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Patterns of failure in locally advanced female breast carcinoma treated with neoadjuvant chemotherapy followed by surgery and radiotherapy – A prospective study

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ABSTRACT

Background: The use of combined modality therapy including surgery, chemotherapy, and radiotherapy increases five survival rates in stage IIA and stage IIIB disease to 80% and 45%, respectively. Neoadjuvant chemotherapy (NACT) eradicates micro metastasis present in the body and also improves resectability. **Aims and Objectives:** The main aim of this study was to determine the locoregional recurrence and distant recurrence rates and thereby define clinical and pathological predictive factors for recurrence. **Materials and Methods:** This was a single institutional prospective study carried out in the Department of Radiotherapy, RG Kar Medical College and Hospital, Kolkata. From January 2017 to December 2019, according to inclusion and exclusions criteria, a total of 1183 histologically and/or cytologically proven breast carcinoma patients were included in this prospective study. **Results:** Breast conservative surgery was done in 16.5% of patients and the rest of the patients underwent modified radical mastectomy. Seven patients had undergone toilet mastectomy with the specimen. From the pathological review of the surgical specimens, 15.0% of patients achieved pathological complete response, while 19.4% of patients had clinical complete response. A total of 150 patients out of 1183 patients (12.67%) had disease recurrence. **Conclusion**: Local treatments, either surgery alone and/or RT alone, are inadequate therapies for locally advanced breast cancer patients, and multidisciplinary treatment should be used, to reach better management. Inoperable locally advanced breast carcinoma can be converted into operable by NACT.

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INTRODUCTION

Worldwide breast cancer was the most common malignancy constituting about 11.7% of all new cases and the 4th common cause of cancer-specific mortality at 6.9%.[1] Although locally advanced carcinoma of the breast is not clearly defined, it includes advanced primary or nodal disease and commonly refers to Stage III disease.[2] The use of combined modality therapy including surgery, chemotherapy, and radiotherapy increases five survival rate in stage IIA and stage IIIB disease to 80% and 45%, respectively.[2] Neoadjuvant chemotherapy (NACT) eradicates micrometastasis present in the body and also improves resectability. After NACCT approximately 80% of patients', tumor sizes were reduced significantly, and only 2–3% have signs of tumor progression. Similarly, NACT neither delays post-operative treatment nor adversely affects surgical complications rate, in fact, patients who

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received NACCT had a lower rate of post-operative seroma formation. In addition, it allows the *in vivo* assessment of the chemosensitivity of the tumor. Although disease-free survival (DFS) and overall survival (OS) were equivalent between adjuvant chemotherapy and NACT, NACT is being increasingly used in locally advanced carcinoma.[2,3]

Aims and objectives

The main aim of this study was to determine the locoregional recurrence and distant recurrence rates and thereby define clinical and pathological predictive factors for recurrence.

MATERIALS AND METHODS

Study design

This was a single institutional prospective study carried out in the Department of Radiotherapy, RG Kar Medical College and Hospital, Kolkata. The inclusion criteria were included in the study: (1) histologically/cytologically confirmed carcinoma of the breast in female patients; (2) of age between 18 and 70 years; (3) locally advanced and non-metastatic breast carcinoma (AJCC Stage III), and (4) patients who are willing to give voluntary consent. The exclusion criteria were excluded from the study: (1) patients without confirmed histopathology/cytology reports, (2) patients who received prior chemotherapy or radiotherapy, (3) patients who are not willing to give voluntary consent, and (4) patients with pre-existing significant comorbidity conditions. At the time of diagnosis along with routine hematological, and biochemical investigations, chest X-ray PA, USG of the whole abdomen a contrast-enhanced computed tomography (CT) scan of the chest, and whole abdomen were done as a part of the staging workup and patients underwent positron emission tomography-CT (PET-CT), whole body bone, and contrast-enhanced magnetic resonance imaging (MRI) brain when indicated. The usual follow-up investigations are as follows: History and physical examinations after every 3 months; mammography every 12 months; gynecologic assessment every 12 months if on tamoxifen and uterus present; bone mineral density determination at baseline; and periodically thereafter if on an aromatase inhibitor. Appropriate laboratory studies (complete blood count, platelets, liver function test and alkaline phosphatase, urea, and creatinine) and imaging studies (Chest X-ray, CT scan of thorax, CT/MRI of abdomen and pelvis, MRI of brain, bone scan, FDG-PET/CT scan, and X-ray of symptomatic bones) were performed as and when indicated.

