Original Research

# Assessment of Pathological Complete Response and Clinical Responses in Locally Advanced Breast Cancer after Neoadjuvant Chemotherapy


## Abstract

**Background:** The use of neoadjuvant chemotherapy in treating breast cancer has shown efficacy in down staging primary tumors and allows breast conservative surgery to be performed instead of mastectomy. This study aims to evaluate clinical and pathological response after the use of neoadjuvant chemotherapy in patients with locally advanced breast cancer.

**Methods:** This is a cross-sectional study of forty-one patients who presented from January 1st, 2021 through June 2022 with locally advanced breast cancer and treated with neoadjuvant chemotherapy were included.

**Results:** In our study included 41 patients with a median age of 41 years. The cumulative clinical response rate was 75%; nine patients (22%) had a complete clinical remission (cCR); 22 had a partial remission (53.3%); six had stable disease (14.6%), and four had progressive disease (9.8%). Seven patients (18.9%) had complete pathological response.

**Conclusions:** Neoadjuvant chemotherapy resulted in high clinical response with complete pathological response in some patients with locally advanced breast cancer. We recommend further research to find Predictors for response.


## Acronyms/Abbreviations

**AA**: Addis Ababa, **AACCR**: Addis Ababa City Cancer Registry, **AAU**: Addis Ababa University, **AJCC**: American Join Committee on Cancer, **ASC**: Adenosquamous Carcinoma, **cCR**: Complete clinical remission, **CHS**: College of Health Science, **CI**: Confidence Interval, **CR**: Complete response, **CXR**: Chest X-Ray, **CT**: Computed Tomography, **CT**: Chemotherapy, **DM**: Distant metastases, **EFS**: Event free survival, **ECOG**: Eastern Cooperative Oncology Group, **GLOBOCAN**: Global Burden of Cancer Study, **LABC**: Locally advanced breast cancer, **NAC**: Neoadjuvant chemotherapy, **OS**: Overall survival, **pCR**: Pathological complete response, **TASH**: TikurAnbessa Specialized Hospital, **TNM**: Tumor, Nodes, Metastasis


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**Received Date**: *02 May 2025*
**Accepted Date**: *12 May 2025*
**Published Date**: *05 Jun 2025*

***Citation:***
*Demeke M. Assessment of Pathological Complete Response and Clinical Responses in Locally Advanced Breast Cancer after Neoadjuvant Chemotherapy. Collect J Oncol. Vol 2 (1) 2025; ART0085.*


## Introduction

Cancer is one of the leading causes of death worldwide , It is the second most common cause of death globally, accounting for an estimated 9.6 million deaths in 2018[1].According to GOLOBOCAN 2018, there were an estimated 18.1 million new cancer cases (excluding 17.0 million non-melanoma skin cancer) and 9.6 million cancer deaths (excluding 9.5 million non-melanoma skin cancer) worldwide [1]. Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women. with approximately 2 million new cases and nearly 626,000 related deaths worldwide in 2018 [1]. In Ethiopia , Breast cancer was by far the commonest cancer The recently reported, first data from the Addis Ababa City Population based cancer registry shows that breast cancer is the most common cancer in women and one of the top Ten cancers in men, constituting 33% of the cancers in women and 23% of all cancers identified from the Addis Ababa cancer registry [2] Neoadjuvant chemotherapy has been used to downstage locally advanced cancer to make it operable but currently is being used in the management of localized breast cancer as an alternative to adjuvant chemotherapy. Studies have shown that the benefit of chemotherapy is similar when given in the adjuvant and neoadjuvant settings, with no difference in survival [3]. However, NAC offers several additional advantages from both a clinical and a research perspective. In patients with large tumors, NAC has the potential to reduce tumor size to improve the rate of Breast Conservation Surgery (BCS) and can lead to less extensive axillary surgery[4] Because the primary tumor remains intact during therapy, the neoadjuvant treatment approach allows for monitoring of treatment response. and collecting information on chemo sensitivity in-vivo including the possibility to switch therapy if the response is inadequate [4].

**Statement of the problem**

Locally advanced breast cancer is a very common clinical scenario especially in developing countries possibly due to various factors like lack of education, lack of awareness among the population regarding cancer, lack of community screening programs, personal and social stigma, societal taboos pertaining to cancer and poor socio-economic status [5]. In Ethiopia most patients with cancer including breast cancer present at the advanced stages of the disease. Locally Advanced Breast Cancer (LABC) constitute 67% of new breast cancer cases in Ethiopia [6].

