

Breast cancer is the most common and most frequently diagnosed cancer in the world. In India, Breast cancer detection rates have risen dramatically. In our Department we get predominantly stage 3 or 4 cases only and modified radical mastectomy is only followed for majority of cases due to the presentation at locally advanced stage. Adjuvant radiotherapy after mastectomy and chemotherapy has been widely accepted as the gold standard of care for patients with tumours > 5 cm in size, 4 or more positive lymph nodes, or positive margins. There is consensus that PMRT should be considered when risk of LRF is greater than 20% such as for patients with 4/> positive axillary lymph nodes, primary tumour size 5 cm or above, T4 disease, and positive or very close margin^[1,2] In our institution, the indications for PMRT generally followed are a) T3 or T4 disease, N + disease, lympho-vascular invasion present, positive margins, high grade tumour- grade III, We also after careful consideration selectively give PMRT for T2N0 disease with no classical indications like triple negative, inadequate nodal dissection etc due to poor follow up of these patients specially people coming from remote areas^[3]. In the past, the benefit of adjuvant radiotherapy to chest wall in early stage breast cancer has been controversial. Though irradiation after mastectomy can reduce loco regional recurrence in women with breast cancer, but whether it prolongs survival has remained controversial^[4,5]. The initiation of PMRT post-surgery is usually done within 6months on account of tumour doubling time to be restricted^[6,7]. In our Institution we get lot of patients who in spite of the best advice given to start radiation at the earliest do not report for therapy due to various reasons. This single institution retrospective analysis focuses on analysing the impact of PMRT in various stages of breast cancer and the impact of tumour doubling time on the benefits of PMRT.

Methodology

This retrospective descriptive study was based on a database of 765 patient case sheets who were diagnosed and treated from 2006 to 2012 with 5 years minimum follow up. age varying between 30 to 72 years at presentation, who underwent Modified Radical Mastectomy and chemotherapy, were selected. male breast cancer were excluded. Since this is a retrospective study based on data from case sheets, without involving patients no ethical committee clearance was obtained

Patients were divided into three arms

1. ARM I – Patients with T1/2 N0 M0 with no classical indication of PMRT-No PMRT given
2. ARM II – Patients with T1/2 N0 M0 with no classical

Indication of PMRT who received PMRT

3. ARM III - – Patients with T3/4 N+ M0 or with classical

Indication of PMRT who received PMRT

ARM III was subdivided as follows

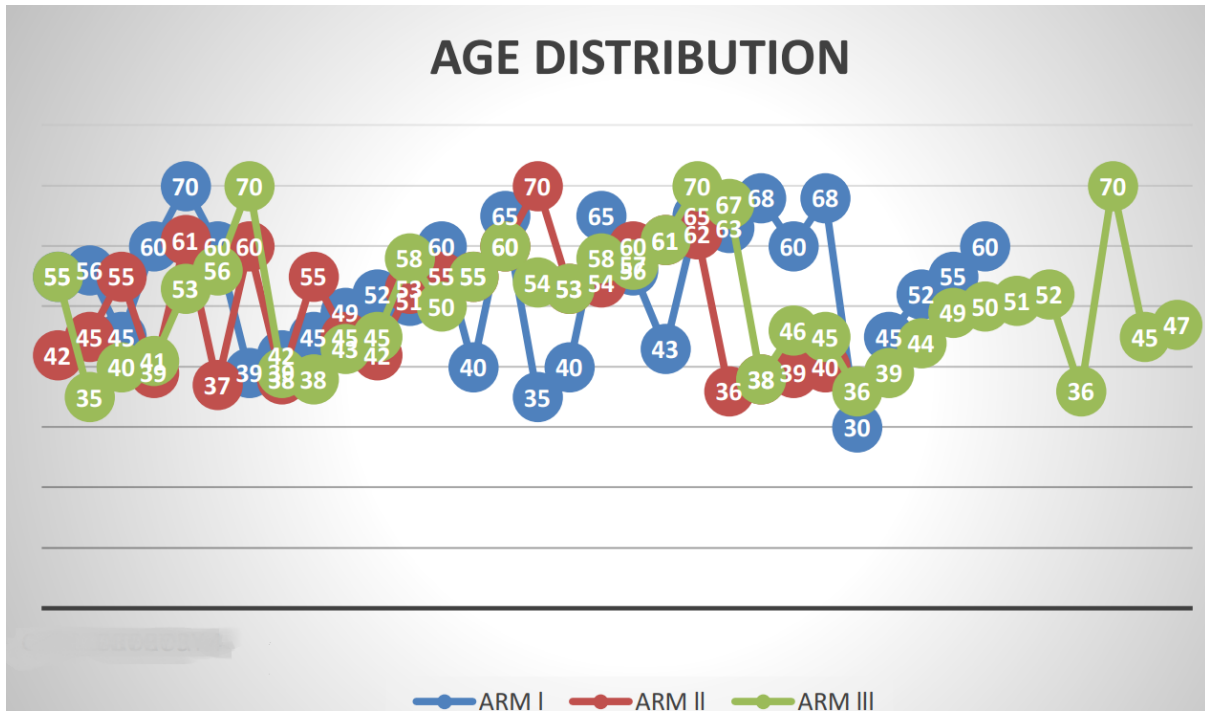
III A – Patients who received treatment within 6 months

