http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v11i7.04

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Prospective Study to Compare Outcomes Following Hypofractionated Radiotherapy versus Conventional Radiotherapy in Carcinoma Breast

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Abstract

Background: *Breast cancer is now the most common cancer worldwide (GLOBOCAN, 2020). It is the most common cancer among women in developed countries. The age standardized incidence rate of breast cancer in India is 25.8% per 100,000 women (GLOBOCAN, 2020). By 2020, breast cancer overtook cervical cancer as the most common type of cancer among all women in India. Breast irradiation has been shown to reduce the risk of local recurrence after breast-conserving surgery from about 30% to <10% at 10 years.*

Aims & Objectives: *Randomize Breast carcinoma into two arms - Arm A :- 39GY in 13 fractions over 2.3 weeks & Arm B:- 50 GY in 25 fractions over 5weeks. Compare locoregional response in two arms 4 weeks after completion of radiation therapy and at the end of six months of follow up. Compare acute and chronic toxicities in the two arms.*

Method: *Total 43 patients were included in the study, 21 belonged to ARM A and 22 belonged to ARM B, Patients were randomised to 50 Gy in 25 fractions over 5 weeks or to 39Gy in 13 fractions over 2.3 weeks. Randomisation was arranged via lottery system by opting chit from a box of multiple chits. Randomisation was blinded. Normal tissue effects in the breast, arm, and shoulder were assessed by RTOG criteria for skin reactions, patient self-reported assessments, and physician assessments.*
ARM A = (39Gy in 13 fractions over 2.3 weeks)
ARM B = (50 Gy in 25 fractions over 5 weeks)

Result: *At the end of radiotherapy all 43 patients (21 in Arm A and 22 in Arm B) were assessed for acute skin toxicity, in arm A, 09(42.86%) patients had grade I reaction, 11(52.38%) patients had grade II reaction,1(4.76%) patients had grade III reaction and no patients had grade IV reaction while in arm B 2(9.09%) patients had grade I reaction, 11(50%) patients had grade II reaction,7(31.82%) patients had grade III reaction and 2(9.09%) patients had grade IV reaction. Arm with 39 Gy have less no. of grade III&IV reactions 1(4.76%) as compared with 50 Gy arm 9(40.91%), which is statistically very significant (p-). At the time of analysis, 1(2.23%) patients had experienced a local-regional relapse in arm A as*

compared with arm B no patients had local-regional relapse, which is statistically not significant (p-). After median follow-up of 9.42 month rate of distant relapse was higher in the 39 Gy group 2(4.65%) in comparison to 50 Gy group 1(2.32%), which is statistically not significant (p-), which contributed to the higher rates of disease-free survival and overall survival in the 50 Gy group.

Conclusion: *After surgery for breast cancer, a radiotherapy schedule delivering 39 Gy in 13 fractions over 2.3 weeks seems to offer significantly less acute toxicity as well as cosmetic appearance which is statistically significant. But in terms of loco regional recurrence as well as distant recurrence 39 Gy schedule appears to be less effective especially in advanced stage, although data was statistically not significant.*

Keywords: *Breast Cancer, Adjuvent Radiotherapy, Hypo-fractionation Radiotherapy, Coventional Radiotherapy, Acute skin toxicity.*

1. Introduction

Breast cancer is now the most common cancer worldwide (GLOBOCAN, 2020). It is the most common cancer among women in developed countries. The age standardized incidence rate of breast cancer in India is 25.8% per 100,000 women (GLOBOCAN, 2020). As per the Indian Cancer registry, breast cancer is the leading cancer across all its Population Based Cancer Registries (PBCRs); 27.3% in Bangalore, 26.8% in Chennai and Delhi, 29.7% in Mumbai and 26.3% in Kolkata (PBCR 2009-2011), and in Hospital based registries (HBCRs) of Mumbai (30.3%), Thiruvanantapuram (28.5%) and Dibrugarh (14.8%).

The Indian Cancer registry derives its data mainly from the metropolitan cities of the country which register a more urban population. Selective reports from rural pockets of India (Mehrotra et al., 2008; Swaminathan et al., 2009; Manoharan et al., 2010; Nandi et al., 2013) had all reported cervix to be the leading cancer site in the country which was followed closely by the breast. The scenario soon changed as all the registries showed an increasing trend in the percentage of breast cancer cases to the total number of cancer cases registered over the years. Bangalore and Chennai have shown more than 3% change over the years while Delhi, Bhopal and Mumbai have shown changes between 1-2% (Takiar et al., 2008). By 2020, breast cancer overtook cervical cancer as the most common type of cancer among all women in India.

2. Materials and Methods

Histologically proven infiltrating carcinoma of breast with biopsy will be registered and will be randomized into two arms.

