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Original Article

Assessment of Predictive Factors for Response to Neoadjuvant Chemotherapy in Breast Cancer

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ABSTRACT

Objectives: The early identification of breast cancer patients who will not respond to neoadjuvant chemotherapy is valuable for timely change in management strategies. Reliable clinical and pathological markers predictive of response to treatment have considerable potential for practical clinical use. Our longitudinal study aimed to assess clinical, pathological, and immunohistological factors predictive of chemotherapy response.

Material and Methods: Thirty Five patients of breast cancer underwent six cycles of Taxotere, Adriamycin, and Cyclophosphamide (TAC) based neoadjuvant chemotherapy (Docetaxel 75 mg/m^2, Doxorubicin 50 mg/m^2 or Epirubicin 100 mg/m^2 and Cyclophosphamide 500 mg/m^2) every three weeks followed by surgery. Histopathological response was assessed after surgery. At a follow up of 12 months, association between factors was tested with Fisher exact test, survival analysis was done with Kaplan Meier analysis and significance was tested by log rank test.

Results: Five patients out of 35 had pathological complete response (pCR). 14.8% of all T4 disease (P = 0.043) and 22.7% of all Estrogen receptor (ER) negative patients had pCR (P = 0.025). Among all patients showing pCR, four patients (80%) had Grade III tumors (P = 0.018) while all five patients had high Ki67 index (P = 0.032). At 12 months, the mean estimated overall survival came out to be 11.6 months. Mean estimated disease free survival was less for patients with pCR (7.2 months) vs. partial response (10.1 months) (P = 0.44).

Conclusion: Our study concluded that tumors with larger size, higher stage, higher grade, ER negativity and higher proliferation index had better response to chemotherapy but these tumors also had a trend towards early relapse.

Keywords: Breast carcinoma, Neoadjuvant chemotherapy, Predictive factors, Relapse, Response

INTRODUCTION

Anthracycline based neoadjuvant systemic therapy with or without a taxane is the standard regimen for locally advanced, inoperable cancer of breast, at presentation.[1] Usually 60–90% of patients show clinical response yet some patients progress or fail.[2] The early identification of these patients is valuable for timely changes in management. Clinical factors, such as age and body mass index can predict pathological complete response (pCR). Other factors like size, histopathologic features, and molecular marker expression are being studied.[3] Our study aimed to assess clinical, pathological, and immunohistological factors predictive of neoadjuvant chemotherapy response in breast cancer.

MATERIAL AND METHODS

This longitudinal observational study was conducted at a single center over a time period of 12 months. The study was performed according to the approval obtained by the Institutional Ethics Committee (IEC) of Swami Rama Himalayan University; approval reference number - SRHU/HIMS/ETHICS/2019/28. The inclusion criteria were: 18–70 years of age, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤2, histologically proven inoperable and borderline operable breast carcinoma. Patients with previous history of breast cancer treatment (surgery, chemotherapy or radiotherapy), concomitant morbid conditions which precluded the use of chemotherapy and metastatic disease were excluded.

Detailed local examination was done with documentation of clinical findings including clinical tumor size, axillary node number and size, presence of skin changes (peau d'orange, skin puckering, nipple retraction) and chest wall involvement. Biopsy tissue examination included histological type and grade. Immunohistochemistry analysis of specimen

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documented: Estrogen receptor (ER) status, Progesterone Receptor Status (PR), Human epidermal growth factor receptor 2 (HER2) receptor status and proliferation Index Ki-67 (in terms of percentage) which were detected by Ultraview universal 3,3′-Diaminobenzidine (DAB) Detection Kit (Roche Ventana). Either of the imaging studies: Mammography/Ultrasound Sonography (USG) breasts or Magnetic resonance imaging (MRI) breasts was done. Metastatic Workup was completed with chest X-ray/Contrast Enhanced Computerized Tomography (CECT) thorax and bone scan.

