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Clinical, Radiological and Pathological Evaluation of Residual Disease in Patients Receiving Neoadjuvant Chemotherapy for Locally Advanced Carcinoma Breast

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Abstract: ***Carcinoma breast is the commonest malignancy among women globally. Epidemiological studies have shown that the global burden of breast cancer is expected to cross 2 million by the year 2030. In India, from being fourth in the list of most common cancers during the 1990s, it has now become the first.Locally advanced breast cancer (LABC) defined as bulky primary tumor with T3, T4 tumorand N2/N3 disease. Neoadjuvant chemotherapy is the first-line treatment to downgrade these tumors. The response can be assessed by various methods like clinical examination and by means of various radiological techniques. The objective of this study is to determine the residual disease among locally advanced carcinoma breast after neoadjuvant chemotherapy, clinically, radiologically and pathologically***

Keywords: Locally Advanced Breast Cancer, Neoadjuvant Chemotherapy, Residual Disease, LABC

1. Introduction

Breast cancer is the most prevalent cancer among women around the world. With a projected 2.3 million new cases per year, or 11.7% of all cancer cases, it will now surpass lung cancer as the most common cancer worldwide in 2020. The World Health Organization (WHO) estimates that Asia has 44% of the world's Breast cancer deaths with 39% of overall new breast cancer cases diagnosed.

Approximately 25% of the female cancer cases in India are breast cancer. The rate of incidence was found to be 25.8 in 100,000 women and the mortality rate is 12.7 per 100,000 women (2017). Delhi had the highest rate of occurrence, it was discovered (41 per 100,000 women).

In Kerala, Thiruvananthapuram district had the greatest rate of occurrence, according to research (33.7 per 100,000 women). India has the lowest 5-year survival rates of any of the countries included in their study, according to the most recent surveillance trends from 2000 to 2014 based on registries from 71 countries. [(1)]

Locally advanced carcinoma breast (LABC) represents a highly diverse group, in terms of clinical, biological and pathological parameters. locally advanced and non-metastatic tumorsinvolve the tumors with a diameter more than 5 cm, large lymph node involvement (N2 or N3), direct involvement of the skin or chest wall, and inflammatory carcinoma

The therapeutic approach of LABC Currently is multidisciplinary, consisting of neoadjuvant chemotherapy (NACT), surgery, radiotherapy and adjuvant chemotherapy. In the past, it was primarily surgery, followed by chemotherapy.

After preoperative treatment, determining the surgical course of action requires an evaluation of the residual tumor size. The established clinical standard for determining tumor size prior to and following neoadjuvant treatment is the physical examination (PE). The most accurate measurement of the size of the residual tumor following treatment is made through pathologic investigation. The evaluation of the tumor response to neoadjuvant therapy also uses other clinical methods, such as mammography (MG) and magnetic resonance imaging (MRI).

It is important to examine the relative accuracy of these evaluation methods because they are cornerstones of contemporary clinical practice that directs treatment. The results of earlier investigations were diverse. Another crucial assessment that affects the decision about axillary care is the clinical examination of the axilla. Mammogram and MRI are not used to evaluate clinical lymph nodes; instead, a physical examination is the standard method. Fluorodeoxyglucose (FDG)-PET has recently come to light as a promising imaging technique for the clinical assessment of lymph node metastases. In order to accurately stage primarybreast cancer and axillary lymph nodes in patients receiving neoadjuvant chemotherapy, physical examination and mammography are the methods that are now available. The aim of this study is to evaluate these tools prospectively.

2. Aim and Objectives

Aim: To evaluate the residual disease in LABC after neoadjuvant chemotherapy clinically, radiologically and comparing with the tumour size pathologically.