III B – Patients who received treatment after 6 months

Case sheets were scrutinised and data regarding stage, Neoadjuvant chemo, surgery dates, timing of starting radiotherapy, completion of radiotherapy and toxicity, regular follow ups and if any disease progression the timing of metastasis etc. were collected.

Statistical Methods

This been a retrospective study all the case sheets available were utilised for data collection no particular sampling size was derived at. The Kaplan–Meier method was used for calculation and Plotting of the LRFS and DMFS curves of the patient groups, and the Log-rank test was used for the comparison of the survival curves. The results were investigated using the Cox proportional hazards model

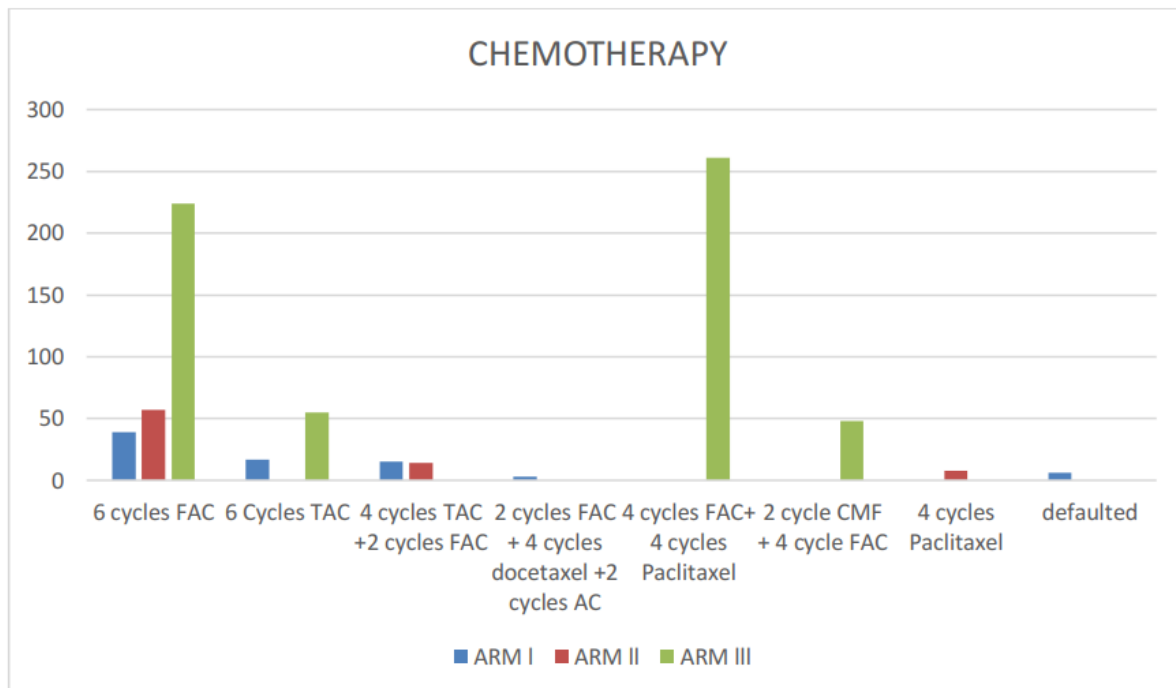


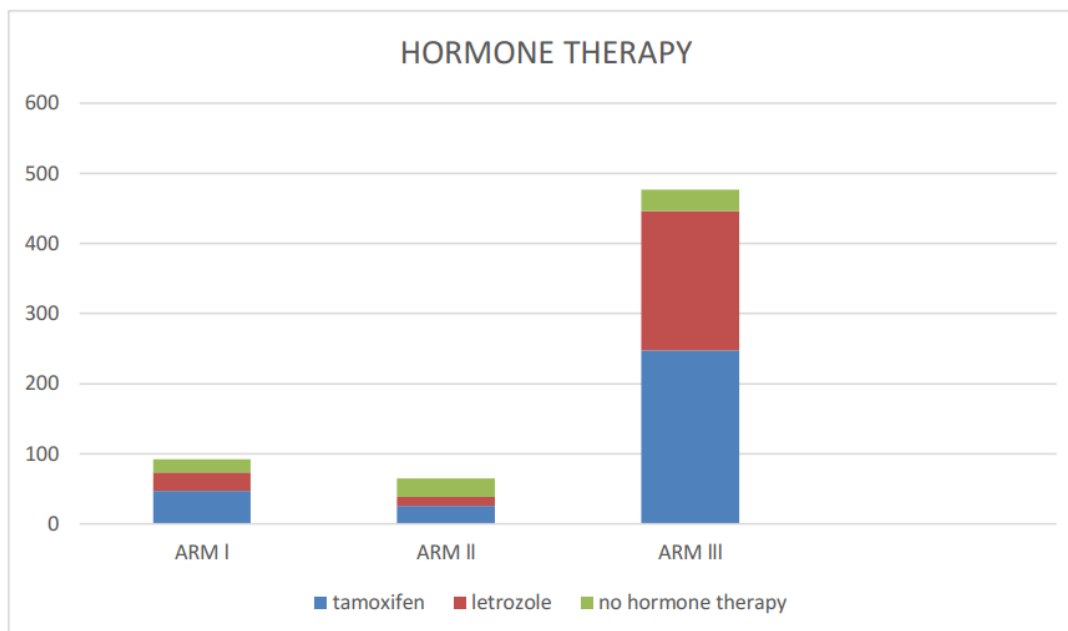
Surgery and Post Operative Pathology Reports

The primary surgical treatment performed at our hospital was Modified Radical Mastectomy with axillary lymph node dissection. Histopathological examination was performed according to

standardized procedure where microscopic examination included tumour classification according to WHO standards and classification according to the system of Bloom and Richardson grading of anaplasia.

Chemotherapy and Hormonal Data





In ARM I, 26 patients were pT1N0M0, and 32 patients pT2N0M0. 43 patients had 6 cycles FAC, 19 had 6 cycles of TAC, 13 had 4 cycles of TAC plus 2 cycles of FAC, 6 had 2 cycles of FAC followed by 4 cycles of docetaxel followed by 2 cycles of AC and 6 patient defaulted chemotherapy. 47 patients were on Tamoxifen, 26 had taken Letrozole and 19 had no hormonal treatment