2.1 Pretreatment Evaluation

- The pretreatment evaluation in all patients will include:-
- Complete history, general physical examination, complete systemic examination.
- Body surface area(BSA)
- The assessment of general condition will be done by using Karnofsky Performance Status.[13]
- Haematological assessment will be done by complete haemogram including haemoglobin, total leukocyte count (TLC), differential leukocyte count (DLC) and platelet count.
- Biochemical assessment to assess the kidney and liver functions will be done by the estimation of blood urea, Serum creatinine, SGOT and SGPT levels.
- Radiological assessment including chest X-ray will be done in all patients and USG whole abdomen will be done in all patients.

2.2 Inclusion Criteria

Based on the above assessment the patients for the study will be selected depending on the following criteria-

1. Histologically proven cases of breast carcinoma,
2. Post mastectomy with clear tumour margins either already received

chemotherapy or planned for chemo after radiation.

3. Patients on hormone therapy are also included.
4. Complete haemogram with Hb>10gm/dL; TLC>4000/cmm, Platelet count >100,000/cmm.
5. Renal function tests with Blood urea < 40mg/dL and Serum creatinine<1.5mg/dL.
6. Liver function tests with SGOT < 35 IU/L and SGPT < 40 IU/L.
7. Patients who sign the informed consent and are ready to be on follow up as required.

2.3 Exclusion Criteria

The patients having any of the following conditions will be excluded from the study:

1. Prior radiation for the same disease.
2. Cases with distant metastasis.
3. Pregnant or lactating patient.
4. Associated medical condition such as renal disease, liver disease or heart disease.

2.4 Radiotherapy Technique-

- ✓ Supine position.
- ✓ Patients will undergo a pretreatment simulation to work out the field borders which will cover the primary tumor, disease extension and neck nodes.
- ✓ Planning target volume will be whole breast with 1cm margin to palpable breast tissue and supraclavicular node with axillary chain with 1cm margin.
- ✓ All fields will be treated every day.

2.5 Assessment During Treatment

All the patients included in the study will be carefully and regularly assessed weekly during treatment. Detailed clinical evaluation for the tolerance of each patient to the delivered treatment will be done by thorough local examination of the patient for local disease status along with observation of acute toxic side effects of radiation.

- ✓ Radiation reactions will be assessed by Radiation Therapy Oncology Group (RTOG) criteria and WHO toxicity criteria.[14]
- ✓ Radiation Therapy Oncology Group (RTOG) acute morbidity scoring criteria are relevant from day 1, the commencement of radiation, through day 90 and thereafter, the RTOG criteria for late effects are to be utilized.
- ✓ Treatment will be done by thorough local examination of the patient for local disease status along with observation of acute toxic side effects of radiation.

2.6 Assessment at the completion of treatment

- ✓ All the patients will be assessed four weeks after the completion of treatment, to detect acute complications like skin reaction.
- ✓ Acute treatment related toxicity will be graded using common terminology criteria for adverse events (RTOG) and late toxicity by RTOG criteria.

Follow Up

All the patients were followed up regularly on OPD basis for a period of at least 6months, once every month after completion of the treatment.

- ✓ At every visit, each patient was clinically evaluated for local control of disease and treatment related complications.
- ✓ The patients were assessed for any evidence of distant metastasis during each follow up.
- ✓ To evaluate the local disease control, local examination using inspection, palpation was done at each follow up and response was assessed.
- ✓ On the suspicion of any local recurrence, biopsy was taken for histopathology and correlated clinically.
- ✓ To evaluate the distant metastasis detailed history pertaining to any symptoms was taken and general physical examination of patients was done.
- ✓ In case of suspicion, relevant investigations was done to rule out the presence of distant metastasis.

The results of the study regarding safety, tolerability, toxicity and response in all the groups was documented

2.7 Statistical analysis

Survival analysis methods were used to compare rates of each endpoint between the fractionation schedules. Length of follow-up was calculated as time from last fraction of radiotherapy until time of first event or last follow-up assessment, whichever occurred first. Patients were still evaluable for late effect of RT local-regional relapse after distant relapse, but were censored at date of death. For the patient quality of life self-assessments of normal tissue effects an event was defined as the first occurrence of a moderate or marked symptom (graded "quite a bit" or "very much").

The chi square test was used to compare fractionation schedules. Crude hazard ratios (with 95% CIs) comparing fractionation schedules for each endpoint were obtained from Cox proportional hazards regression models. Since point estimates of differences in event rates can, by chance, be atypical of the overall pattern of differences between schedules, estimates of the absolute difference in 10 month event rates taking the whole range of observation times into account were obtained by applying the hazard ratios obtained from the Cox model to the Kaplan-Meier estimate of the rate in the 50 Gy control group. Both one-sided and two-sided 95% CIs were calculated for the absolute difference in local-regional relapse rates at 10month, since the upper limit is of greater clinical interest, in view of concern about a possible excess risk caused by hypofractionated schedules.