**Justifications of the study**

The fact that the incidence of breast cancer in Ethiopia is increasing with most patients presenting at an advanced stage where upfront surgery not usually an option, for this reason patients with LABC are started with NAC to be Followed by surgery. To identify a subset of patients who would most likely benefit from NAC, it is reasonable to detect predictors of pathological complete and clinical responses in these patients. Despite the well-described role of racial disparity in response to NAC, the incidence and predictors of pathological complete and clinical responses among Ethiopian breast cancer patients have not previously been characterized. The aim of the present study was to identify pathological complete and clinical responses and factors associated in breast cancer patients receiving NAC at our institution. To our knowledge there is no published research predictor of pCR and clinical responses patient in Ethiopia.

**Literature Review**

Pathological complete response and clinical responses were related to tumor size and surrogate for the efficacy of neoadjuvant chemotherapy in Locally Advanced Breast Cancer (LABC). Csaba 2002 retrospectively studied 144 patients with locally advanced breast cancer treated with NAC Complete clinical response was noted in (8%) and complete pathologic response was achieved in (13%). Smaller tumors were more likely to respond to chemotherapy than larger tumors. Distant disease-free ($P = 0.039$) and overall survival ($P = 0.035$) were related to the number of involved axillary lymph nodes [7]. The Clinical stage, tumor proliferation index and getting optimal chemotherapy determine Pathological complete response. Study in Egypt analyzed the predictive clinical factors for pathological responses and survival outcomes. The median follow-up time was 3 years. The clinical tumor stage (T3–4) represented 58%, with 80% having positive axillary nodes. The objective response rate (ORR) reached 78%, and 16% of patients achieved pCR. The clinical node stage and optimal chemotherapy were associated with higher ORR ($p = 0.035$ and $p = 0.001$, respectively). Predictors of pCR were clinical T-stage ($p = 0.026$), high Ki-67 index > 20 ($p = 0.05$), and receiving optimal chemotherapy ($p = 0.014$). Achieving pCR were associated with better DFS with hazard ratios of 0.56, $p = 0.008$; 0.38, $p = 0.04$; and, $p = 0.007$, respectively [8]. Prospective study from Sudan evaluates patterns of clinical and pathological response after two cycles of neoadjuvant chemotherapy in patients with locally advanced breast cancer. Ninety-eight patients who presented from April 2009 through May 2011 with locally advanced breast cancer and treated with neoadjuvant chemotherapy were included. The clinical response rate was 83%; 11 patients (11.2%) had a complete clinical remission (cCR); 71 had a partial remission (72.4%); 13 had stable disease (13.3%), and 3 had progressive disease (3.1%). Seven patients had complete pathological response [9]. Patients with triple-negative and HER2-positive breast cancers have the highest rates of breast-conserving surgery and pCR after neoadjuvant chemotherapy. The ACOSOG Z1071 prospective multicenter clinical trial of the 756 patients enrolled. Rates of breast-conserving surgery were significantly higher in patients with triple-negative (46.8%) and HER2-positive tumors (43.0%) than in those with hormone-receptor-positive, HER2-negative tumors (34.5%) ($P = 0.019$). Rates of pCR in both the breast and axilla were 38.2% in triple-negative, 45.4% in HER2-positive, and 11.4% in hormone-receptor-positive, HER2-negative disease ($P < 0.0001$)[10]. Chemotherapy response based and pCR was not better in young patients (<35 years) with ER-positive BC than in older premenopausal patients with ER-positive BC. ,Joohyun, et al. conducted a large, multicenter, observational study on 1048 ER-positive and 797 ER-negative patients aged <50 years included for analysis. Breast conservation rates were not significantly different according to age (44.2% vs. 46.8% in ER-positive group, 55.2% vs. 48.0% in ER-negative group). pCR rate was not different according to age in ER-positive group ($P = 0.71$) but significantly better in patients aged <35 years in ER-negative group ($P = 0.009$). The higher probability of pCR than older patients in ER-negative tumors. However, pCR rate did not differ according to age in ER-positive tumors [11]. The use of neoadjuvant chemotherapy in treating breast cancer has shown efficacy in down staging primary tumors, and allows breast conservative surgery to be performed instead of mastectomy. CALGB 40601 (Alliance) Of 292 patients with pre- and post-NAC surgical assessments, 59% were non-BCT candidates at baseline. Of the 43% of these patients who converted with NAC, 67% opted for BCT, with an 80% success rate. NAC increased the BCT-eligible rate from 41 to 64%. Common factors cited for BCT-ineligibility prior to NAC including tumor size (56%) and probable poor cosmetic outcome (26%) were reduced by 67 and 75%, respectively, with treatment, while multicentricity, the second most common factor (33%), fell by only 16%. Since [12] the use of neoadjuvant chemotherapy early breast cancer yields similar results in terms of PFS, OS, and locoregional control compared with conventional postoperative chemotherapy. In