In ARM III, 278 were T3 (163 in arm IIIa and 115 in arm IIIb), 310 patients were T4 (167 in arm IIIa 143 in arm IIIb). 168 patients were N0 (97 in arm IIIa and 71 in arm IIIb), 185 were N1 (102 from arm IIIa and 83 from arm IIIb), 235 patients were N2 (131 from arm IIIa and 104 from arm IIIb). 224 patients had 6 cycles of FAC (127 in arm IIIa and 97 in arm IIIb), 261 patients had 4 cycles FAC followed by 4 cycles Paclitaxel (141 from arm IIIa and 120 from arm IIIb) 55 patients had 6 cycles of TAC (36 from arm IIIa and 19 from arm IIIb) 48 patient took 2 cycles CMF with 4 cycles of FAC (26 from arm IIIA and 22 from arm IIIB). 247 patients took Tamoxifen (139 from arm IIIa and 108 from arm IIIb) 199 patients took Letrozole (107 from arm IIIa and 92 from arm IIIb) 142 patients had no hormone therapy (84 from arm IIIa and 58 from arm IIIb)

Post Mastectomy Radiotherapy Details

All 765 patients received irradiation to the chest wall and the regional lymph nodes using Cobalt

60 teletherapy. The target volume of chest wall field was the whole chest wall within the field and apart of lung beneath that chest wall treated in two tangential portals with half beam block. The target volume of supraclavicular field includes ipsilateral supraclavicular nodes infraclavicular nodes and axillary nodes treated with single Anterior-Posterior portal. For the supraclavicular field, the dose was prescribed at D-max level and the remaining depth dose at mid axillary level was calculated and a posterior axillary boost was given. All the patients received conventional fractionation only.

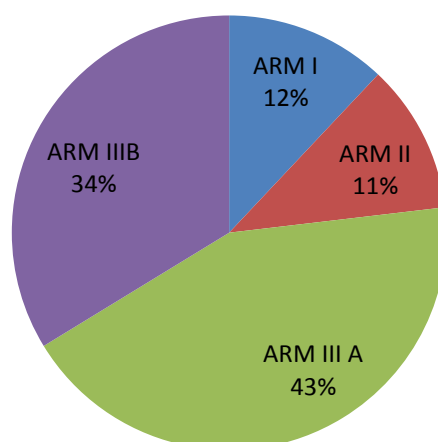
The case sheets were retrospectively analysed for any local or regional recurrence or any metastases till 2017. Local regional recurrence was defined as the appearance of local or regional tumour (chest wall, axilla or supraclavicular or infraclavicular area) alone. Distant metastases were defined as the metastases to bone, liver, lung or brain. Disease free survival was defined as the duration of survival without loco-regional recurrence or distant metastases, cancer in opposite breast or other malignant disease

Results

Patient distribution

ARM I	92	12.02 %
ARM II	85	11.11 %
ARM III A	330/588 (56.1%)	43.13 %
ARM III B	258/588 (43.9%)	33.72 %

DISTRIBUTION OF CASES



Here is the number of the patients based on the side of the breast; there was predominance with left breast.