Objectives:

1) To assess locally advanced carcinoma breast, clinically and radiologically among the patients attending at general surgery OPD of Amala institute of medical sciences.
2) To determine the residual disease among locally advanced carcinoma breast after neoadjuvant chemotherapy, clinically, radiologically and pathologically

3. Materials and methods

Study was carried out among the patients presented with LABC, to general surgery Department of a tertiary centre in Kerala. After undergoing neoadjuvant chemotherapy, the residual disease was assessed, clinically and radiologically by means of mammogram. They were categorized to complete response, partial response, stable disease and progressive disease, according to RECIST criteria. After surgical treatment (MRM), the residual disease was assessed pathologically.

Inclusion Criteria:

- Patients with locally advanced breast cancer
- who are undergoing NACT
- patient compliance

Exclusion Criteria:

- Patients who are failed to ensure follow up
- Metastatic disease
- Bilateral disease

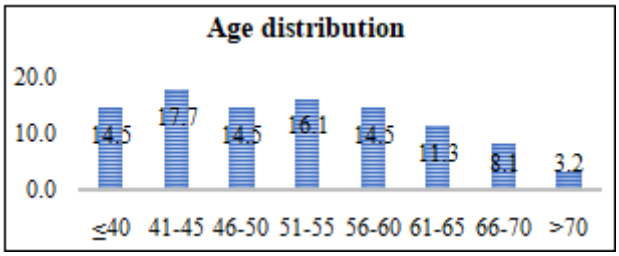
Best response	WHO change in sum of products	RECIST change in sum longest diameter
Complete response	Disappearance of all target lesions without any residual lesion; confirmed at 4 weeks	Disappearance of all target lesions; confirmed at 4 weeks
Partial response	50% or more decrease in target lesions, without a 25% increase in any one target lesion; confirmed at 4 weeks	At least 30% reduction in the sum of longest diameter of target lesions, taking as reference baseline study; confirmed at 4 weeks
Stable disease	Neither PR or PD criteria are met	Neither PR or PD criteria are met, taking as reference smallest sum of longest diameter recorded since treatment started
Progressive disease (PD)	25% or more increase in size of measurable lesion or appearance of new lesions	At least 20% increase in sum of longest diameter of target lesions, taking as reference smallest sum longest diameter recorded since treatment stared or appearance of new lesions

4. Results and Discussion

The response after Neoadjuvant chemotherapy was assessed using RECIST criteria, and by analysis there is significant reduction in the size of the tumor, assessed by clinical examination and mammogram with a P value of 0.0001, and the sensitivity of mammogram (68.6%) in assessing the residual tumor found to be higher than the clinical examination (64.7%), it was relatable with the previous studies

1) Age Distribution

Age group	Frequency	Percentage
≤40	9	14.5
41-45	11	17.7
46-50	9	14.5
51-55	10	16.1
56-60	9	14.5
61-65	7	11.3
66-70	5	8.1
>70	2	3.2
Total	62	100.0



The total number of subjects included in the study is 62. All have fulfilled the inclusion criteria