addition, NAC enables more patients to be treated with breast-conserving surgery. EORTC trial 10902 Six hundred ninety-eight breast cancer patients (T1c, T2, T3, T4b, N0 to 1, and M0) were enrolled. At a median follow-up of 56 months, there was no significant difference in terms of OS (hazards ratio, 1.16; P =.38), PFS (hazards ratio, 1.15; P =.27), and time to LRR (hazards ratio, 1.13; P =.61). Fifty-seven patients (23%) were downstaged by the preoperative chemotherapy, whereas 14 patients (18%) underwent mastectomy and not the planned breast-conserving therapy [13]. Pathological complete response as a surrogate endpoint for improved EFS and OS.The CTNeoBC pooled analysis We obtained data from 12 identified international trials and 11 955. Eradication of tumor from both breast and lymph nodes better associated with improved EFS (: hazard ratio [HR] 0·44, 95% CI 0·39-0·51;: 0·48, 0·43-0·54) and OS (0·36, 0·30-0·44; 0·36, 0·31-0·42) than was tumor eradication from the breast alone (; EFS: HR 0·60, 95% CI 0·55-0·66; OS 0·51, 0·45-0·58).. The association between pathological complete response and long-term outcomes was strongest in patients with triple-negative breast cancer (EFS: HR 0·24, 95% CI 0·18-0·33; OS: 0·16, 0·11-0·25) and in those with HER2-positive, hormone-receptor-negative tumors who received trastuzumab (EFS: 0·15, 0·09-0·27; OS: 0·08, 0·03, 0·22) [14]. Achieving pCR following NAT is associated with significantly better EFS and OS, particularly for triple-negative and $HER2^+$ breast cancer A Comprehensive Meta-analysis 27,895 patients. Patients with a pCR after NAT had significantly better EFS (HR = 0.31; 95% PI, 0.24-0.39), particularly for triple-negative (HR = 0.18; 95% PI, 0.10-0.31) and $HER2^+$ (HR = 0.32; 95% PI, 0.21-0.47) disease. Similarly, pCR after NAT was also associated with improved survival (HR = 0.22; 95% PI, 0.15-0.30). The association of pCR with improved EFS was similar among patients who received subsequent adjuvant chemotherapy (HR = 0.36; 95% PI, 0.19-0.67) and those without adjuvant chemotherapy (HR = 0.36; 95% PI, 0.27-0.54), with no significant difference between the two groups ($P$ = 0.60) [15]. Hormonal status for ER, HER2 were not significantly different in primary breast carcinomas before and after neoadjuvant chemotherapy. A single institutional experience of the 38 carcinomas studied, 45% were positive for ER by IHC both pre- and post- neoadjuvant treatment (P=1.00). IHC studies for PR in these 38 patients showed 37% positivity for PR pre-neoadjuvant therapy and 21% positivity post-treatment (p=0.03). For 37 patients with HER2 IHC, 32% were positive pre-treatment, and 22% were positive post-treatment (P = 0.20). For 7 patients, HER2 FISH was positive in 71% pre-therapy and in 57% post-treatment (P=0.32) [16].

**Objective of the Study**

**General Objective**

To describe magnitude of Pathological complete response and clinical responses in locally advanced breast cancer patients receiving NAC

- **Specific objectives**To describe Pathological complete response in locally advanced breast cancer patients receiving NAC
- To describe clinical response in LABC
- To describe factors associated with PCR in LABC
- To describe factors associated with clinical response in LABC

**Methodology**

**Study Design**

Institution based Cross sectional study design was used.

**Study area and period**

The study area was oncology department of Tikur Anbessa Specialized Hospital from January 1st, 2021 to June 1st, 2022. Tikur Anbessa Specialized Hospital (TASH) is a tertiary hospital located in Addis Ababa, which is a capital city of the country. It is the largest & oldest public hospital of the country, providing high level of clinical care for millions of people and training to health science students from different parts of the country and from the Horn of Africa. The hospital has the leading oncology center in the country, providing tertiary specialist care for a catchment population of approximately 100 million people from different parts of the country with a range of malignancies. It provides palliative and curative therapy for all patients with histopathologically -proven arrange of cancers, including breast cancers. The Clinical Oncology Department of TASH is among the most commonly visited units in the hospital. On average, at least 10,000 cancer patients are evaluated annually in this facility. The department caters oncologic service to a wide range of population with varying demographic, clinical characteristics, and social background.