3. Results

Total 43 patients were included in the study, 21 belonged to ARM A (39Gy in 13 fractions over 2.3 weeks) and 22 belonged to ARM B (50 Gy in 25 fractions over 5 weeks). Figure-1

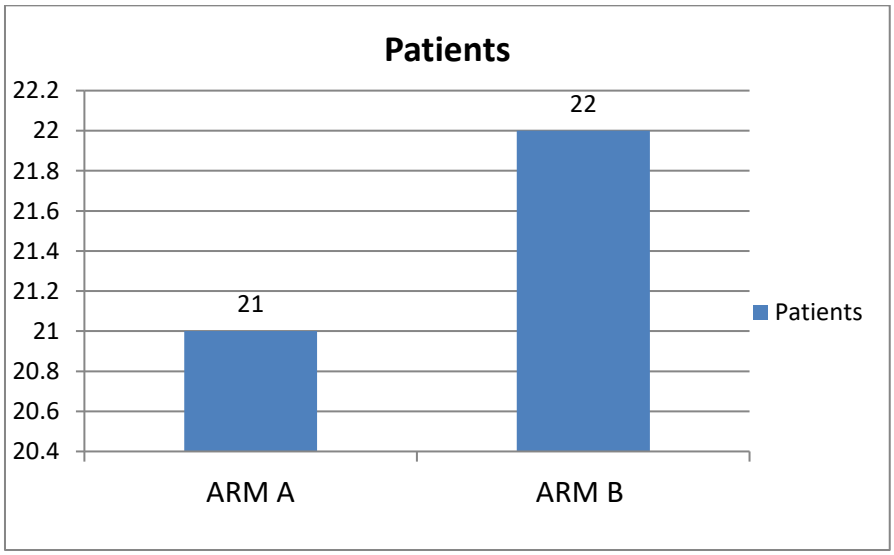


Figure 1 : Graph show the patient characteristics from Arm A and Arm B

In ARM A the youngest patient was of the age of 28 years and oldest was 66 years and in ARM B the youngest patient was of 25 years and oldest was 63 years. The average of age of patients in ARM A (39Gy in 13 fractions over 2.3 weeks) was 47.62 years and 44.36 in ARM B(50 Gy in 25 fractions over 5 weeks).

The peak incidence was seen in <50 years of age in both ARM A and B. Figure-2

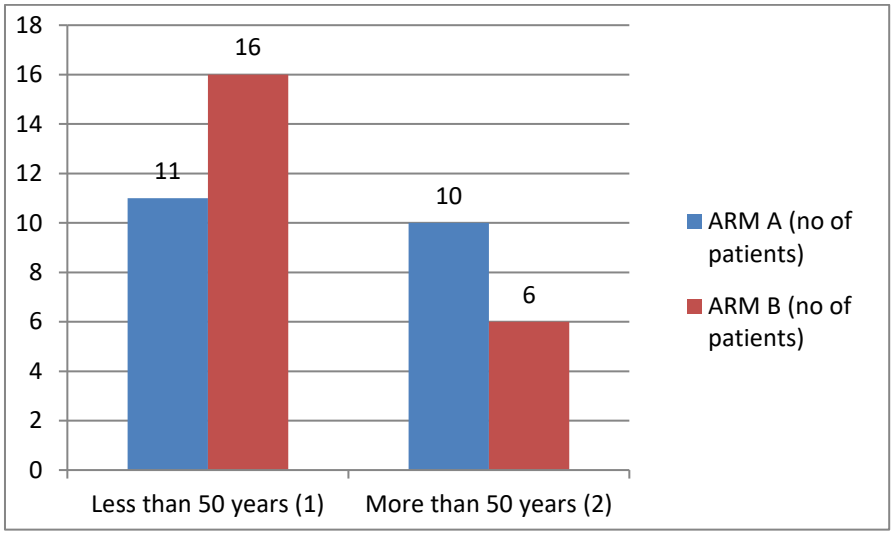


Figure 2 : Graph show the age from Arm A and Arm B patients

Out of the 43 cases 19 patients belong to rural background while 24 patients belonged to urban background. Rural: Urban ratio is 1:1.26 showing that the disease is relatively prevalent in urban surroundings. **Figure-3**