Data collection and analysis

From January 2017 to December 2019, according to inclusion and exclusions criteria, as mentioned earlier, a total of 1183 histologically and/or cytologically proven breast carcinoma patients were included in this prospective study. All the collected data were recorded on an excel sheet and analyzed on SPSSVs20. Categorical data including locoregional response rates after NACT, and recurrence after surgery, and adjuvant therapy would be written as percentages and compared with the Chi-squared test. Continuous data would be summarized as mean±SD and compared with an independent t-test. Survival curves would be generated by the Kaplan–Meier method to compare progression-free survival (defined as the time from time of initiation of treatment until disease progression locoregional or metastatic) and would be compared with the Log Rank test. The multivariate analysis would be done using multinomial logistic regression for predicting relations between the event incidence (response rates after NACT), and a set of covariates such as age, tumor size, histological type, and grade, ER/PR/Her-2neu status, and chemotherapy regimens (non-taxane non-anthracyclines/anthracyclines non-taxanes/anthracyclines – taxanes-based CT regimens). All statistical tests would be two-tailed and the difference would be considered statistically significant if $P \leq 0.05$.

Ethical consideration

Our prospective study was approved by the Institutional Ethics Committee (IEC, NMC-5591dated 23/12/16) and as per the ethical guideline Helsinki, the confidentiality of patients was assured.

RESULTS

A total of 1183 locally advanced breast cancer patients were treated with neoadjuvant chemotherapy and 468 patients were in the age group of 41–50 years with the mean age of patients being 48.51±10.5 years. The majority of the patients were in premenopausal status. About 72% of patients were in ECOG performance status 2. The most common breast cancer subtype was infiltrating ductal carcinoma (96.0%) with the majority of them being moderately differentiated (44.5%). The estrogen receptor, progesterone receptor, and Her 2 neu receptor positivity rate were 50.2%, 54.9%, and 28.7%, respectively. Pre-neoadjuvant chemotherapy tumor staging was 42.3% of patients with T3 disease with only 13 patients being diagnosed with T4 disease of breast cancer. The most common nodal presentation was N1 disease (44.8%). TNM group staging was 51.0% of stage IIIB. The baseline demographic profile and chemotherapy details are depicted in Tables 1 and 2, respectively.

Breast conservative surgery (BCS) was done in 16.5% of patients and the rest of the patients underwent modified

Table 1: Tumor characteristics

Tumor	N	%
Histopathology		
IDC	1136	96
Lobular	26	2.2
Medullary	13	1.1
Tubular NOS	8	0.7
Breast side		
Left	667	56.4
Right	516	43.6
Grade		
MD	526	44.5
WD	251	21.2
PD	406	34.3
Breast site		
C	227	19.2
LI	66	5.6
LO	142	12
UI	66	5.6
UO	682	57.7

IDC: Infiltrating ductal carcinoma, MD: Moderately differentiated, PD: Poorly differentiated, WD: Well differentiated, C: Central, LI: Lower inferior, LO: Lower outer, UI: Upper inner, UO: Upper outer

Table 2: NACT regimens used in our patients

NACT Regimens	N	%
AC	202	17.1
FAC	252	21.3
FEC	240	20.3
TAC	289	41.3%

NACT: Neoadjuvant chemotherapy, AC: Adriamycin cyclophosphamide, FAC: 5-FU Adriamycin cyclophosphamide, FEC-5-FU: Epirubicin Cyclophosphamide, TAC: Taxane Adriamycin cyclophosphamide

radical mastectomy (MRM). Seven patients had undergone toilet mastectomy with the specimen. From the pathological review of the surgical specimens, 15.0% of patients achieved pathological complete response (pCR), while 19.4% of patients had clinical complete response (cCR). A total of 150 patients out of 1183 patients (12.67%) had disease recurrence. Twenty percentages of patients (30 out of 150) had locoregional recurrences and 73% of patients (110 of 150) had metastatic disease progression and rest seven percent of patients (ten out of 150) had both locoregional and distant failure. On comparison of clinical response with ECOG performance status, there was no statistically significant difference (P=0.738). However, for premenopausal patients, cCR was significantly higher than in menopausal individuals, but a reverse trend was seen with clinically stable disease in 96% of patients in menopausal patients (P<0.001). Approximately 74.7% of Her 2 neu receptor negative patients had a cCR rate against 25.3% of patients with positive her 2 neu receptor (P<0.002). About 40.2% of patients with ER positivity (P=0.05) and 40.2% with PR positivity had cCR (0.03). The upfront use of taxanes was not adding to any statistically significant advantage in downstaging (P<0.292). For ER-positive patients, 87.8% of individuals had no CR against 12.2%, P<0.007. pCR was not significantly affected by other parameters. Kaplan–Meier's survival analysis showed that the use of trastuzumab in Her 2 neu positive patients delayed disease progression. Individuals with Her 2 neu positivity who did not receive trastuzumab were due to fall in LVEF below 50%. None of the patients receiving trastuzumab had fallen in LVEF requiring discontinuation or interruptions.