**Source population**

All locally advanced breast cancer patients visited at Tikur Anbessa Hospital oncology center.

**Study population**

Patients diagnosed locally advanced breast cancer and took NACT at Tikur Anbessa specialized Hospital oncology center from January 1st, 2021 to June 1 2022.

**Inclusion and Exclusion Criteria**

**Inclusion criteria**

- Biopsy confirmed locally advanced breast cancer cases
- Patients who are on treatment in Tikur Anbessa Hospital oncology center
- Adequate clinical, laboratory and imaging information

**Exclusion criteria**

- Patients outside the study period
- Patients who refused to be part of the study
- Patient discontinued NACT

**Study Variables**

**Dependent variable**

- Clinical response
- Pathological response

**Independent variables**

- Demographic characteristics such as sex, and age
- Clinical profile of breast cancer patients
- Tumor characteristics and stage of the disease

**Sampling Methods**

All eligible patients with diagnosis of locally advanced breast cancers will be included into the study.

**Sample size determination**

All patients who took NACT for locally advanced breast cancer from January 1st, 2021 to June 1 2022 and fulfilled the inclusion criteria were considered in the study without the need to do a separate sample size calculation.

**Data collection tools and procedures**

Data was collected from Oncology unit of TASH using a structured checklist containing closed ended questions specifically designed for the study. The tool was prepared by reviewing related literatures done in other areas. The data collected from the medical chart of each participant by two trained health professionals, under close supervision and facilitation by the principal investigator. Each day, the collected data checked for accuracy and completeness.

**Operational Definitions**

**Staging :**Breast cancer stage of the patients based on TNM staging primarily sourced from AJCC cancer staging manual, eighth edition (2017) [17]. It can be clinical mainly based on imaging if the patient presentation is pre-op or pathological based on histopathological and imaging study if the patient presentation is post op.

**Performance status**: The scales and criteria are used to assess general well-being and activities of daily life, to determine appropriate treatment and prognosis.

**Treatment response**: The method to monitor how the cancer is responding to the treatment provided, from information acquired clinically, by imaging and/or tumor markers. The RECIST criteria is one of the tools widely used to monitors treatment response in solid tumors.

**Complete Pathological response**: Defined as having no residual invasive tumor in the breast surgical specimen removed following neoadjuvant therapy. Patients who had only ductal carcinoma in situ (DCIS) in the breast tissue following neoadjuvant therapy were considered to have a pCR [21].

**Locally advanced breast cancer** :defined as subset of patients with stage IIB disease (T3N0) and patients with stage IIIA to IIIC disease .This includes patients with T3 (>5 cm) or T4 tumors (chest wall fixation or skin

ulceration and ) and N2/N3 disease (matted axillary and/or internal mammary metastases) [22,23].

### Data quality Assurance

An English version of the checklist used to collect data Brief training for the data collectors (two health professionals) about the process of data collection will be given before the process of data collection. Close supervision maintained during data collection and filled checklist double-checked daily for consistency and completeness by data collectors and principal investigator.

### Methods of data analysis

The data collected was analyzed using SPSS statistics software version 26 (SPSS Inc., Chicago,IL). Basic descriptive analyses like frequency, mean, median, percentile and Quartile ranks were used. Chi-square test was done for test of association using level of significance set at 5%.

### Ethical considerations

This study started after obtaining ethical approval from ethical review board of clinical oncology department. Verbal consent was taken prior to proceeding with the phone conversations. Patients 'confidentiality was protected at all times. The researcher and the data collector followed ethical principles and anticipated any ethical dilemma to ensure all participants were protected against any potential harm. The name of patients stayed unspecified and the data collection was restricted to the objectives listed above**.**

## Chapter Five: Result

### Socio demographic characteristics

There were total of 41 patients that were included in the study, and 40 (97.6%) of the study participants were females while only one (2.4%) of the participants was male. The Age of the participants ranged from 22 years- 71 years with a mean age of 41.93±11.18 years. 23 (56.1%) of the study participants resided in Addis Ababa while the rest 18(43.9%) came from outside Addis Ababa. Corresponding to marital status 27 (65.9%) were married, while 7 (17.1%) were divorced/widowed and 7 (17.1%) of the study participants were single. Considering job status 11(26.8%) of study populations are civil servants, 6(14.6%) daily laborer, 3(7.3%) farmer, 2(4.9%) and the rest are house wife 19 (46.3%) (See Table 1).