The patients were administered three cycles of neoadjuvant chemotherapy (Regimen – Taxane (Docetaxel 75 mg/m^2 i/v), Anthracycline (Doxorubicin 50 mg/m^2 or Epirubicin 100 mg/m^2 i/v) and Alkylating Agent (Cyclophosphamide 500 mg/m^2 i/v) which was given every three weeks.[4] Response assessment was done clinically after three cycles of neoadjuvant chemotherapy and further three cycles of chemotherapy were administered. Complete haemogram, Kidney function tests and/or Liver function test levels were checked before administration of every cycle of chemotherapy. Evaluation was done after three cycles of chemotherapy and then after six cycles of chemotherapy. Histopathological response was assessed after completion of surgery. Assessment of response to treatment was done by using Revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).

Patients were recruited after written and informed consent and ethical committee clearance. The decision regarding administration of neoadjuvant chemotherapy was taken in the multidisciplinary tumor board after consultation between surgical oncologist and medical oncologist.

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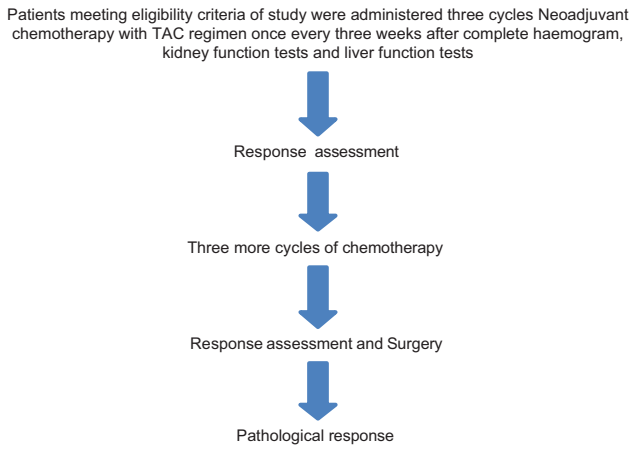

For cross tabulation, markers were categorized dichotomously. Ki 67 was taken dichotomously as low and high. Association between marker expression and tumor response was tested with the Fisher exact test. Survival analysis was done with Kaplan Meier estimates and significance was tested by log rank test.

RESULTS

We assessed the response of Taxotere, Adriamycin, Cyclophosphamide (TAC) based neoadjuvant chemotherapy in 35 locally advanced breast cancer patients and its relation with clinical, pathological, radiological and immunohistological markers [Tables 1 and 2]. All patients were women.

The mean age of patients in this study came out to be 48 years (22–69 years). Higher T stage showed more complete response with four patients (14.8%) of all with T4 disease having pathological complete response ($P = 0.043$) [Figure 1].

Tumors with higher grade (Grade II and III) showed more number of partial response with 14 patients (58.3%) with Grade II and five patients (50%) with Grade III showing partial response [Figure 2]. Among all patients showing complete response, four patients (80%) had Grade III tumors ($P = 0.018$).

Only five (22.7%) of all ER negative patients had complete response ($P = 0.025$) while eight (36.4%) of all ER negative patients were partial responders. 11 (84.6%) of all ER positive patients were partial responders while none of the ER positive patients showed complete response [Figure 3]. Thus ER negative patients had a higher probability of pathological complete response.

All patients who achieved pathological complete response had high Ki67 index (>20%) ($P = 0.032$) while only no patients with low Ki67 index achieved pathological complete response. 11 (42.1%) patients with low proliferative index (<=20%) showed partial response [Figure 4]. Thus higher proliferative index was associated with more probability of pathological complete response.

Mean estimated disease free survival was low for patients with complete response (7.2 months) as compared to partial response (10.1 months) ($P = 0.44$) showing a trend that patients with good response also have early relapse [Figure 5]. Patients with stable disease and progression had a mean estimated freedom from disease for 10.1 months and 11 months respectively.

DISCUSSION

The data analysis revealed that tumors with larger size, higher stage, higher grade, ER negativity and higher proliferation index had a better response to chemotherapy. ER status, human epidermal growth factor receptor 2 (HER2/neu) status, Immunohistochemistry (IHC) subtype and overall

Table 1: Patient characteristics.