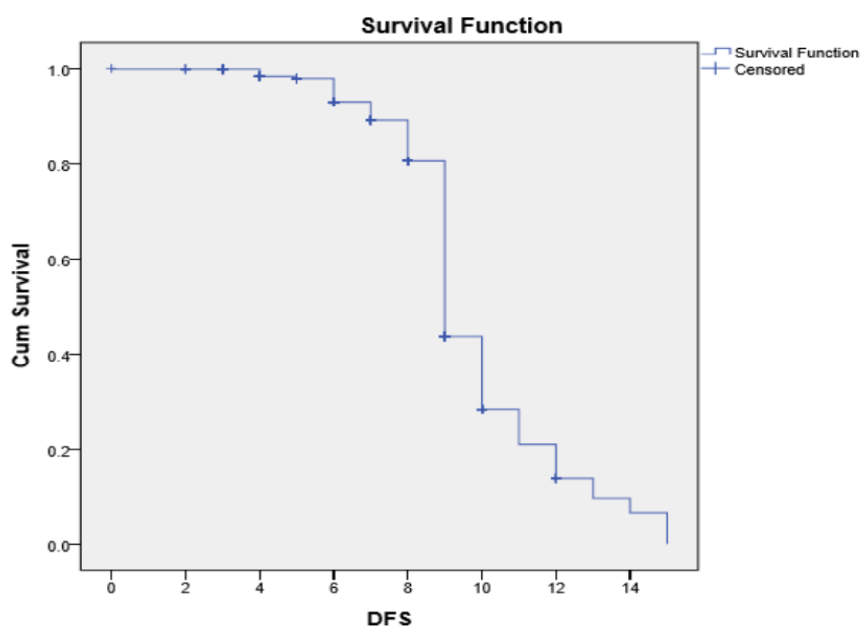
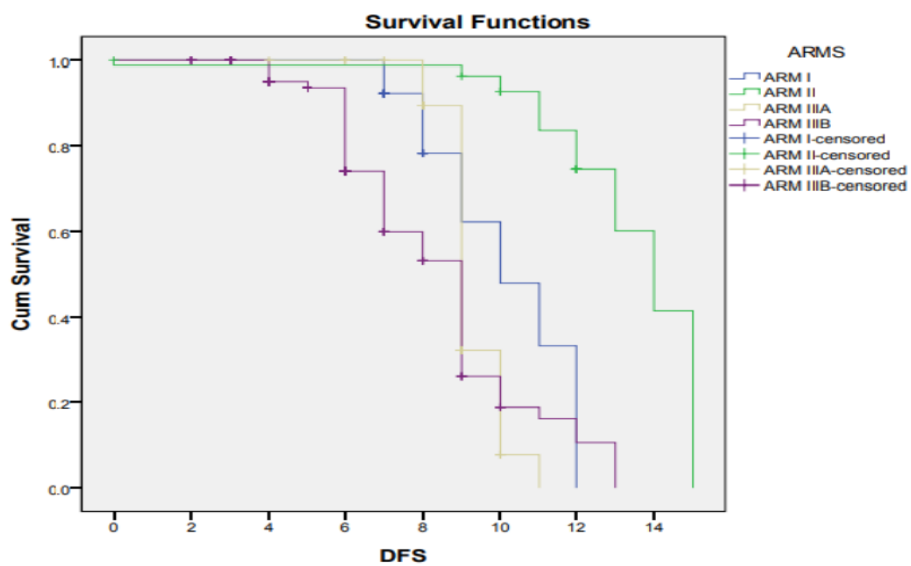
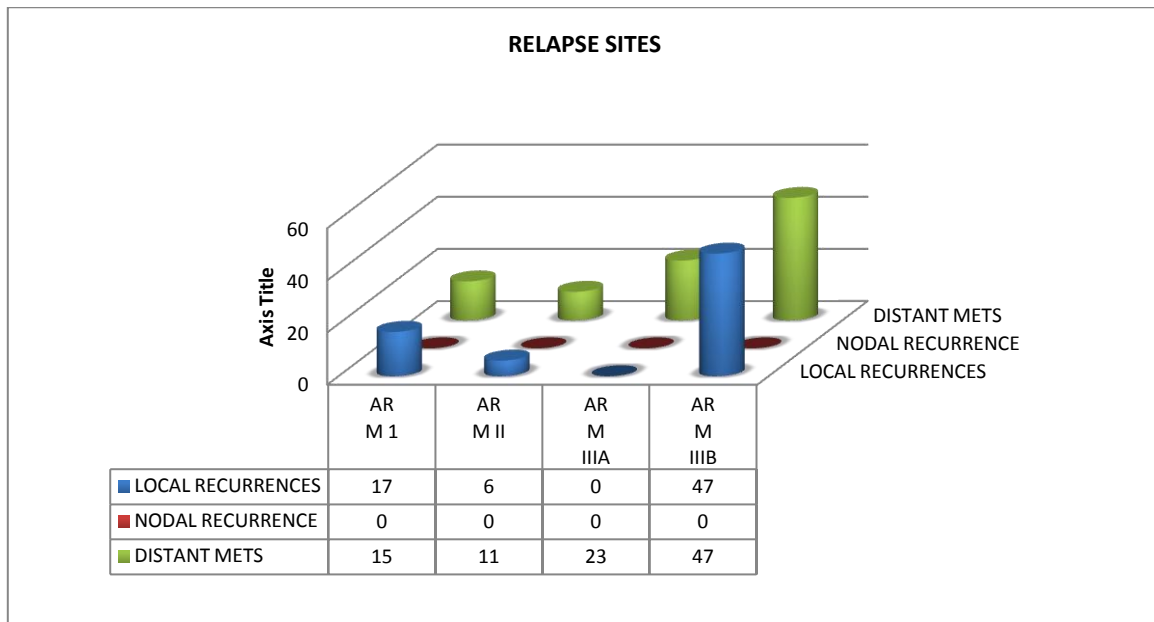
	LEFT BREAST	RIGHT BREAST
ARM I	43	49
ARM II	46	39
ARM IIIA	197	133
ARM IIIB	155	103