### Clinical Characteristics of Patients and workup at Diagnosis

Considering overall clinical characteristics of participants at presentation, all total study participants presented compliant was breast lump. The predominant finding on physical examination was breast lump 27(65.9%) while concomitant axillary lymphadenopathy with breast lump was seen in 14(34.1%) of the study participants.

**Table 1:** Socio demographic data.

| Variable | | Frequency(n) | Percent (%) |
|---|---|---|---|
| **Age** | Min=22, max= 71, mean ± SD 41.93±11.18 Median = 41 | | |
| **Age stratified** | <50 yr | 31 | 75.6% |
| | >=50yr | 10 | 24.4% |
| **Gender** | Female | 40 | 97.6% |
| | Male | 1 | 2.4% |
| **Job** | Civil servant | 11 | 26.8 |
| | Daily laborer | 6 | 14.6 |
| | Farmer | 3 | 7.3 |
| | Merchant | 2 | 4.9 |
| | House wife | 19 | 46.3 |
| **Marital status** | Married | 27 | 65.9 |
| | Divorced/widowed | 7 | 17.1 |
| | Single | 7 | 17.1 |
| **Address** | A. A | 23 | 56.1 |
| | Outside A. A | 18 | 43.9 |
| **Religion** | Orthodox | 25 | 61 |
| | Protestant | 6 | 14.6 |
| | Muslim | 10 | 24.4 |

**Table 2:** Clinical Characteristics of Patients and workup at Diagnosis.

| Variable | | Frequency, n | Percent, % |
|---|---|---|---|
| **Comorbidity** | Yes | 8 | 19.5 |
| | No | 33 | 80.5 |
| **Complaint at presentation** | Breast lump | 41 | 100 |
| **Pertinent P/E finding** | Breast lump | 27 | 65.9 |
| | Breast lump + axillary LAP | 14 | 34.1 |
| **ECOG at presentation** | 0 | 4 | 9.8 |
| | I | 36 | 87.8 |
| | II | 1 | 2.4 |
| **Clinical TNM stage** | | | |
| **cT stage** | T2 | 1 | 2.4 |
| | T3 | 5 | 12.2 |
| | T4 | 35 | 85.4 |
| **cN stage** | N0 | 16 | 39.0 |
| | N1 | 21 | 51.2 |
| | N2 | 4 | 9.8 |
| **Clinical group stage** | Stage IIb | 2 | 4.9 |
| | Stage IIIa | 8 | 19.5 |
| | Stage IIIb | 31 | 75.6 |
| **Diagnostic work up** | | | |
| **Breast imaging, n=8** | Mammography | 3 | 7.3 |
| | Breast U/S | 5 | 12.2 |
| **FNAC** | Ductal carcinoma | 38 | 92.7 |
| | Lobular carcinoma | 1 | 2.4 |
| | Malignant Breast carcinoma | 2 | 4.9 |
| **Core needle biopsy** | Invasive Ductal carcinoma | 3 | 7.3 |
| | Not done | 38 | 92.7 |

Additionally, 8 (19.5%) had comorbidity and almost all 40(97.6%) patients had ECOG 0-1 while only one (2.4%) patient had ECOG 2 at presentation. Clinically, cT4 disease represented 85.4% (n=35), cT3 12.2% (n=5), and axillary node-positive were 61% (n=25) from which 21 (51.2%) and 4 (9.8%) were cN1 and cN2 respectively, at presentation. Considering clinical stage of the disease at presentation, 31(75.6%) had stage IIIb disease, 8(19.5%) had stage IIIa disease and the rest 2 (4.9%) had stage IIb disease. (See Table 2). Among the study participants, all had FNAC biopsy, and 3 (7.3%) had both FNAC and Core Needle Biopsy (CNB). Almost all patients 38 (92.7%) FNAC results were reported as ductal carcinoma, and only 1 (2.4%) was lobular carcinoma and the rest 2 (4.9%) were reported as "malignant breast carcinoma". All CNB results were reported as invasive ductal carcinoma (IDC) (See Table 2).