Characteristics ($n = 35$)	Number	Percentage
Age		
20–39	10	28.6
40–59	18	51.4
>=60	7	20.0
Menstrual status		
Premenopausal	13	37.1
Perimenopausal	3	8.6
Postmenopausal	19	54.3
Mammographic features		
Spiculated	10	28.6
Lobulated	6	17.1
Round	1	2.9
Irregular	11	31.4
Others	7	20.0
cT stage		
1	1	2.9
2	2	5.7
3	5	14.3
4	27	77.1
cN stage		
0	8	22.9
1	11	31.4
2	6	17.1
3	10	28.6
Histological type		
IDC	31	88.6
ILC	2	5.7
Others	1	5.8
Histological Grade		
1	1	2.9
2	24	68.6
3	10	28.6
ER status		
Positive	13	37.1
Negative	22	62.9
PR status		
Positive	9	25.7
Negative	26	74.3
Her2Neu status (IHC)		
0	19	54.3
2*	7	20.0
3	9	25.7
Ki67		
<=20%	9	25.7
>20%	26	74.3
Immunological subtype		
Luminal A	8	22.9
Luminal B	5	14.3
Her2Neu	7	20.0
TNBC	15	42.9
ycT Post 3 cycles†		
1	8	22.9
2	17	48.6
3	4	11.4
4	5	14.7
ycN Post 3 cycles†		
0	20	57.1
1	12	35.3
2	2	5.9

*FISH for Her2Neu testing could not be done. The patients were classified and treated as Her2Neu negative. cT: clinically palpable and radiologically discernable tumour, cN: clinically palpable and radiologically discernable nodes, ycT: clinically palpable and radiologically discernable tumour after neoadjuvant therapy, ycN: clinically palpable and radiologically discernable nodes after neoadjuvant therapy, IDC: Invasive ductal carcinoma, ICL: Invasive lobular carcinoma, TNBC: Triple-negative breast cancer, HER2/neu: human epidermal growth factor receptor 2, IHC: Immunohistochemistry, n: patient characteristics

†1 patient underwent surgery post 2 cycles in view of Grade III neutropenia

Table 2: Response and disease status (at 1 year).

$n = 35$	Number	Percentage
Pathological response		
Complete response	5	14.3
Partial response	19	54.3
Stable disease	8	22.9
Progressive disease	3	8.6
Disease free at 1 year		
Yes	25	71.4
No	10	28.6

n: number of patients

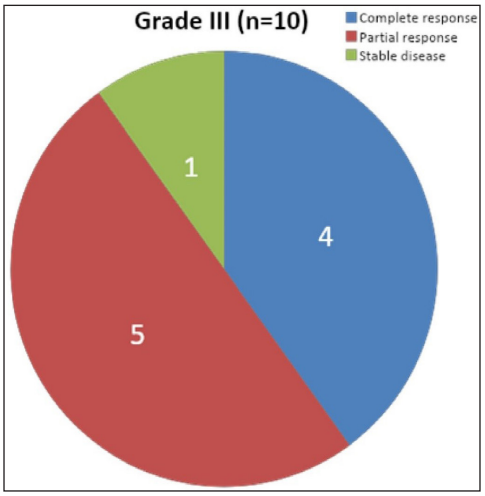

Figure 1: cT4 stage (n = 27) and response. cT4: Clinically tumour stage 4, n: number of patients

stage did not show any statistically significant correlation with response. Overall tumors with aggressive features responded better but also had a trend toward early relapse.

Markers that can predict response to the standard taxane, anthracycline and cyclophosphamide based chemotherapy are clinically relevant and useful. This study explored and found various clinical and pathological factors that can predict chemotherapy response [Figure 6].