Local Recurrence

17 patients in arm I, 6 patients in arm II and 47 patients in arm IIIb had chest wall recurrence. Regional nodal recurrence was not seen in all the three arms. Distant metastases- 15 patients in arm I, 11 patients in arm II and 70 patients in arm III (23 patients in arm IIIa and 47 patients in arm IIIb) had distant metastases. Among the 15 patients in arm I, 1 patient had supraclavicular metastases, 9 were spine metastases and 1 clavicular metastases and 4 lung metastasis. In arm II 9 patients had spine metastases, 2 patients had brain metastasis. In arm III, 14 patients in arm IIIa and 21 patients in arm IIIb had spine metastases, 3 patients in arm IIIb had supraclavicular nodal metastases, 2 patient in arm IIIb had hip metastases and 4 patient in arm IIIA and 9 patient in arm IIIb had liver metastases and 5 in arm III A and 12 patient in arm III b had brain metastasis.

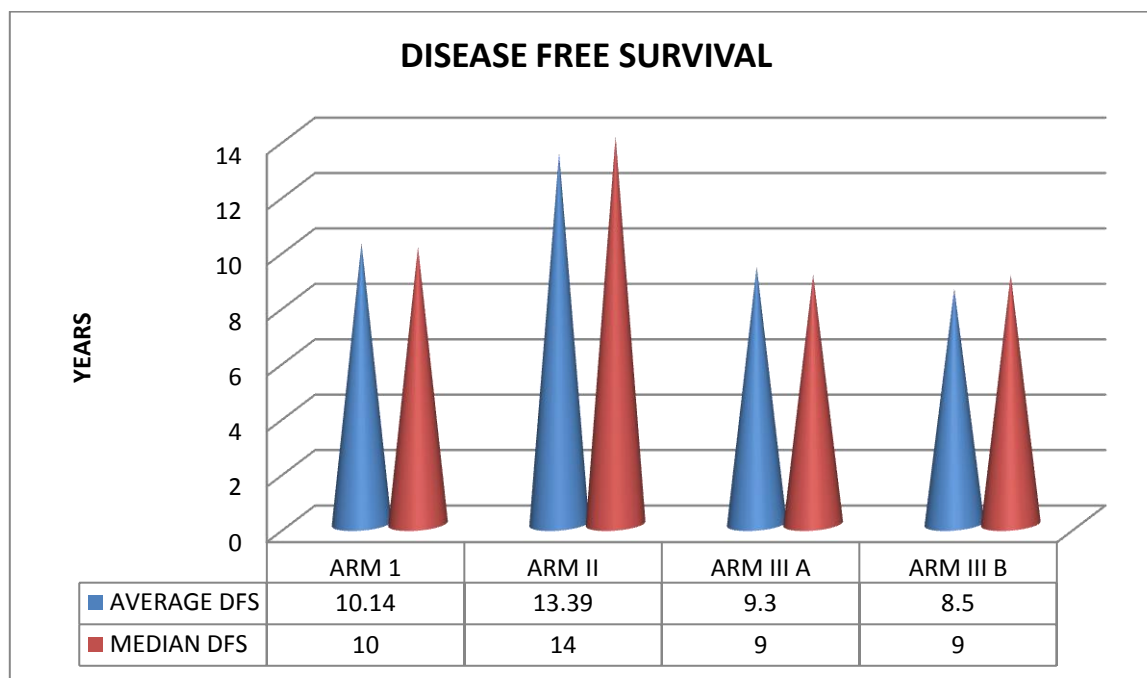
In ARM I local recurrence occurred as early as 1 year and distal metastases occurring at an average of 3 years for SCN, 5 year for spine metastases and 9 years for clavicular metastasis. Local recurrence occurred at 2 years or 3 years as compared to 1 year in arm I. Distant metastases was commonly to bone, especially to spine occurring at 4 and 5 years. Local recurrence was common in arm IIIb, occurring as early as 2 years. No local recurrence in arm IIIa.