DISCUSSION

For women, breast cancer is a major public health issue throughout the world including India. Due to a lack of awareness, appropriate health-care facilities, and inadequate screening methods, many cases are diagnosed in advanced stages.[4,5]

Locally advanced breast carcinoma (LABC) remains a difficult problem, and even with multidisciplinary treatment, breast cancer recurrence will occur in many patients. NACT for the treatment of breast cancer was introduced in the 1970s for patients with locally advanced diseases. As previously stated, NACT can result in the downstaging of tumors, thus increasing the rate of breast-conserving surgery. In cases of more advanced disease, NACT can render inoperable tumors operable.[2,3] Other advantages to neoadjuvant therapy include the ability to obtain information on *in vivo* tumor response that can be used to study the biological effects of chemotherapy and determine long-term DFS or OS.

In our study, BCS was done in 16.5% of patients with others who underwent MRM. This clearly shows that BCS is a possibility in LABC patients treated with NACT. Fisher et al., reported results of the effects of neoadjuvant chemotherapy (NACCT) on 1523 patients and showed a significant increase in breast conservation in patients receiving neoadjuvant chemotherapy, but there was no difference in DFS or OS at 5 years.[6] From the pathological review of the surgical specimens in our study, 15.0% of patients achieved pCR, while 19.4% of patients had cCR. A study by Hennessy et al., investigated the significance of downstaging of axillary lymphadenopathy after neoadjuvant chemotherapy and concluded that response to axillary lymphadenopathy to NACCT is a better predictive factor than primary tumor response to NACT[7] and this finding also validated in another study by Rouzier et al.[8]

NACT in the case of locally advanced breast cancer has been found effective in our study and 92.3% of patients had a partial response. For patients who had a CR to NACT, none of the patients showed disease recurrence. Our results were consistent with the National Surgical Adjuvant Breast

and Bowel Project B-18, where the response rate to NACT was seen in approximately 80% of patients.[6]

Our data support the initiation of treatment with NACT, as it increases the rate of BCS and may render inoperable LABC resectable. In addition to an increased chance of breast-conserving surgery in LABC patients treated with neoadjuvant therapy, completion of all anthracycline-taxane-based chemotherapy in the neoadjuvant setting increases the chance of pCR as well as clinical response.[3,7] pCR, as well as clinical response after NACCT corelates well with DFS or OS, and thus these two factors, are very important prognostic factors.[3,9,10]

Another phase III study by van Nes et al., (EORTC trial 10902) demonstrated an increase in breast conservation rate (23%) in their group of patients who underwent neoadjuvant therapy, but there was no difference in DFS or OS between neoadjuvant chemotherapy arm and post-operative chemotherapy arm.[11,12]

National Comprehensive Cancer Network (NCCN) guidelines indicate a preference for neoadjuvant regimens that contain both an anthracycline and taxane for patients with locally advanced breast cancer given the better outcome of these regimens in the adjuvant setting for the patient with lymph node-positive disease.[13]

Factors that may be predictive of response to NACT are smaller tumor size, poorly differentiated and hormone receptor-negative tumors are significantly more likely to respond to NACT than larger, well-differentiated, and hormone receptor-positive tumors.[2,3] At present, tumor-infiltrating lymphocyte is being investigated as a predictor response to NACT in triple-negative breast carcinoma.[14]

It needs to highlight that many individuals with Her 2 neu score of 2+ were not confirmed by further tests and this remains a drawback of our study.

Limitations of the study

Our study was single arm and single institutional. Hence may be not representative of whole population.

CONCLUSION

Local treatments, either surgery alone and/or RT alone, are inadequate therapies for locally advanced breast cancer patients, and multidisciplinary treatment should be used, to reach better management. Inoperable LABC can be converted into operable by NACT. Although the long-term survival rate of these patients did not show an obvious increase after systemic treatment, the mean survival time and quality of life may be considerably improved.

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