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COMPARISON OF RESPONSE ASSESSMENT TO NEO-ADJUVANT CHEMOTHERAPY IN LARGE OPERABLE AND LOCALLY ADVANCED BREAST CANCER BY CLINICAL METHODS, MAMMOGRAPHY AND ULTRASONOGRAPHY

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ABSTRACTS

Breast Cancer is the most common female cancer in the world. It is leading cause of Cancer mortality among woman aged 20-59 years.The aim of screening of breast cancer is to identify preinvasive disease or invasive disease before dissemination.In our study twenty patients of histologically proved and locally advanced breast cancer were evaluated for response to Neo-Adjuvant chemotherapy were assessed by clinical methods. Mammography and USG after 2nd and 4th cycle of chemotherapy and results were compared. Again post operative histopathological examinations of the specimens were compared to the results of clinical methods, mammography and USG. It is seen that triple assessment is better than any single modality of response assessment. In our study, the response to neoadjuvant chemotherapy was assessed by mammographic response in 17 cases and by ultrasonography in 16 cases. Mammography response was seen 82% cases (15).

KEYWORDS: Neo-adjuvant Chemotherapy, Clinical Method, Mammography, Ultrasonography.

INTRODUCTION

Breast cancer is the commonest malignancy of females in the world and the second most common cancer of females in India.[1]

Though majority of patients present in early breast cancer in western countries due to increased awareness and screening programmes, but most of the patients in our country still present with either locally advanced or metastatic breast cancer.

Most of these patients are treated by mastectomy. Hospital based experimental study from April 2004-to June 2006 in North Bengal Medical College & Kolkata Medical College & its follows up upto July 2018.

Twenty female patients of histologically proved breast cancer with T3 & T4 lesions, aged below 65 years were included in this study. Staging done by clinical examination, x-ray chest, skeletal survey, baseline mammogram & ultrasonography of breasts and abdomen.

Response to NACT were assessed clinically, USG & mammopgraphy after 2^{nd} cycle of chemotherapy. In case of good response to NACT, reassessment again done after 4^{th} cycle NACT as breast cancer is systemic disease at the beginning hence chemotherapy may cure the patient. Aim of our study Comparison of response assessment to Neo-adjuvant Chemotherapy in large operable and Locally Advanced Breast Cancer by clinical methods, Mammography and USG.

MATERIAL AND METHODS

Twenty female patients of histologically proved breast cancer were included in this study, informed consent was taken from all patients. Patients with large T2(>4 cm), T3 and T4 lesions were included in this study. Patients with age > 65 years, small tumours (< 4 cm) and those with metastatic disease were excluded.

Staging was done by clinical examination, X-ray chest, skeletal survey, a baseline Mammogram and Ultrasonography of breast & abdomen.

Routine work up included complete blood picture, liver function tests, renal function tests, ECG and Echocardiography.

Based on preoperative assessment patients were catergorised – a) Those who were suitable for breast conservation surgery (WLE or quadrantectomy + Axillary clearance).b) Those who were suitable for breast conservation.

All patients joining the trial were fully informed on the object of trial.

Chemotherapy regimens : CAF or CMF were used in following schedule.

Cyclophgosphamide 600 mg/ m^2 IV day 1,8

Adriamyamycin 30 mg/m^2 IV day 1,8

OR

Methotrexate 40mg/ m^2 IV day 1,8

5- fluroracil 600 mg/m^2 IV day 1,8

For patients with altered cardiac function, CMF regime was used. Instead of adriamycin, methotrexate was given 40 mg/IV day 1 and 8.

All patients were advised to take light food on the day of chemotherapy and injection Ondensetron 8 mg IV was given before chemotherapy.

A peripheral blood count was performed before each course of chemotherapy and if TLC was found less than 4000/$mm^{3,}$ chemotherapy was postponed. All patients were assessed clinically, mammographically and used by USG after 2nd and 4th cycle of chemotherapy, to assess tumour response.