Mean age of the subjects: 51.87±10.33

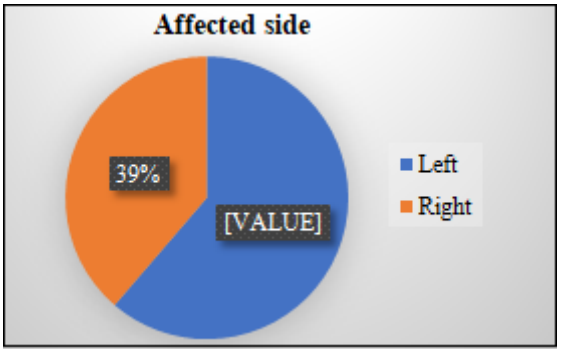
Minimum: 31 and Maximum: 76

The maximum number of patients were in the age group of 41- 45 years of age

Breast lump parameters

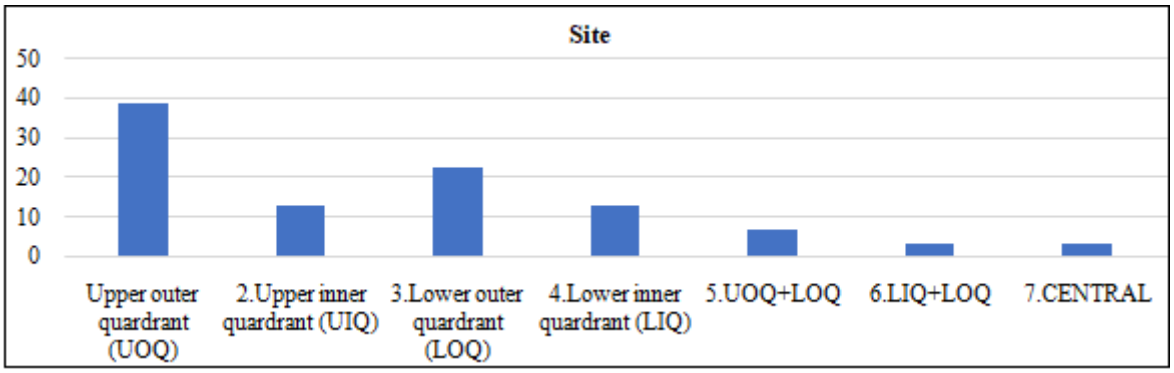
1) Side

Carcinoma breast was common on left side in the studied population



Quadrant	Frequency	Percentage
1.Upper outer quadrant (UOQ)	24	38.7
2.Upper inner quadrant (UIQ)	8	12.9
3.Lower outer quadrant (LOQ)	14	22.6
4.Lower inner quadrant (LIQ)	8	12.9
5.UOQ+LOQ	4	6.5
6.LIQ+LOQ	2	3.2
7.Central	2	3.2
Total	62	100.0

2) Site



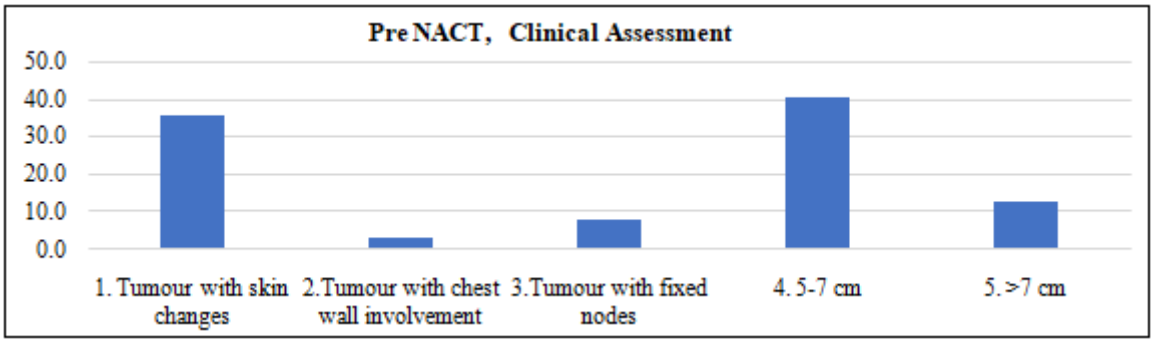
Side	Frequency	Percentage
Left	38	61.3
Right	24	38.7
Total	62	100.0

Carcinoma breast was common in the upper outer quadrant (38.7%)

3) Pre NACT clinical assessment:

Parameters	Frequency	Percentage
5-7 cm	25	40.3
>7 cm	8	12.9
Tumour with skin changes	22	35.5
Tumour with chest wall involvement	2	3.2
Tumour with fixed axillary nodes	5	8.1
Total	62	100.0

Pre TNM Staging	Frequency	Percentage
T2N2	5	8.1
T3N1	**18**	**29.0**
T3N2	8	12.9
T3N3	3	4.8
T4AN1	2	3.2
T4BN1	16	25.8
T4BN2	10	16.1
Total	62	100.0