**Treatment regimens, surgical interventions and Clinical response**

Regarding the treatment, majority of treatment decisions 85.4% were made on MDT (multidisciplinary meeting), while 12.2% and 2.4% were individually decided by oncologist and surgeon respectively. Considering the type of treatment regimens, ACT-T was given for 37(90.2%) patients, AC was given for 3(7.3%) and FAC was given only in one case. Among the study participants, majority 32 (78%) of patients received eight cycles of NACT, while eight (14.6%) and one (2.4%) received four cycles and seven cycles respectively. Whereas, regarding surgical intervention following chemotherapy, MRM was done in 37 (90.2%) of cases and in the rest 4 (9.8%) cases were not operated (Table 3).

On mid-cycle partial clinical response was seen in 30 (73.2%) cases, 10 (24.4%) were stable, and complete response was seen only in one (2.4%) case. In majority of cases 33 (80.5%) the mid-cycle treatment plan was to continue the NACT treatment whereas, in 8 (19.5%) cases definitive surgery was planned. All patients had ECOG-1 on mid-cycle assessment (Table 3). At end-cycle clinical assessments of patients, partial clinical response accounted 22 (53.7%), complete clinical response accounted for 9(22%), local progression of tumor seen in 4 (9.8%) and 6 (14.6%) cases had stable disease. All patients had ECOG-1 on end-cycle assessment. Overall,

**Table 3:** Treatment decisions.

| Variable | | Frequency (n) | Percent (%) |
|---|---|---|---|
| **Frist treatment decision after diagnosis** | MDT | 35 | 85.4 |
| | Oncologists | 5 | 12.2 |
| | Surgeon | 1 | 2.4 |
| **Type of Surgery** | MRM | 37 | 90.2 |
| | Inoperable | 4 | 9.8 |
| **Type of CT given** | ACT-T | 37 | 90.2 |
| | AC | 3 | 7.3 |
| | FAC | 1 | 2.4 |
| **Cycles of CT given** | 8 cycles | 32 | 78.0 |
| | 4 cycles | 8 | 19.5 |
| | 7 cycles | 1 | 2.4 |
| **Mid cycle clinical response** | Complete | 1 | 2.4 |
| | Partial | 30 | 73.2 |
| | Stable | 10 | 24.4 |
| **ECOG at midcycle** | Stage I | 41 | 100% |
| **Mid cycle plan** | Continue same Rx | 33 | 80.5 |
| | Surgery | 8 | 19.5 |
| **ECOG at end cycle** | Stage I | 41 | 100 |
| **End cycle response** | Complete | 9 | 22.0 |
| | Partial | 22 | 53.7 |
| | Progression (local) | 4 | 9.8 |
| | Stable | 6 | 14.6 |
| **Clinical response** | Yes (Partial & complete) | 31 | 75.6 |
| | No (Stable & progression) | 10 | 24.4 |
| **End cycle plan** | Surgery | 37 | 90.2 |
| | Second line CT | 3 | 7.3 |
| | Hormonal therapy | 1 | 2.4 |
| **Sequence of treatment given** | NACT followed by Surgery | 29 | 70.7 |
| | NACT followed by Surgery followed by CT | 8 | 19.5 |
| | NACT->second line CT or HRT | 4 (progressed cases) | (9.8%) |

patterns of the sequences of treatment received by the patients were: 29 (70.7%) NACT followed by surgery, 8 (19.5%) NACT followed by surgery followed by chemotherapy, and NACT followed by second line or hormonal therapy (HRT) accounted 9.8% (4) given for patients having progressed or stable disease. Finally, in majority of cases 37 (90.2%) the end-cycle plan was surgery, while second line CT was planned in 3 (7.3%) cases, and HRT was planned in only one case (Table 3 and Figure 1).

### Pathologic response and pathologic parameters

Infiltrative ductal carcinomas accounted for 26 (86.7%) of the cases, while 3 (10%) had infiltrative lobular and only 1 (3.3%) was mucinous carcinoma. From the total study participants for 11 (26.8%) histologic subtype of the original tumor was unknown, because it was originally diagnosed by FNAC or because complete pathologic response was seen at the time of definitive surgery or definitive surgery was not due to progression at end cycle response assessment. Among patients having known histologic type of tumor pathologic grade was done, and majority of cases 12(40%) were poorly differentiated (grade3), 10 (33.3%) were well differentiated (grade1) and the rest 8(26.7%) were moderately differentiated (grade2). Margin status was reported as free (not involved) in 23 (76.7%) and positive (involved) in 4 (13.3%), however margin status was not stated on the pathologic biopsy-report of 3 (10%) of cases. Lymphovascular invasion (LVSI) and perineural invasion (PNI) was reported in 56.7% (17) and 53.4% (16) of cases. LVSI was seen in 11 (36.7%) of cases, while PNI was seen in 8(26.7%) (Table 4). Concerning pathologic staging, pT2 was reported to be found in 9 (30%), while pT3 and pT4 were found ion 10(33.3%) and 11(36.7%) of cases respectively, pN0, pN1 and pN2 accounted for 3(10%), 19(63.3%) and 8(26.7%) of the cases respectively. However, the number of lymph nodes harvested was inadequate in the majority