Clinical assessment of tumour response

Maximum diameter of the tumour was measured by calipers—Two greatest perpendicular diameter of the tumour was in the breastwas taken a product of both was taken as overall clinical tumour.

Response was categorized as follows

a. Complete Response: Total disappearance of primary tumour and lymphnodes.

b. Partial Response: Greater than 50% reduction of the product of two perpendicular diameters.

c. Stable Response: Reduction of tumour size < 50% or increase of tumour size≤ 25%.

d. Progressive :Increase in tumour size≥ 25%

Mammographic Assessment

Bilateral mammograms were obtained during baseline staging and was repeated after 2nd and 4th cycle of the chemotherapy for the affected breast.

Pre and post treatment mammograms were assessed by consultant radiologist.

The following criteria was assessed

a. Mass: Size measured on mammogram using a scale in three perpendicular directions(2 maximum dimensions considered). The shape and margins of the lesion and its density compared with the adjacent breast parenchyma.

b. Microcalcification: Distribution and extent.

c. Associated features: Architectural distortion, skin thickening, nipple retraction, additional masses and associated lymphandenopathy.

Response assessment by Mammography

a. Complete Reponse: Complete disappearance of the mass with no residual abnormality.

b. Partial mammographic response: suggested by the following features.

I. Mass resolved in mammography but microcalcification present.

II. Variable decrease in size and density of mass.

III. Decrease in size of a mass with no change in density.

IV. Size unchanged but density decreased.

c. Stable Disease:- Findings unchanged from previous mammographic examination.

d. Progressive disease: Enlargement of mass or increase in the extent of abnormality.

Ultrasonographic Assessment

Ultrasonography was done both as baseline (prechemotheraphy) and after 2^{nd} and 4^{th} cycles of chemotheraphy to see the response. Baseline study included assessment of both brests for tumour size, shape, margins and echotexture.

Response assessment by USG

1. Complete Reponse: Complete disappearance of the mass with no residual abornmality.
2. Partial Response: Tumour size reduction > 50%.
3. Stable Response: Reduction < 50% or increase in≤ 25%.
4. Progressive: Tumour size increasing ≥ 25%.

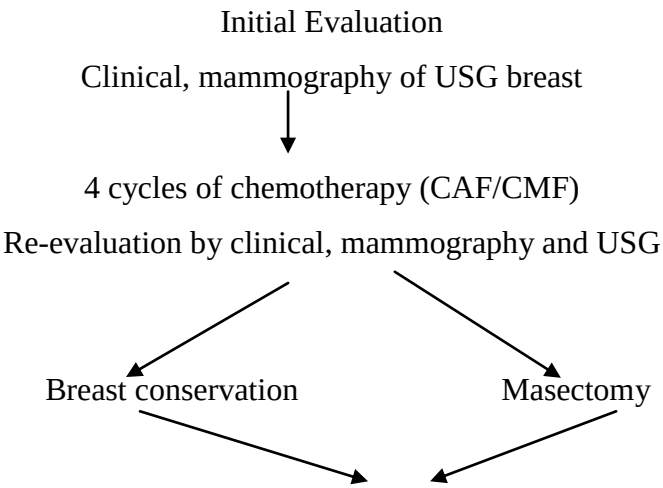
In addition bilateral axillae and the liver was also also evaluated on ultrasound for any abnormality and for staging.

Following completion of 4 cycles of chemotheraphy patients were reassessed clinically, mammographically and by Ultrasonogram and suitability for the breast conservation was assessed.

The actual surgical procedure performed was then recorded. A detailed histopathological evaluation was doneand a formal pathological TNM (p TNM) staging was recorded.

Postoperatively completion chemotherapy and? Or radio therapy was given where indicated. Patients were followed up regularly in breast cancer clinic and any evidence of locoregional or distant metastatis was recorded.