In our study, it was found that higher T stage showed more complete response. Fisher *et al.* showed in National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial, that

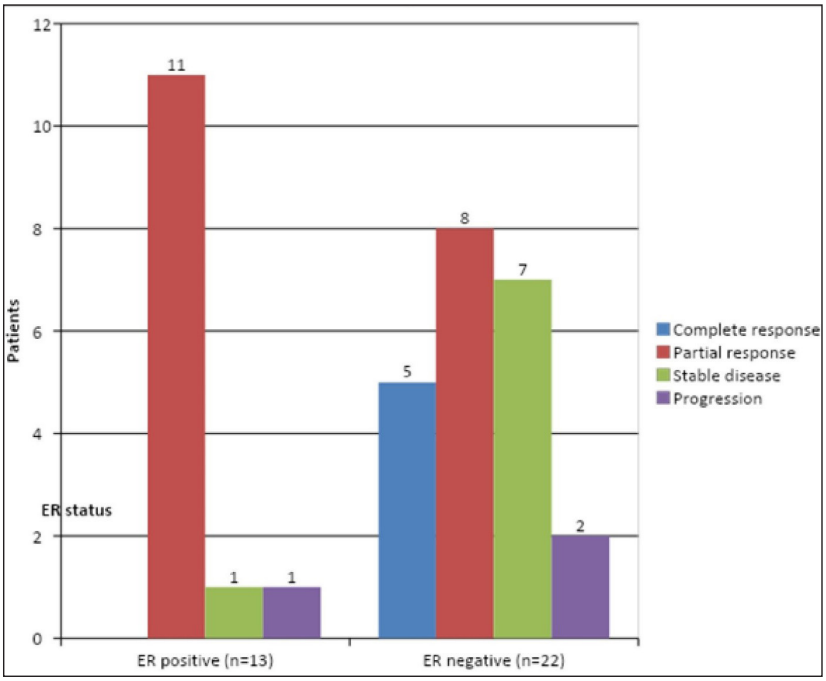

Figure 2: Grade III (n = 10) and response; ER: Estrogen receptor.

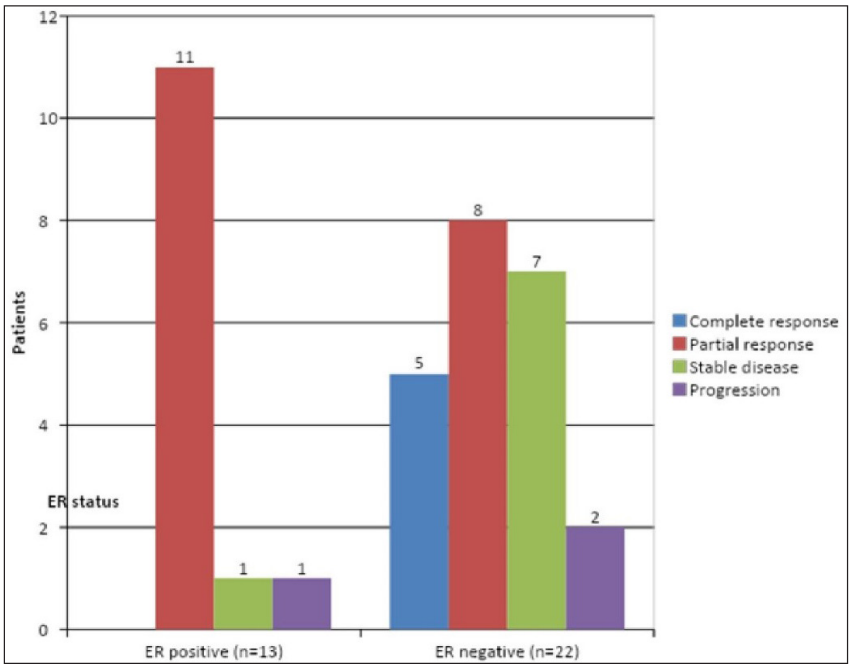

Figure 3: ER status and response. ER: Estrogen receptor.

size of tumor and clinical nodal status could independently predict complete response[5] and Fernandez-Sanchez M *et al*. showed that only initial tumor size predicted tumor regression.[6] Higher T stage is associated with rapidly growing tumor cells. Rapid growth takes the cell through cell cycle more quickly. This allows for a larger number of cells to be exposed to cytotoxic drugs in their chemosensitive phase. This leads to more tumor cell killing and better response to neoadjuvant chemotherapy.