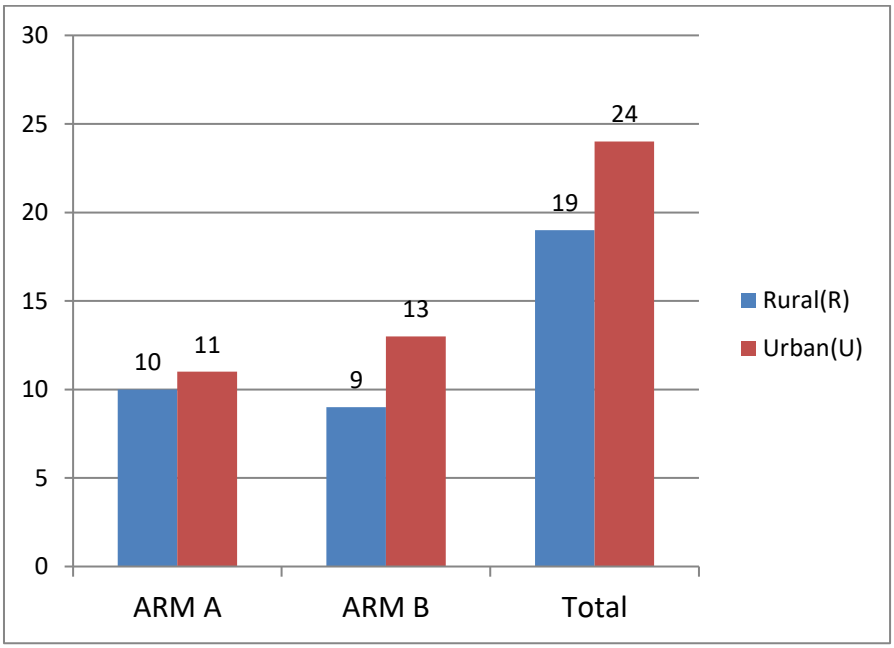


Figure 3 : graph show geographical distribution from Arm A and Arm B

Hormone Status

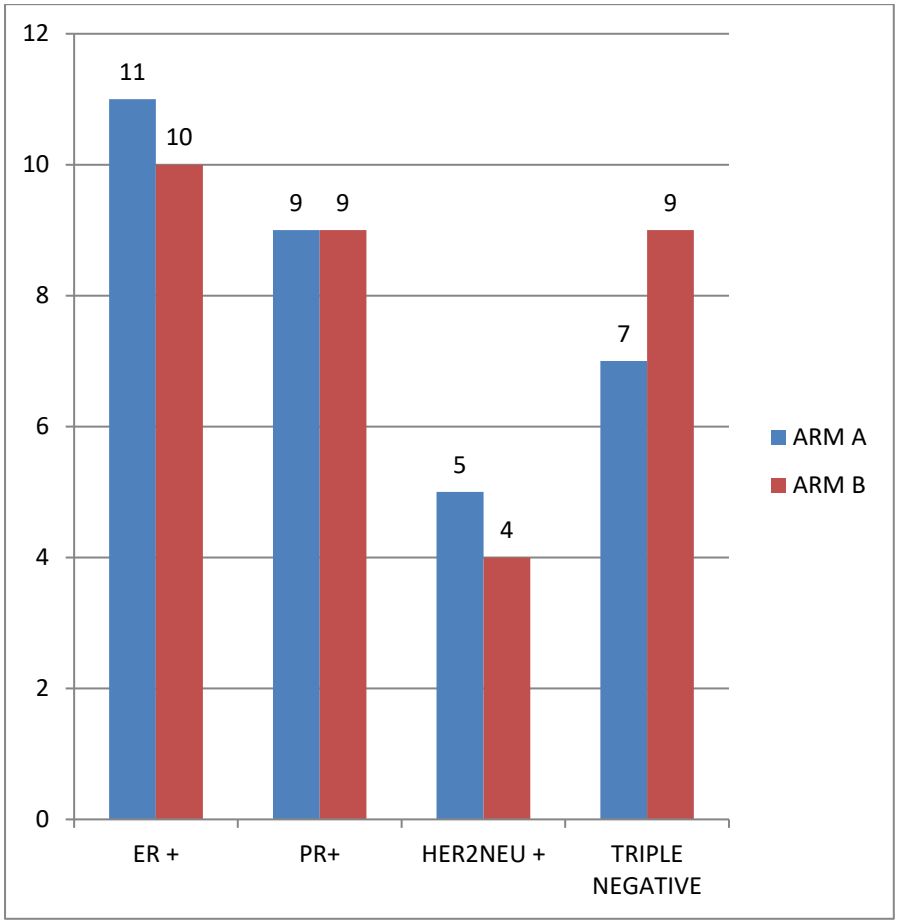


Figure 4 : Graph show hormone status from Arm A Arm B[5]4

The histopathological reports of the patients who were studies revealed that infiltrating duct carcinoma is the commonest histology – (79.07%) patients. **Figure-5**[6]