**Table 4:** Pathological parameter and pathologic stage.

| Variable | | Frequency, n | Percent, % |
|---|---|---|---|
| **Pathological response, n=37** | Complete response seen | 7 | 18.9 |
| | Complete response not seen | 30 | 81.1 |
| **Histologic sub-type, n=30** | IDC | 26 | 86.7 |
| | ILC | 3 | 10.0 |
| | Mucinous | 1 | 3.3 |
| **Grade(differentiation)** | Well | 10 | 33.3 |
| | Moderately | 8 | 26.7 |
| | Poorly | 12 | 40.0 |
| **Margin status** | Not involved | 23 | 76.7 |
| | Involved | 4 | 13.3 |
| | Not reported | 3 | 10.0 |
| **Hormonal status** | ER PR+ve Her2-ve | 5 | 16.7 |
| | Her2+ve | 2 | 6.6 |
| | Triple –ve | - | - |
| | Not done | 23 | 76.7 |
| **Number of LN harvested** | Adequate | 13 | 43.3 |
| | Inadequate | 17 | 56.7 |
| **LVSI** | Yes | 11 | 36.7 |
| | No | 6 | 20.0 |
| | Not reported | 13 | 43.3 |
| **PNI** | Yes | 8 | 26.7 |
| | No | 8 | 26.7 |
| | Not reported | 14 | 46.7 |
| **Pathologic staging** | | | |
| **T** | T2 | 9 | 30.0 |
| | T3 | 10 | 33.3 |
| | T4 | 11 | 36.7 |
| **N** | N0 | 3 | 10.0 |
| | N1 | 19 | 63.3 |
| | N2 | 8 | 26.7 |
| **Pathologic stage group** | Stage IIA | 1 | 3.3 |
| | Stage IIB | 9 | 30.0 |
| | Stage IIIB | 8 | 26.7 |
| | Stage IIIC | 12 | 40.0 |

of cases 17 (56.7%). Considering the pathologic stage group, 40% (12) of cases were stage IIIc, 26.7% (8) cases were stage IIIb, 30% (9) cases were stage IIb and one case was stage IIa. Hormonal status was done only in 7 (23.3%) of cases, among which 5 (16.7%) were ER, PR (+ve) HER2 (-ve) and 2 (6.6%) were HER2 (+ve). (Table 4). Overall, among patients who have MRM the pathologic response rates were as follows: complete pathologic response, 18.9% (7); non-complete pathologic response, 81.1% (30) (Table 4), (Figure 1).

### Determining factors of Clinical and pathologic response

Clinical response (complete and partial) was significantly related to cN stage at the time of diagnosis (p=0.014). Clinical response (complete and partial) was more prevalent in patients having cN0 and cN1 stage 48.8% (n=15) each, whereas in cN2 the clinical response was seen only in one patient. Additionally, clinical stage of disease at presentation was the only variable significantly related to pathologic complete response (P=0.025). The majority of patients 80% (n=24) that didn't show complete pathological response had clinical stage IIIb disease and the rest 20% (n=6) had clinical stage IIIa disease at presentation. Considering age of patients, among patients that show complete clinical response 22 (71%) were age <50 years and 9 (29%) were age 50 year and above. But there were no statistically significant differences according to the clinical and pathological response in terms of