In our study, more Grade III tumors achieved pathological complete response in comparison with Grade II and Grade I tumors. Both Hanrahan E.O. *et al*. and Prisack H.B. *et al*. have also shown that high nuclear grade and poor differentiation

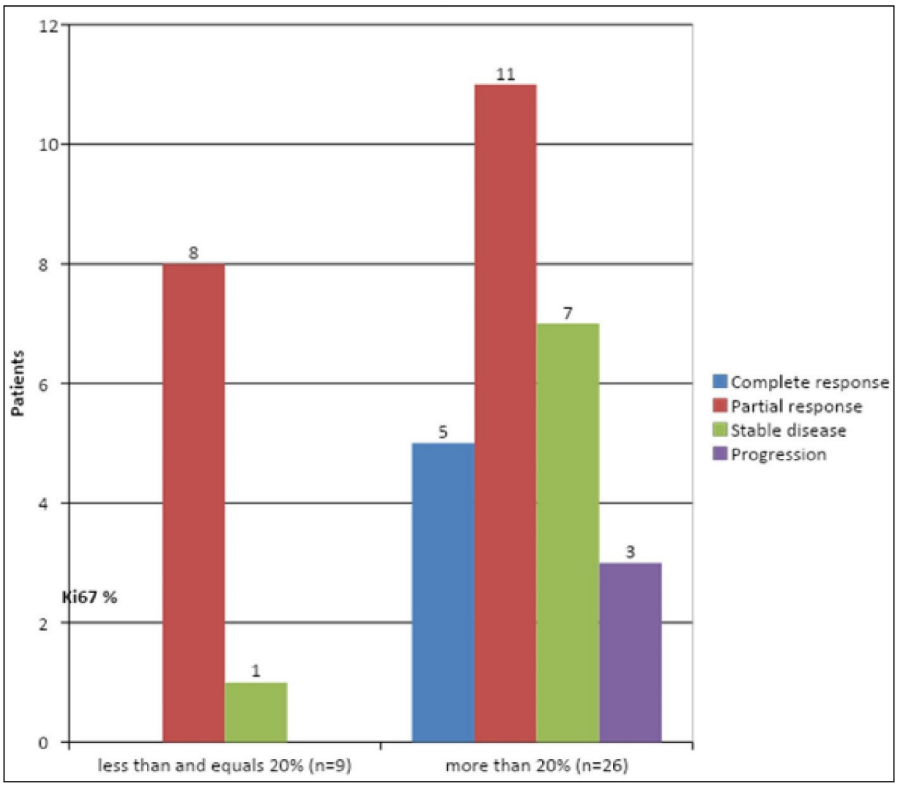

Figure 4: Ki67 and response.