Flow diagram and the treatment protocol



Comparision of response assessment by clinical methods, Mammography, USG by correlation of histopoathological examination reports of the post operative specimens.

RESULT

Table showing Distribution of patients according to Age, Tumour size, Lymph node status		
Age Grps (yrs)	No.	%
20-30	2	10
31-40	5	25
41-50	9	45
51-60	4	20
Tumour size (cm)		
5-6	11	55
6-7	3	15
7-8	2	10
8-9	4	20

20 female patients with breast cancer were included in this study, conducted in the department of surgery between 1999-2000. The demographic data of the patient is as follows.

Age: Mean age of the patient was 44.65 years with a range of 29 – 60 years. Age distribution and percentage of patients undergoing study is shown in table 1 as follows.

Table 1.

Age Group (years)	`No. of patients Percentage
20-30	2 (10%)
31-40	5 (25%)
41-50	9 (45%)
51-60	4 (20%)

Menopausal Status

10 Patients were premenopausal and 2 patients were perimenopausal and 8 patients were post menopausal of which 2 patients had undergone hysterectomy.

Tumoursize(Tumour Status)-

Tumour size of patients is shown in table 2 as follows.

Table 2

Tumour	No. of patients Percentage
T2 (4-5)	5 (25%)
T3	7 (35%)
T4a	8 (40%)

Details of tumour size are shown in table 3 as follows.

Table 3.

Tumour size in cm	No. of patients Percentage
4-5	5 (25%)
5-6	6 (30%)
6-7	3 (15%)
7-8	2 (10%)
8-9	4 (20%)

Distribution of patients according to lymphnodes status is shown in Table 4 as follows.

Table 4.

Lymph node (N)	No. of patients Percentage
Node negative	9 (425%)
Node positive	11 (55%)
Total	20 (100%)

Distribution according to clinical staging (TNM) is shown in Table 5 as follows.

Table 5.

Tumour	No. of patients Percentage
IIA	4 (20%)
IIB	4 (30%)
IIIA	4 (10%)
IIIB	8 (40%)

Neoadjuvant Chemotherapy

19 patients received CAF and 1 patient received CMF regimen. All patients received preoperative chemotherapy. 14patients completed all 6 cycles. 5 patients took only one cycle of post operative chemotherapy.

Post Chemotherapy Evaluation

Clinical Response

The overall response rate of the primary tumour to the neoadjuvant chemotherapy was 95% (complete response 45% partial response 50%). One patient had progression of disease and was offered surgery after two cycles. However for some personal reasons she delayed the surgery and got operated only after 4 cycles.

Distribution according to clinical response is shown in Table 6 as follows

Table 6.

Response	No. of patients	Percentage
Complete response (CR)	9	45%
Partial Response (PR)	10	50%
No Response(NR)	0	0%
Progressive	1	5%
Total	20	100%

Post Chemotherapy down – staging is shown in table 7 as follows:

Stage	No. of patients Percentage (%)	
	Pre Chemotherapy	Post Chemotherapy
No tumour (Clinically)		9 (45%)
I		5 (25%)
IIA	4 (20%)	4 (20%)
IIB	4 (20%)	2 (10%)
IIIA	4 (20%)	0 (0 %)
IIIB	8 (40%)	0 (0 %)

Mammographic Response

18 patients underwent mammographic examination before neoadjuvant, while 19 patients had mammogram done following chemocherapy. In one patient mammogram did not show any measurable lesion and thus pre and post chemotherapy mammogram could be compared in 17 patients. Overall mammographic response rate was 82.2%. Responses were complete in 2 (11.7%) patients and partial in 12 (70.5%) patients. No response / or progressive in 3 (17.6%) patients.

Distribution of patients according to ultrasonographic response is shown in table 8 as follows.

Table 8.