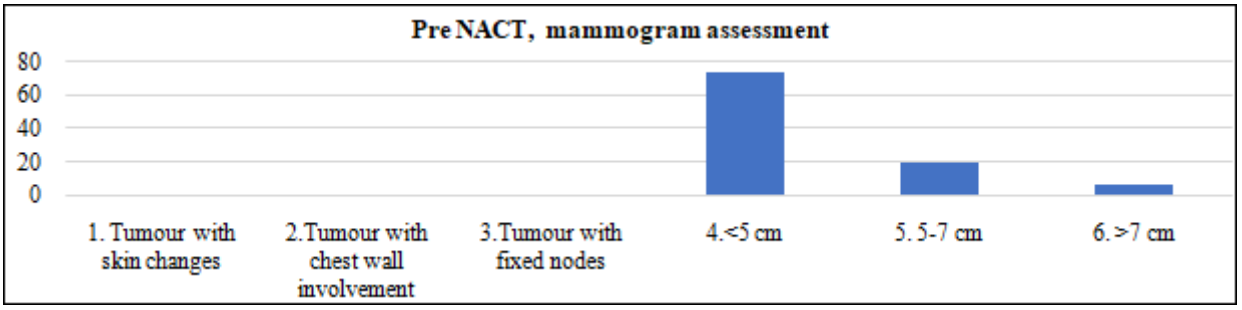


Before giving NACT the size of most of carcinoma breast belonged to 5- 7 cm clinically

4) Pre chemo mammogram assessment:

parameters	Frequency	Percentage
1. Tumour with skin changes	0	0
2.Tumour with chest wall involvement	0	0
3.Tumour with fixed nodes	0	0
4. <5 cm	46	74.2

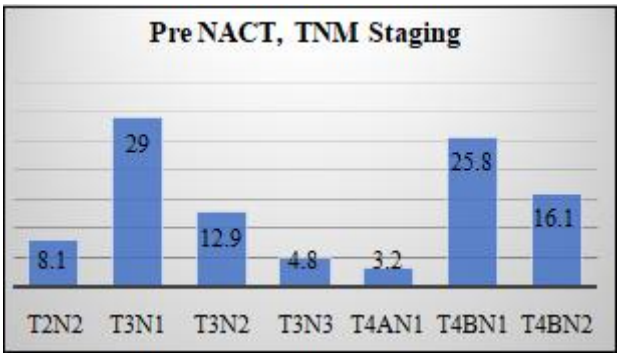
5. 5-7 cm	12	19.4
6. >7 cm	4	6.5
Total	62	100.0



Before giving NACT, on mammogram assessment major number of patients belonged to Tumour with skin changes of locally advanced carcinoma breast

5) Pre NACT staging:

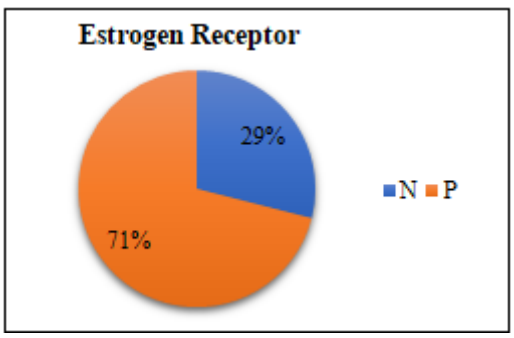
HER2NEU	Frequency	Percentage
Negative	**44**	**71.1**
Positive	22	35.5
Total	62	100.0



Before giving Neo adjuvant chemotherapy, highest number of cases of locally advanced carcinomabreast belonged to T3N1Stage

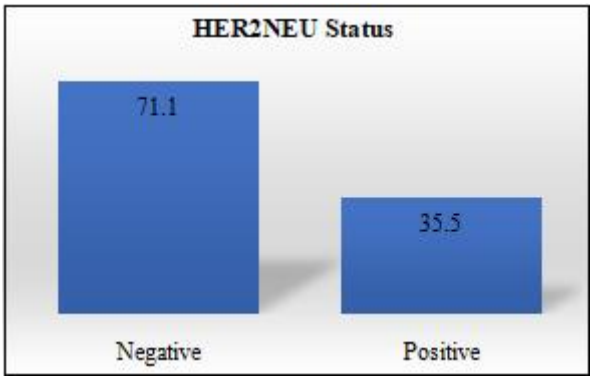
6) Estrogen receptor status:

ER	Frequency	Percentage
Negative	18	29.0
Positive	**44**	**71**
Total	62	100.0



Estrogen receptor for carcinoma breast was shown positive among 71%

7) HER 2 Neu status



HER2NEU receptor for carcinoma breast was shown negative among 71.1%

8) Progesterone receptor status:

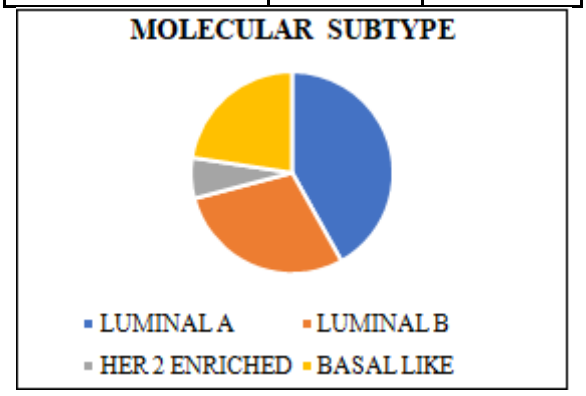
PR	Frequency	Percentage
N	23	37.1
P	**39**	**62.9**
Total	62	100.0

Progesterone receptor for carcinoma breast was shown positive among 62.9%

9) Molecular type

Molecular subtype	Frequency	Percentage
LUMINAL A	**26**	**41.9**
LUMINAL B	18	29
HER 2 ENRICHED	4	6.5
BASAL LIKE	14	22.6

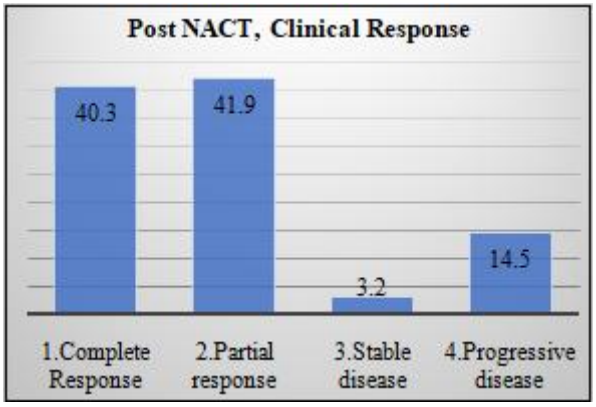
Total	62	100



Among Molecular subtypes of carcinoma breast -Luminal A was predominant -41.9%

10) Post NACT, clinical Response:

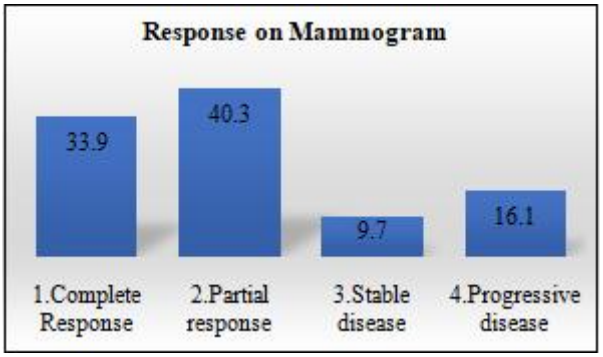
Clinical Response	Frequency	Percentage
1.Complete Response	25	40.3
2.Partial response	**26**	**41.9**
3.Stable disease	2	3.2
4.Progressive disease	9	14.5
Total	62	100.0



After administering chemotherapy, the clinical response was mainly Partial response-41.9%