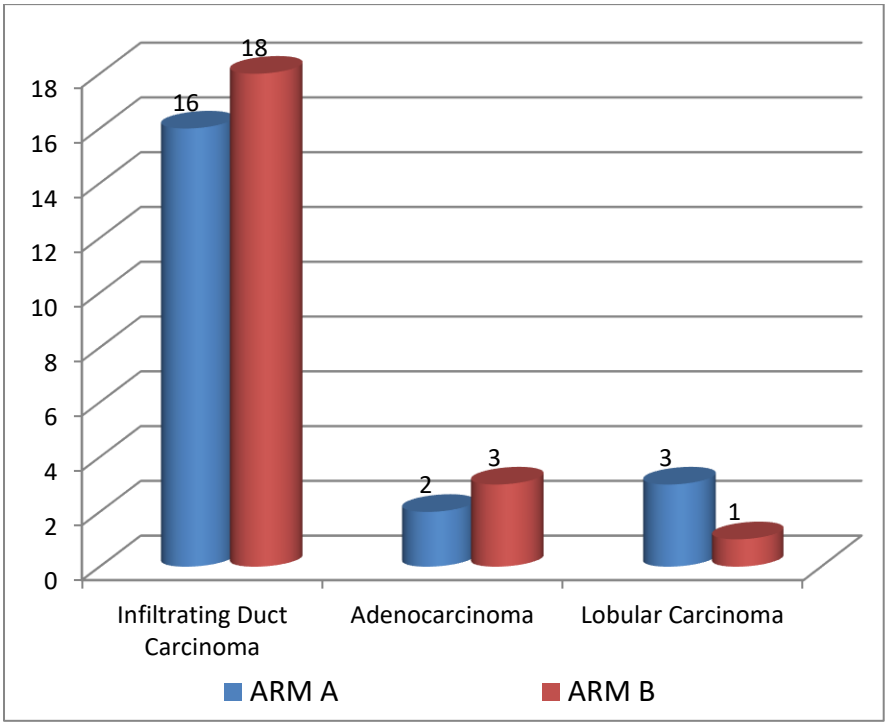


Figure 5 : Graph show the histopathology from Arm A and Arm B

Stage

Stage IV was in exclusion criteria. **Figure-6**

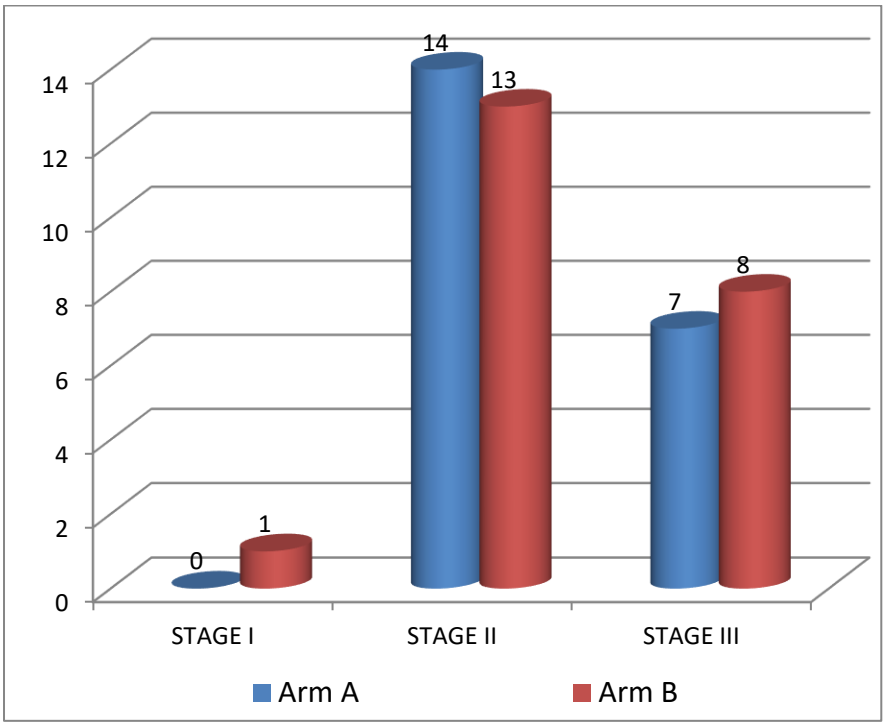


Figure - 6 : Graph show the stage from Arm A and Arm B[7]