Response	No. of patients	Percentage
Complete response (CR)	5	25%
Partial response (PR)	12	60%
No response (NR)/Progressive	3	15%
Total	20	100%

Ultrasonographic response

17 patients underwent ultrasonographic examination of the breast before starting neoadjuvant chemotherapy while 19 patients underwent Ultrasonography, post CT. The overall objective response of primary tumour to neoadjuvant chemotherapy was above 88.1% (complete 5.8% and partial 82.3%).

Distribution of patients according to ultrasonographic response is shown in table 9 as follows.

Table 9.

Response	No. of patients	Percentage
Complete response (CR)	1	5.8%
Partial response (PR)	14	82.3%
No response (NR)/Progressive	1	11.7%
Total	16	100%

Correlation between imaging and Histopathology

We correlated the post-chemotherapy findings with final histopathology using 2×2 table and calculated the severity, specificity, positive and negative predictive values.

Clinical, mammographic, ultrasonographic and pathological responseis shown in table 10 as follows.

Response	Clinical Response	Mammographic Response	USG Response	Pathological Response
Complete response (CR)	9(45%)	2(11.7%)	1(5.58%)	5(25%)
Partial response (PR)	10(50%)	12(70.5%)	14(82.3%)	Tumour Present
No response (NR)/Progressive	1(5%)	3(17.6%)	1.(11.7%)	15(75%)

Clinical Correlation

Clinical Tumour	Pathological Tumour	
	YES	NO
YES	9	2
NO	6	3

Sensitivity	:	9/15	= 60%
Specificity	:	3/5	=60%
Positive predictive values	:	9/11	=81%
Negative predictive value	:	3/9	= 33%

Mammographic Correlation

Mammographic Tumour	Pathological Tumour	
	YES	**NO**
YES	15	1
NO	0	2

Sensitivity	:	15/15	= 100%
Specificity	:	2/3	= 66%
Positive predictive values	:	15/16	= 93%
Negative predictive values	:	2/2	= 100%

Ultrasonographic Correaltion

Ultrasonographic Tumour	Pathological Tumour	
YES	14	4
NO	1	0

Sensitivity	:	15/15	= 93.7%
Specificity	:	2/3	= 0%
Positive predictive values	:	15/16	= 83%
Negative predictive values	:	2/2	= 0%

Response	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
Clinical Evaluation	60	60	81	*33*
Mammography	100	66	93	100
US	93.7	0	83	0

DISCUSSION

Neo-adjuvant chemotherapy is being used increasingly in the treatment of patients with large operable locally advanced breast cancer with the aim of reducing the size of the primary tumour and eliminating the micro metastatis, in order to improve prognosis.[2,4,5]

A wide variety of regimen have been used as neo-adjuvant chemotherapy. Most regimens incorporate doxorubicin (Adriamycin). These regimens produce a complete pathological remission ranging from 3-18%. We used CAF in 19 patients while one patient received CMF. There are no randomized trials comparing CAF with CMF in the setting of neo-adjuvant chemotherapy. Two trials have suggested that response rates are lower with CMF.[6,7] In a previous trial reported from AIIMS NEW DELHI, significantly better response rates were seen with CAF regiment as compared to CMF.[7] Therefore we prefer CAF in neo-adjuvant setting and use CMF only in there is any contraindication to use CAF. There is no apparent trend towards better response, among various doxorubicin containing regimens.[4]

Nineteen of our patients (95%) showed some degree of tumour reduction. Nine patients (45%) had complete clinical response, while 10 patients showed partial response (50%). Only one patient had progression of disease on clinical examination. These response rates are similar to those reported in literature using different regimens.[8,9]

Singletary et al[8] used three cycles of vinscristine, doxorubicin, cyclophosphamide and prednisolone(VACP) at 21 days intervals and found 16% complete clinical response and 84% partial clinical response of which 23% became potential candidate of breast conservation surgery.

Scholl et al[9] used 4 cycles of CAF as neo-adjuvant chemotherapy and achieved objective rates of 65%.