Distant metastases were seen in 23 patients in arm IIIa and 47 patients in arm IIIb. In arm IIIa spine metastases were common occurring at 3 years and 5 years. Pelvic metastasis was seen in one patient at 4 yrs. New papillary carcinoma thyroid was reported in 1 patient after 2 years. In arm IIIb SCN metastases and spine metastases were common, spine metastases occurring earlier than SCN metastases. Liver metastases occurred in one patient at 6 years.



The Kaplan–Meier method was used for calculation and plotting of the LRFS and DMFS curves of the patient groups, and the log-rank test

was used for the comparison of the survival curves. The results were investigated using the Cox proportional hazards model



Disease Free Survival

DFS in arm I was at an average of 10.14 and median DFS was at 10, DFS in arm II was at an average of 13.39 and median DFS was at 14, in arm III A was at an average of 9.3 years and median DFS at 9 years, In arm IIIB was at an average of 8.5 years and median DFS at 9 years. In the whole study, ARM II was significant $p=0.541$ in comparison with ARM I and ARM III A and III B. When you compare ARM III A and III B, there is no significant difference $p<0.103$

Discussion

In our whole series T1-2N0M0 breast carcinoma patients who underwent modified radical mastectomy, all receiving adjuvant radiotherapy, DFS was significantly better in patients receiving RT compared with those not receiving RT when compared with ARM I and ARM II. Thus signifying some beneficial role in T1-2N0M0 [8,9,10]

three large cohort studies found that women with primary tumors ≤ 5 cm and only one to three involved axillary nodes (T1-2 N1) experienced

locoregional recurrence rates of only 6% to 13% after treatment with mastectomy and systemic chemotherapy. 7-10. For such patients, the potential mortality benefit from PMRT would be minimal. As a result, recent consensus statements from the National Institutes of Health, American Society of Clinical Oncology, and American Society for Therapeutic Radiology and Oncology have emphasized the need for further study of PMRT for T1-2 N1 breast cancer.

The Early Breast Cancer Trialists Collaborative Group Overview indicates that as a rule of thumb, every 4 local recurrences avoided by RT prevents 1 death 15 years after diagnosis. So all these studies provided an clue to role of radiotherapy in early breast cancer patients but it is still controversial. Our study aimed at disease free survival and the role of RT in early breast cancer patients was also studied. [11,12]

Our study mainly focused on T1/2N0M0 who received RT. These group of patients were found to have a median DFS of 14 years and a mean of 13.39 years with a C.I. of 12.9-13.8. Thus suggesting that RT has a significant role. Even with

complications associated with RT was a problem, but it was not such a major problem with patients who were under follow up and had preventive methods for the various complications^[13,14].

Our study was a single institution study in a prestigious institute, and most patients were on regular follow up. Patients were in general satisfied with the treatment especially the ones who were T1/2N0 M0 and received Radiotherapy with regular follow up and complications were being treated early. The timing of initiating pmrt do not seem to affect the overall survival as the p value between arm iii a and iiib were insignificant^[15,16] however further trials to know the exact cutoff time or completion time from surgery date to completion of pmrt date is needed to further define the timings.