11) Post-NACT Response on Mammogram

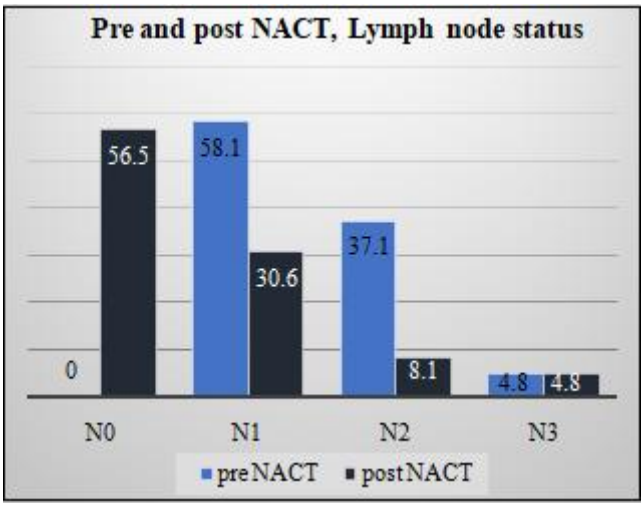
Response on mammogram	Frequency	Percentage
1.Complete Response	21	33.9
2.Partial response	25	40.3
3.Stable disease	6	9.7
4.Progressive disease	10	16.1
Total	62	100.0



After administering chemotherapy, the Response on Mammogram was mainly Partial response-40.3%

12) Axillary lymph node Assessment

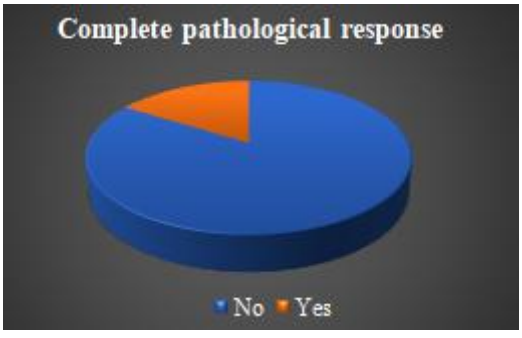
Prechemotherapy			Post chemotherapy		
Nodal status	Frequency	Percentage	Nodal status	Frequency	Percentage
N0	-	-	N0	56.5	56.5
N1	36	58.1	N1	30.6	30.6
N2	23	37.1	N2	8.1	8.1
N3	3	4.8	N3	4.8	4.8
Total	62	100.0	Total	62	100.0



56.5 % of the patients became, pathological N0, after NACT

13) Post-Chemotherapy pathological Response :

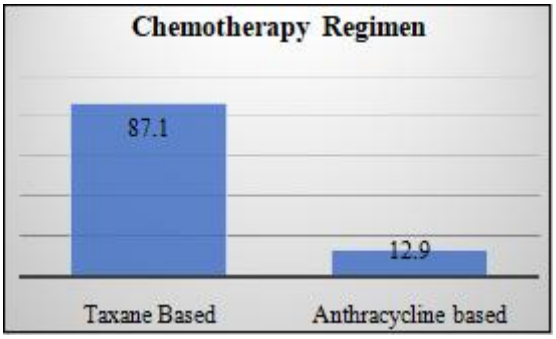
Complete pathological response	Frequency	Percentage
No	52	83.9
Yes	10	16.1



Only 16.1% had complete pathological response, among 62 participants

14) Chemotherapy Regimen

Chemotherapy Regimen	Frequency	Percentage
Taxane based Regimen	54	87.1
Anthracycline based Regimen	8	12.9
Total	62	100



87.1% received Taxane based chemotherapy (ACD, ACP) while 12.9% received Anthracycline based regimen (FEC, FAC)

5. Discussion

Evaluation of tumor prior and after NACT

	N	Mean	Std. Deviation	P value (student t test)
Clinical - Maximum diameter (Before NACT)	40	6.545	2.2889	0.0001
Clinical - Maximum diameter (After NACT)	40	3.535	3.2927	
Size of the tumor by mammogram(Before NACT)	62	4.008	1.7955	0.0001
Size of the tumor by mammogram(After NACT)	62	2.558	2.4771	

The mean value of maximum diameter of the tumor assessed clinically before NACT, was found to be 6.5 with standard deviation of (+/- 2.28), and which when assessed post NACT, was found to be 3.5 with standard deviation (+/- 3.2), which clearly demonstrate a clinically significant reduction in the tumor size with NACT, and the test was significant with a P value of 0.0001.