Acute skin reaction at the end of radiation therapy Figure - 7

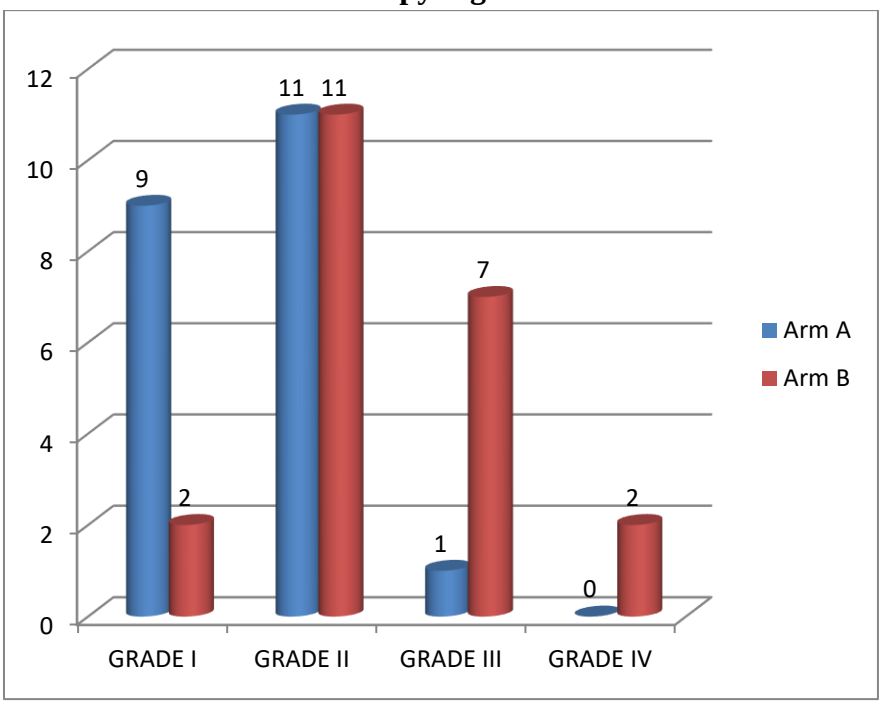


Figure - 7 Graph show skin reaction from Arm A and Arm B

ARM A

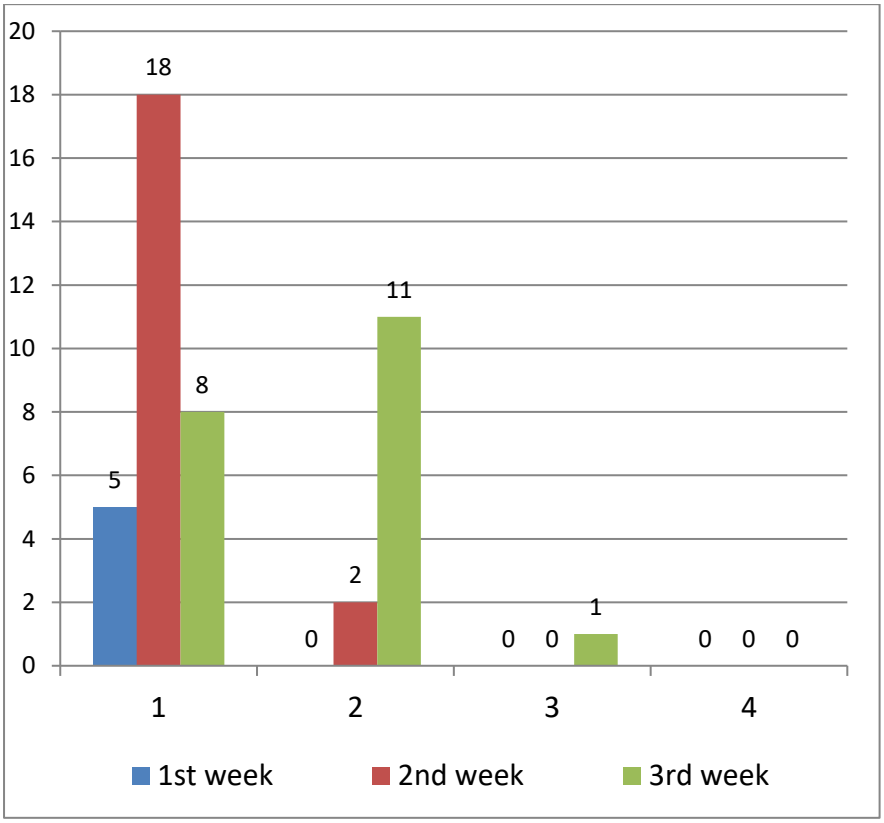


Figure - 8 : Graph show the week from Arm A