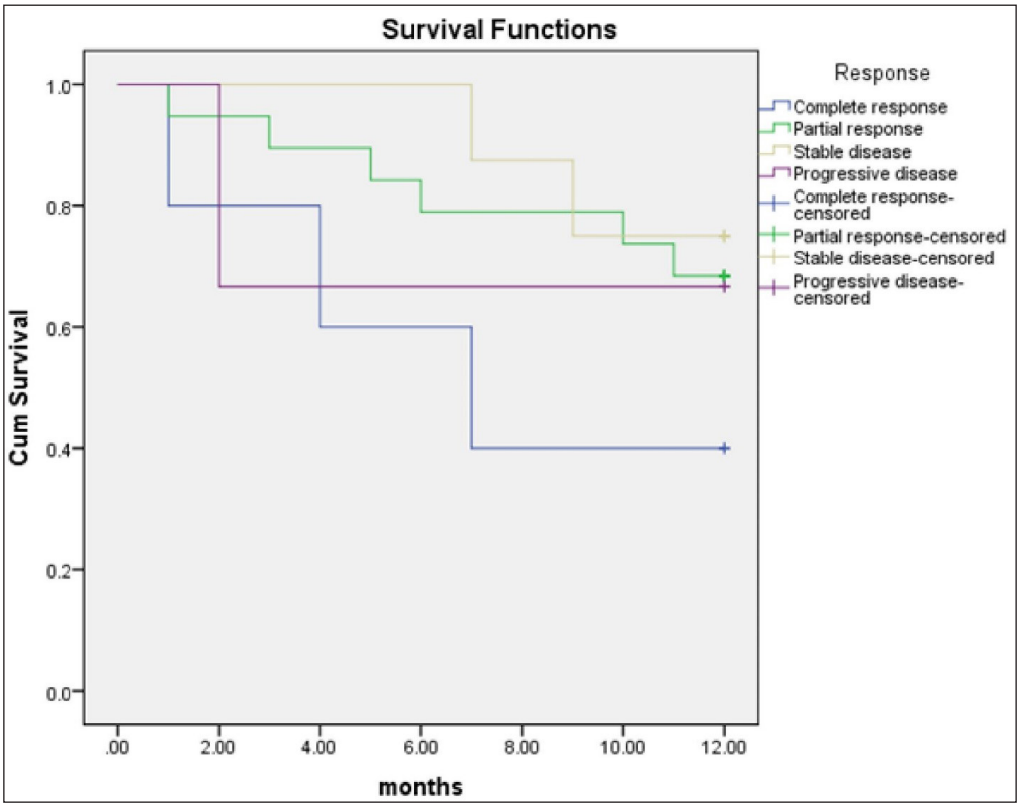

Figure 5: Kaplan Meier graph for freedom from disease and response.