References

1. Recht A1, Edge SB. Evidence-based indications for postmastectomy irradiation. *The Surgical Clinics of North America* 2003;Aug;83(4):995-101
2. Van de Steene J, Soete G, Strome G. Adjuvant radiotherapy for breast cancer significantly improves overall survival: the missing link. *Radiother Oncol.* 2000;55:23-73
3. EBCTCG Favourable and unfavourable effects on long term survival of radiotherapy for early breast cancer; an overview of the randomized trials. *Lancet.* 2000;355:757-70
4. Overgaard M, Hansen PS, Overgaard J, Rose C, Anderson M, Bach F, et al. Postoperative radiotherapy in high risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast cooperative 82b Trial. *N Engl J Med.* 1997;337:949-55
5. Whelan TJ, Julian J, Wright J, Jadad Ar, Levine ML. Does radiation therapy improve survival in breast cancer? A Meta-analysis. *J Clin Oncol.* 2000;18:1220-9
6. Tsoutsou PG, Belkacemi Y, Gligorov J, et al. Optimal Sequence of Implied Modalities in the Adjuvant Setting of Breast Cancer Treatment: An Update on Issues To Consider. *The Oncologist.* 2010;15(11):1169-1178. doi:10.1634/theoncologist.2010-0187.
7. Clinical impact of adjuvant radiation therapy delay after neoadjuvant chemotherapy in locally advanced breast cancer. Silva SB1, Pereira AAL1, Marta GN2, de Barros Lima KML1, de Freitas TB1, Matutino ARB1, de Azevedo Souza MCL1, de Azevedo RGMV1, de Viveiros PAH1, da Silva Lima JM1, Filassi JR3, de Andrade Carvalho H1, Piato JRM3, Mano MS4.
8. He Z-Y, Wu S-G, Zhou J, et al. Postmastectomy Radiotherapy Improves Disease-Free Survival of High Risk of Locoregional Recurrence Breast Cancer Patients with T1-2 and 1 to 3 Positive Nodes. *Camphausen K, ed. PLoS ONE.* 2015;10(3):e0119105. doi:10.1371/journal.pone.0119105.
9. van der Hage JA, Putter H, Bonnema J, Bartelink H, Therasse P, van de Velde CJ, et al. (2003) Impact of locoregional treatment on the early-stage breast cancer patients: a retrospective analysis. *Eur J Cancer* 39:2192-2199. pmid:14522378
10. Radiotherapy can decrease locoregional recurrence and increase survival in mastectomy patients with T1 to T2 breast cancer and one to three positive nodes with negative estrogen receptor and positive lymphovascular invasion status. Yang PS1, Chen CM, Liu MC, Jian JM, Horng CF, Liu MJ, Yu BL, Lee MY, Chi CW.
11. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, Gray R, Pan HC, et al. (2014) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer

- mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 383:2127–2135. pmid:24656685
12. Duraker N, Demir D, Bati B, Yilmaz BD, Bati Y, Çaynak ZC, et al.(2012) Survival benefit of post-mastectomy radiotherapy in breast carcinoma patients with T1–2 tumor and 1–3 axillary lymph node(s) metastasis. *Jpn J Clin Oncol* 42:601–608. pmid: 22511807
 13. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, Gray R, Pan HC, et al. (2014) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 383:2127–2135. pmid:24656685
 14. Smith BD, Smith GL, Haffty BG. Postmastectomy radiation and mortality in women with T1-2 node-positive breast cancer, *J Clin Oncol* , 2005, vol. 23 (pg. 1409-19)
 15. Impact of timeliness of adjuvant chemotherapy and radiotherapy on the outcomes of breast cancer; a pooled analysis of three clinical trials Omar Abdel-Rahman.
 16. Clinical impact of delaying initiation of radiotherapy in patients with breast cancer: stages 0, I and II, a retrospective observational study Raquel Cobos Campos¹, Antxon Apiñaniz Fernández de Larrinoa², Arantza Sáez de Lafuente Moriñigo¹, Naiara Parraza Diez¹, Felipe Aizpuru Barandiaran^{1,3,4}, Avelino Alia Ramos⁵, Aurora Lasso Varela