ARM – B

Tumor Response and Recurrence

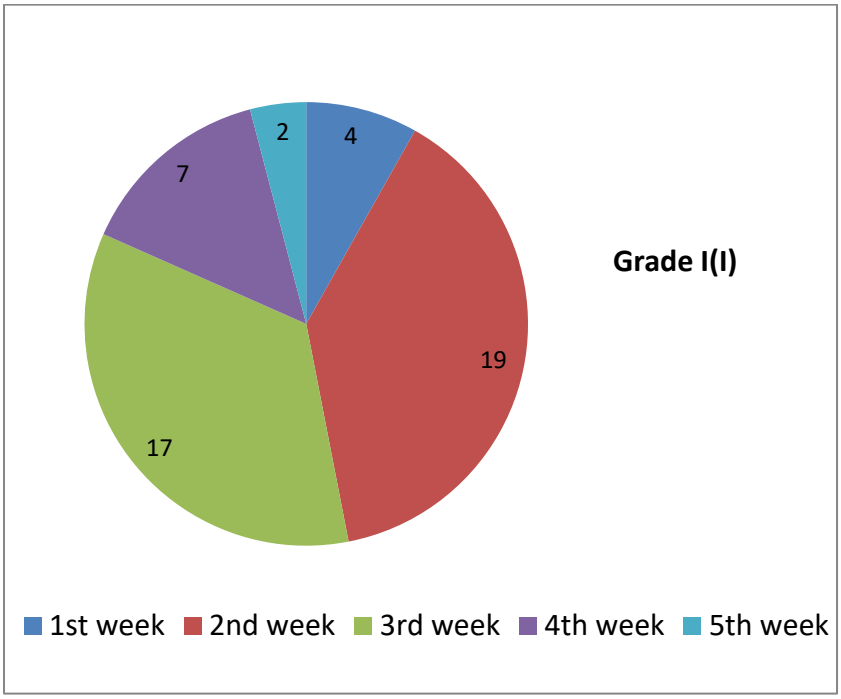


Figure- 9 : Graph show the week skin reaction from Arm B

Recurrence

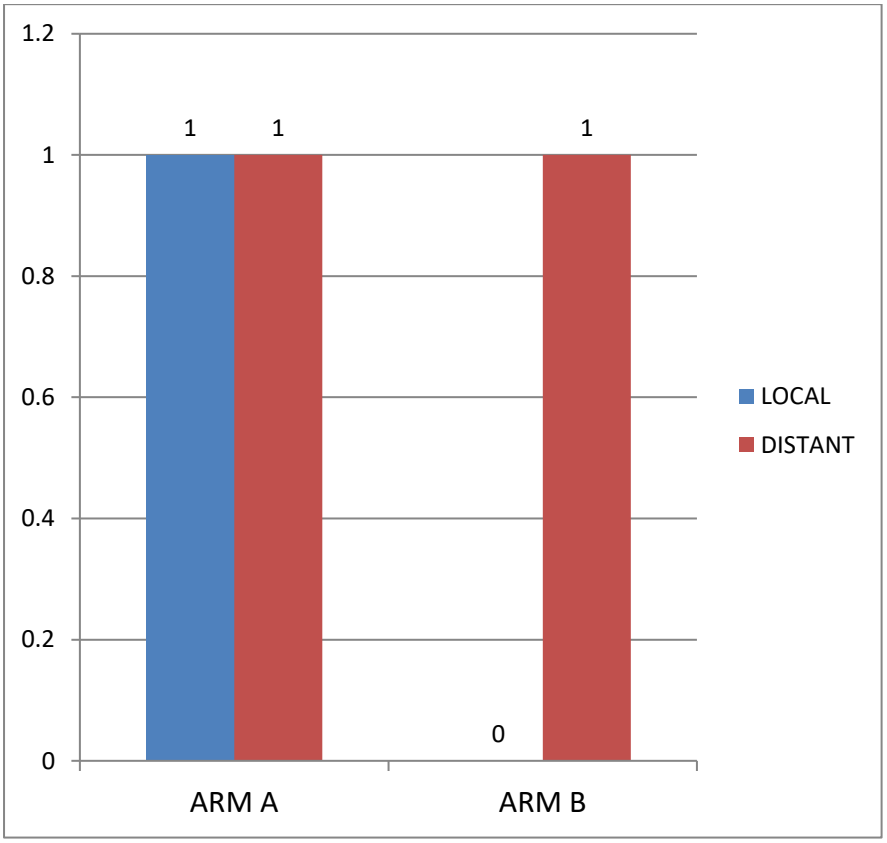
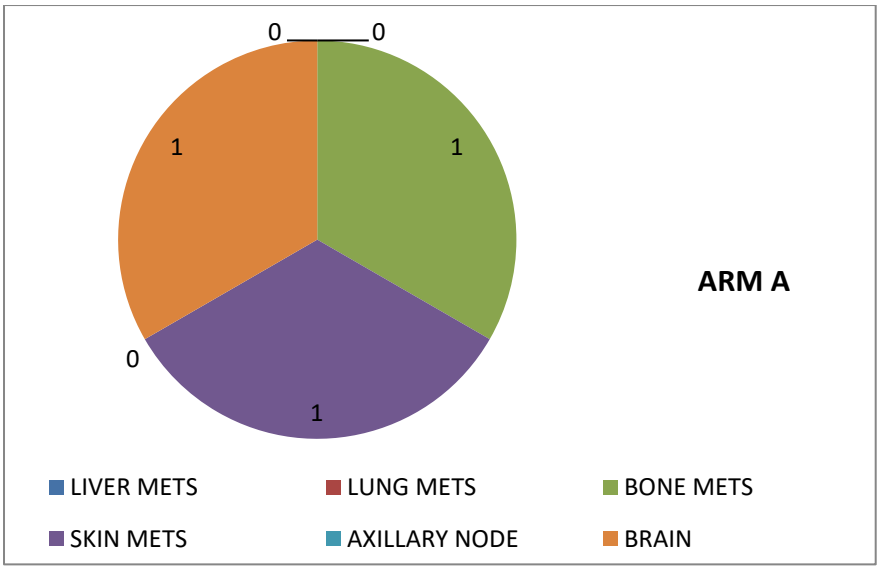