A complete clinical response of 65% and overall response rate 98% was reported by Smith et al[10], using chemotherapy regimen requiring continuous infusion of drugs for 6 months..But this study patient compliance was not good and complications were common.

In our study, the regimen used, resulted in excellent patient compliance and low incidents of minor toxicities, like vomiting, anorexia, superficial thromobophelbitis etc. Only one patient develop severe neutropenia for which she was hospitalized and treated. She subsequently received schedules preoperative chemotherapy. All other patients completed scheduled chemotherapy.

Clinical response rates are believed to be important because this may correlate and patient survival[9] and also help in deciding the further surgical treatment. However it is found that response to chemotherapy is over estimated with clinical examination.[11,12] As many as one

third of the patient thought to be in complete remission on clinical grounds, many may have residual disease on pathological examination.[13,14] On the other hand persistence of residual abnormalities on physical examination or mammography does not always mean persistence of pathological disease.[13]

In our study 9 patient had clinically CR but only 5 patient had pathological CR, 3 out of 9 patient who have clinical CR, pathologically they have complete response. On the other hand, 2 patients, those who had partial response clinically, were found in complete remission pathologically.

Therefore, in addition to clinical examination, patients in our study were also assessed by mammography and ultrasonography at the end of 2^{nd} and 4^{th} cycle chemotherapy.

Mark C. Segal et al reported excellent and moderate mammographic response in 82% cases. Coccini et al[6] reported a complete response rate of 8% with clinical examination, of 0% with mammography and out of 14% with pathological examination.

Assessment of response of therapy by imaging modalities is important because this is crucial in choosing optimal surgical therapy and also because clinical examination often over estimates in tumour size.[15,16]

In our study, the response to neoadjuvant chemotherapy was assessed by mammographic response in 17 cases and by ultrasonography in 16 cases. Mammography response was seen 82% cases.[15] Cocconi et al[6] reported a complete response rate of 8% with clinical examination, 0% with mammography, in one patient with clinically palpable lesion, mammogram did not show lesion due to presence of dense glandular parenchyma.

When we compared clinical CR to clinical nodal status at presentation, it was found that four out of 11 lymphnode positive patients (37) had clinical CR as compared to S out 9 node negative patients (55%). This is also consistent with the findings of Fisher et al (5) who found that C-CR rates were neatly similar in patients with ≥ 5 cm tumours regardless of their nodal status of presentation, in constrast only 1 out of 9 clinically nodes negative patient (11%) showed pathological CR as compared to 4 out of 11 node positive patients (37%). This is also consistent with the findings of Fisher et al (5) who found p CR to be higher in women with clinically nodes as compared to women with clinically negative nodes (30% vs 24%).

SUMMARY AND CONCLUSION

20 patients of histologically proven large operable and locally advanced breast cancer were evaluated for response assessment by clinically methods, mammography and USG following down staging by neoadjuvant chemotherapy after second cycle of chemotherapy and finally before operation.

19 patients received CAF and 1 patient received CMF regimen.

Clinically, 9(45%) patients had complete response, 10(50%) patients had partial reponse and 1(5%) had progressive disease.

Pre and post chemotherapy mammograms were compared in 17 patients. On mammography 2(11.76%) had complete response, 12(70.58%) had partial response and 3(17.64%) had no response / progression. Ultrasonography was compared pre and post chemotherapy in 16 patients. One (6.25%) patient had complete response, 14 (87.5%) had partial response/ progression was seen in 1(6.25%).

On pathological examination of the operated specimens, 5 patients had no microscopic tumours.

On correlating post chemotherapy evaluation by clinical method, mammography and USG, with histopathology, it was found that mammography was the most sensitive (100%) followed by ultrasonography (93.7%) and clinical examination (60%).

Thus we conclude that clinical assessment is not sufficient for assessment of chemotherapeutic response and should be supplemented by mammography and USG imaging.

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