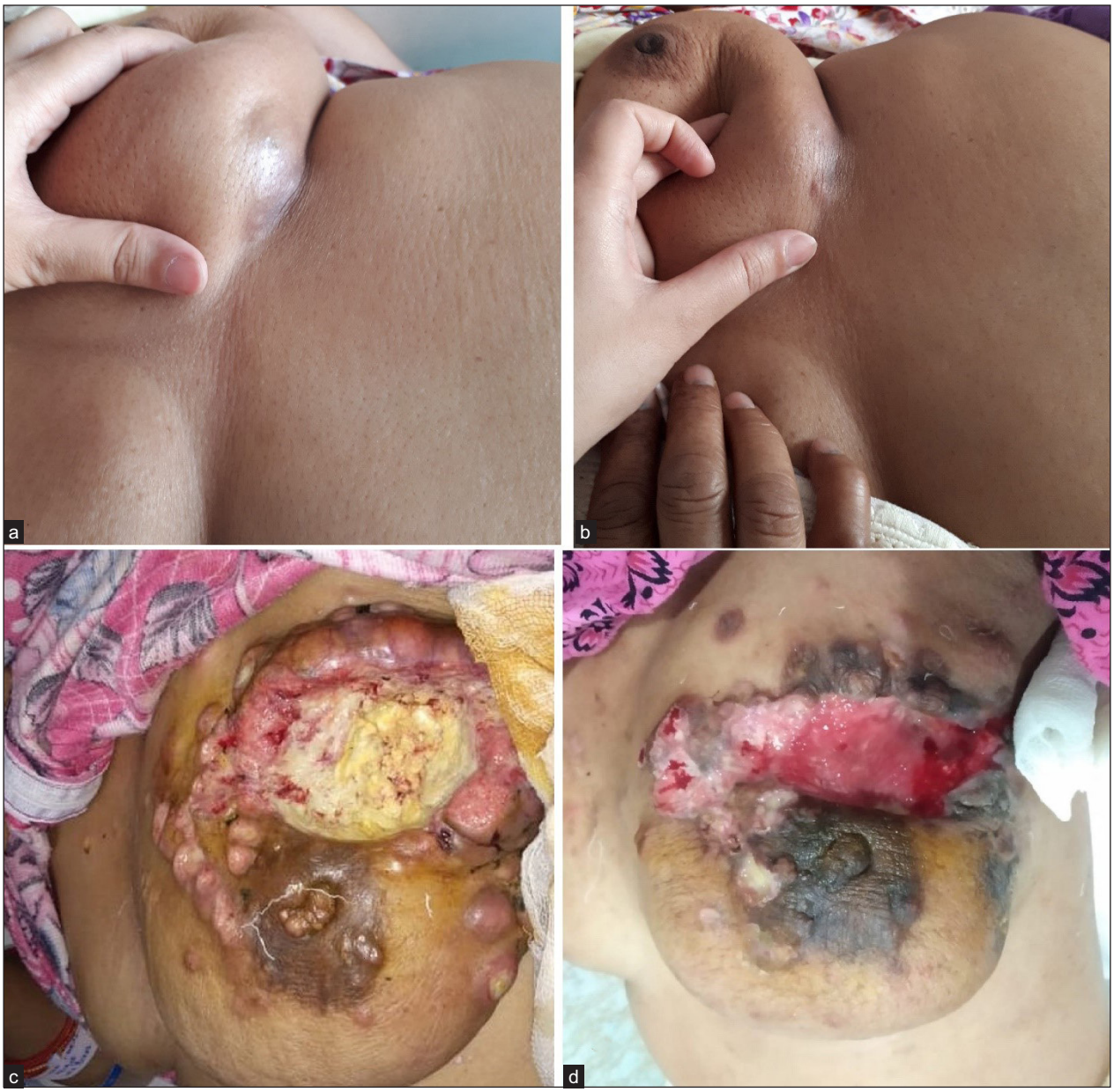

Figure 6: Clinical response in patients. (a) Pre chemotherapy (b) Post chemotherapy (c) Pre chemotherapy (d) Post chemotherapy.

can conceive a tumor more sensitive to chemotherapy in comparison with well differentiated and low grade tumors.[7,8] Another study by Marcus C. Tan *et al* also proved that factors associated with an increased percentage of pathological complete response included high tumor grade.[9] A possible explanation to this can be the fact that high grade tumors have a small turnover time. These cells come into the chemosensitive phase more quickly.

Our study showed that ER negative patients had a higher probability of pathological complete response. Ring *et al*. analyzed in their research that ER negative tumors had a higher chance to achieve a pathological complete response in comparison with patients who were ER positive.[10] Kuerer *et al*. studied locally advanced breast cancers treated with upfront chemotherapy and also found higher pathological complete response rates in patients who were ER negative.[11]

In the European Cooperative Trial in Operable breast cancer (ECTO) it was noted that 42% of patients who had estrogen receptor negative tumors had pathologic complete response while only 12% of the patients in the estrogen receptor positive group had pathological complete response. In their multivariate analysis, estrogen receptor status came out to be the only independent variable with a significant association

with the likelihood of the achievement of a clinically complete response and most importantly a pathological complete response.[12] In another retrospective analysis by Guarneri V *et al*., pathological complete response rates were 24% in estrogen receptor negative tumor patients and 8% in ER positive tumor regardless of the treatment regimen used.[13] Estrogen receptor negative patients are aggressive tumors with high proliferation rate and cellular atypia. Their short turnover time takes them through the chemosensitive phase of cell cycle more often thus making these tumors more chemosensitive than estrogen receptor positive.

Uncontrolled proliferation is one of the central elements of malignant neoplasms. In our study, all patients who achieved pathological complete response had a high Ki67 proliferation rate (>20%). Petit *et al*. revealed in their study that breast cancers with high Ki67 proliferation rate, showed a good response to upfront chemotherapy. Further the authors concluded that absence of hormone receptors and high Ki67 proliferation rate in post neoadjuvant chemotherapy specimens was predictive of a complete response.[14] In a study by Peter A Fasching *et al*. all ER positive tumors that have a low Ki67 index show an association with pathological complete response in 2.9% of patients, and tumors with a high Ki67 index show an association with pathological complete response in 8.0% of patients.[15] An explanation to high proliferative index showing more response could lie in the fact that quickly proliferating cells enter chemosensitive phase of cell cycle more frequently than slowly dividing cells, thus, becoming a successful target for cytotoxic drugs. However, a consensus had not been reached in the international circles in view of the conflicting findings that have been documented in various studies on this subject.