The mean value of maximum diameter of tumor assessed with mammogram, prior to NACT was found to be 4.0 with standard deviation of (+/- 1.7), and the same when assessed post NACT was found to be 2.55 with standard deviation of (+/- 2.47), which clearly demonstrated a significant reduction in the tumor size, post NACT, detected with mammogram. The test was significant with P value of 0.0001.

The Data, obtained by the clinical and mammogram evaluation, after NACT was tabulated according to the measurement of maximum diameter of the tumour, and showed, 49 participants (79 %) of the patients have max diameter of the residual tumor <5 cms,

Size (cm)	Clinical examination Post-chemotherapy (Number of cases)	Mammographic Examination Post-chemotherapy (Number of cases)	Pathological Examination Post-chemotherapy (Number of cases)
≤2 cm	33 (53.2%)	31 (50%)	36 (58.1%)
2-5 cm	16 (25.8%)	23 (37.1%)	18 (29%)
5-8cm	10 (16.1%)	5 (8.1%)	6 (9.7%)
>8 cm	3 (4.8%)	3 (4.8%)	2 (3.8%)
Total	62 (100%)	62 (100%)	62 (100%)

The Data, obtained by the clinical and mammogram evaluation, after NACT was tabulated according to the measurement of maximum diameter of the tumour, and showed, 49 participants (79 %) of the patients have max diameter of the residual tumor <5 cms,

By mammogram evaluation, 54 participants (87%) had the maximum diameter of residual tumor <5 cms, Post MRM, pathological evaluation, also showed the same number of participants ie, 54 (87%) had the maximum diameter of residual tumor <5 cm.

The mean size of residual tumor was 8% underestimated by clinical evaluation, but it was statistically insignificant with p value <0.05And the Mammogram assessment Gives Comparable Mean value with Post NACT pathological response for maximum diameter of the residual tumor.

By the data analysis, shows that, 40.3% of the patients had a clinical complete response, Whereas the complete response obtained by mammogram was 33.9 %, these parameters were then correlated with post MRM, pathological complete responders.

The pathological complete response cPR, was obtained in 16.1% of the total study subjects.

The clinical assessment of the residual disease over estimated the complete response, by about 24.2 %, and the sensitivity of clinical examination in finding the residual disease was found to be 64.7 %, with a specificity of 30.1 %

The mammogram assessment of the residual disease over estimated the complete response by 17.8%, and the sensitivity of mammogram in detecting the residual disease is 68.6 %. And the specificity of mammogram is 28%.

Pearson correlation test was used to assess the significance, Correlation coefficient between post NACT, clinical assessment and post NACT pathological assessment is 0.836, with P value <0.01

Correlation coefficient between Post NACT mammogram assessment and Post NACT pathological assessment is 0.933 with P value <0.01

Both the clinical and mammogram assessment, over estimated the complete response, Hence both the methods are not much reliable in assessing the residual disease,Inaccurate measurement of the residual disease by clinical and mammogram assessment can be due the challenge in differentiating residual tumor from chemotherapy-induced fibrosis, biopsy-site changes, and tumor necrosis.

Nevertheless, a mammography assessment can detect residual illness with greater sensitivity.

6. Conclusion

Proper response assessment to neoadjuvant chemotherapy is required for better prognosis of Locally advanced carcinoma breast, Even though the sensitivity of mammogram (68%), in assessing the residual tumor was higher as compared to clinical examination, its low specificity (28%) necessitates for a better evaluation method in detecting residual disease.

7. Limitations

- The Mammogram reporting can vary according to the radiologists
- Physical examination is often considered unsatisfactory for assessment of response, because the palpation of fibrotic and necrotic mass may mimic residual tumor mass.
- The changes in LABC such as skin / chest wall involvement, and fixed axillary lymph nodes are findings which can be detected by clinical examination, and may not be detected with mammogram.

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