Figure – 10 : Graph show the recurrence from Arm B And Arm B

Tabmode of Failure



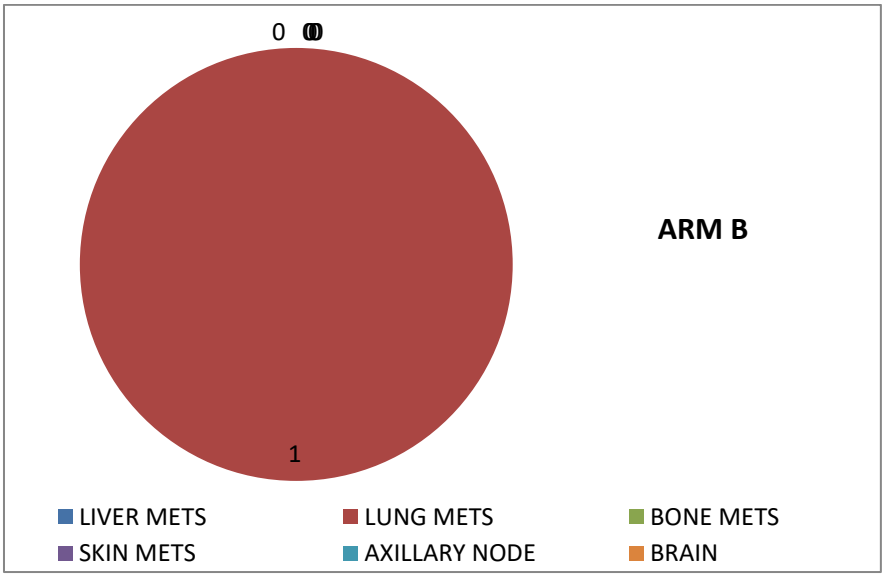


Figure – 11 : Graph show the mode of failure from Arm B and Arm B

Between oct. 2019, and nov. 2021,944 Ca breast patients were enrolled in study at J K cancer institute Kanpur. A total of 43 patients were enrolled in the study who were post MRM and received 6-8 cycles of anthracycline or taxane or both-containing regimen, which was balanced between randomised radiotherapy schedules. Cyclophosphamideand fluorouracil com- bination therapy was also prescribed in combination with anthracycline, which was similarly balanced between randomised groups.[11] Of women ER or PR positive, hormone therapy also prescribed either tamoxifen or letrozole.[15]

At the end of radiotherapy patients were assessed for acute skin toxicity with RTOG criteria in arm A, 09(42.86%) patients had grade I reaction, 11(52.38%) patients had grade II reaction, 1(4.76%) patients had grade III reaction and no patients had grade IV reaction while in arm B 2(9.09%) patients had grade I reaction, 11(50%) patients had grade II reaction,7(31.82%) patients had grade III reaction and 2(9.09%) patients had grade IV reaction. Arm with 39 Gy have lessno. of grade III&IV reactions 1(4.76%) as compared with 50 Gy arm 9(40.91%), which is statistically very significant (p-). 2 cases of 50 Gy group were severe grade IV skin reactions (extensive moist desquamation), one was an infected seroma in the scar area, and one had severe pain in the chest wall and ribs while in 39Gy group no patients hadgrade IV skin reaction.[12]

Median follow-up of patients was 9.42 months with a maximum follow-up of 24months and minimum follow up of 6 months. At the time of analysis all patients (100%) were alive and 39 (90.70%) were without relapse. Patients with relapse were 4(9.30%) of which 1(2.32%) with local-regional relapse and 3(6.70%) distant relapse.

At the time of analysis, 1(2.23%) patients had experienced a local-regional relapse in arm A as compared with arm B no patients had local-regional relapse, which is statistically not significant (p-). Which was higher in 39 Gy 13 fraction arm.

After median follow-up of 9.42 month rate of distant relapse was higher in the 39Gy group 2(4.65%) in comparison to 50 Gy group 1(2.32%),[9] which is statistically not significant (p-), which contributed to the higher rates of disease-free survival and overall survival in the 50 Gy group.

The incidence of ischemic heart disease, symptomatic rib fracture, brachial plexopathy and symptomatic lung fibrosis was not reported during follow-up in both the arms, and long term follow-up is required to comment on these late toxicities.

There were no patients with contralateral breast cancer reported in follow up period.

Limitation of study

A median follow-up of 9.42 month is too short to allow assessment of all the potential late normal tissue effects such as cardiac damage.

4. Conclusion

After surgery for breast cancer, a radiotherapy schedule delivering 39 Gy in 13 fractions over 2.3 weeks seems to offer significantly less acute toxicity as well as cosmetic appearance which is statistically significant.[8]

But in terms of loco regional recurrence as well as distant recurrence 39 Gy schedule appears to be less effective especially in advanced stage, although data was statistically not significant.

- A long term follow up on the patients of this study will analyse the exact figure of loco regional relapse as well as distant relapse.

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