In our study, 14.3% patients achieved pathological complete response, 54.3% achieved partial response while 22.9% had stable disease and 8.6% had progression. This is concordant with a pooled analysis of ten trials by Early Breast Cancer Trialists'. Collaborative Group (EBCTCG) in which 28% had complete response, 41% had partial response and 31% had stable disease or progression.[16] Most of the patients achieved partial response only, but all tumors became operable.

During the study period of 12 months, the mean estimated overall survival of patients in our study was 11.6 months while median survival could not be estimated as the required number of events could not be reached. In a study by Li Yan Lim *et al*, the median survival of patients receiving preoperative chemotherapy was 11.4 years and overall 5-year survival was 71.5% on a follow-up of 20 years.[17]

Out of a total of 35 patients in our study, 25 were disease free at 1 year while 10 had developed metastasis within 1 year of treatment completion. During a median follow-up of 46.3 months (0 to 127 months) after treatment completion, Gunter von Minckwitz *et al*. observed that 23% of patients relapsed and 12.2% died.[18]

In our study, mean estimated disease free survival was low for patients with complete response (7.2 months) as compared to partial response (10.1 months) showing an unexpected trend that patients with good response also have early relapse.

In a study by IF Faneyte *et al*, the 5 year overall survival (59 and 54%, respectively) and 5 year disease free survival (43 and 48%, respectively) was equivalent in patients with any histopathological response in comparison with patients with no signs of response.

In their study as well, patients with a pathological complete response had a relatively worse outcome.[3]

The 15-year overall survival was not significantly different in patients with pathological complete response when it was compared with the group of patients with residual invasive tumors in a study by P. Chollet *et al*.[19]

On the contrary, Ring *et al*. showed that there was a trend towards better disease free survival in patients who had a pathological complete response, but without any statistical significance. In their study, pathological complete response did not influence the rate of isolated local recurrence.[10]

Cornelia Lidekte *et al*. also showed that patients with pathological complete response after preoperative chemotherapy had excellent survival. They also showed that in the first 3 years, triple negative breast cancer patients with residual disease had significantly worse survival in comparison to non-triple negative breast cancer.[20]

According to the follow up results at 9 years of National Surgical Adjuvant Breast and Bowel Project B-18 published by Norman Wolmark *et al*., the overall survival rate for patients achieving a pathological complete response was 85% while for patients with residual disease it was 73%. The disease free survival was 75% and 58% respectively.[21]

However, the relation of response and survival is still under contest in literature with results of various studies giving opposite evidence.

Our study was limited by its small sample size and heterogeneous population. Another limitation was that targeted therapy or hormonal therapy was not used in neoadjuvant setting and all patients were given TAC based chemotherapy. The follow up period was short and the required number of events could not be reached to estimate median survival. Almost all patients in our study were infiltrating ductal carcinoma and thus our study was extremely underpowered to reveal any association between histological type and response.

CONCLUSION

The data analysis revealed that tumors with larger size, higher stage, higher grade, ER negativity and higher proliferation index had a better response to chemotherapy. ER status, Her2Neu status, IHC subtype and overall stage did not show any statistically significant correlation.

Our study demonstrated that aggressive tumors with higher stage, grade and proliferative index responded well to neoadjuvant chemotherapy but they were also quick to relapse. Pathological complete response did not appear to be an indicator of better survival however a larger sample size and longer follow up is required for a better analysis.

Ethical approval

The author(s) declare that they have taken the ethical approval from IEC (SRHU/HIMS/ETHICS/2019/28).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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