**Table 5:** Distribution of Clinical and pathologic response according to determining factors.

| Variable | | Clinical response,n=41 | | pvalue | Pathological complete response (n= 37), n (%) | | pvalue |
|---|---|---|---|---|---|---|---|
| | | Yes | No | | Yes | No | |
| **Age** | <50 | 22(71%) | 9(90%) | 0.40 | 4(57.1%) | 23(76.7%) | 0.36 |
| | >=50 | 9(29%) | 1(10%) | | 3(42.9%) | 7(23.3%) | |
| **cT staging** | T2 | 1(3.2%) | - | 0.48 | - | 1(3.3%) | 0.07 |
| | T3 | 5(16.1%) | - | | 3(42.9%) | 2(6.7%) | |
| | T4 | 25(80.6%) | 10(100%) | | 4(57.1%) | 27(90%) | |
| **cN staging** | N0 | 15(48.4%) | 1(10%) | 0.014 | 2(28.6%) | 14(46.7%) | 0.45 |
| | N1 | 15(48.4%) | 6(60%) | | 5(71.4%) | 13(43.3%) | |
| | N2 | 1(3.2%) | 3(30%) | | - | 3(10%) | |
| **Histologic sub-type** | IDC | 21 (87.5%) | 5 (83.3%) | 0.61 | | | |
| | ILC | 2 (8.3%) | 1 (16.7%) | | | | |
| | Mucinous | 1 (4.2%) | - | | | | |
| **Grade (Differentiation)** | 1 | 7(29.2%) | 3(50%) | 0.62 | - | - | - |
| | 2 | 7(29.2%) | 1(16.7%) | | - | - | - |
| | 3 | 10(41.7%) | 2(33.3%) | | - | - | - |
| **cGroup stage** | IIb | 2(6.5%) | - | 0.12 | 2(28.6) | - | 0.025 |
| | IIIa | 8(25.8%) | - | | 2(28.6%) | 6(20%) | |
| | IIIb | 21(67.7%) | 10(100%) | | 3(42.9%) | 24(80%) | |

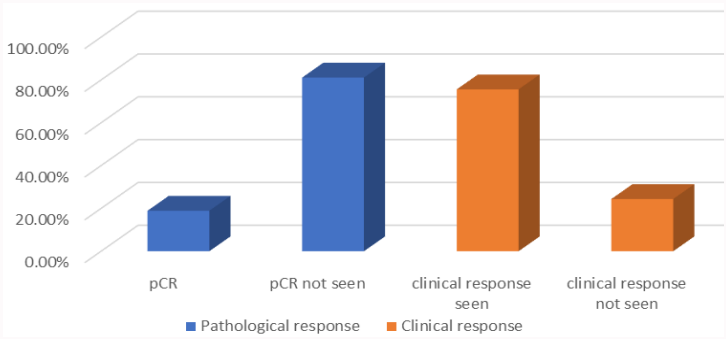


**Figure 1:** Distribution of pathological and clinical response.

age, histologic sub-type and pathologic grade (differentiation) of tumor (p>0.05) (Table 5). Comparison between clinical and pathologic response was also done. Based on end cycle clinical assessment, 7 of the 9 patients (77.8%) who were considered as complete clinical responder, in fact, had pathological complete response (pCR).

## Discussion

In our study the majority of patients with LABC were younger female patients, median age of 41 years, which is 21 years younger than the western population median (62 years). Our finding is in line with other study done in Egypt, which shows the first presentation of LABC 10 years younger than the western population with median age (65 years) [27]. In our study clinical stages IIIA and IIIB accounted 8 (19.5%) and 31 (75.6%) of LABC cases respectively. This is in concordance with previous studies done in Sudan were the number of patients with clinical stage IIIA 13 (13.3%) and IIIB 77 (78.6%) [30, 14, 31, 32]. The use of NACT to treat locally advanced breast cancer has been shown to be effective. In our study, the overall clinical response rate was 75.6% (n=31). This finding was comparable to other prior studies done in Sudan, Bangladesh, India, and USA which shows 83.6%, 88%, 80.4% and 80% of the clinical response rate respectively [9, 24, 25, 26]. Considering nodal status, the cN stage of patients at presentation was found to be significantly associated with the clinical response (p=0.014). Clinical response (complete and partial) was more prevalent in patients having cN0 and cN1 stage 48.8% (n=15) each, whereas in cN2 the clinical response was seen only in one patient. This was in line with a study done in Bangladesh which showed that Clinical response was higher in patients having cN0 and cN1 stage 100% and 91% respectively, whereas in cN3 the clinical response was seen in 5% 0f patients [24]. Considering the pathological grade (differentiation) of tumor, in our study 41.7% of patients who had clinical response were

Grade 3 tumor, which is in line with other studies where it was found that the better responses could be achieved in rapidly proliferating tumors with a higher grade. Also, in our study the majority of patient with clinical repose are high grade However, it was statically not significant [9,24, 28, 29, 23]. The pathological complete response of LABC after using NACT was seen in 7 patients which were 18.9% of those patients who undergone surgical intervention. Our result was comparable to other prior study done in Brazil and Egypt which were16.5% and 16% respectively [33, 8]. Additionally, clinical stage of disease at presentation was the only variable significantly related to pathologic complete response (P=0.025). The majority of patients 80% (n=24) that didn't show complete pathological response had clinical stage IIIb disease and the rest 20% (n=6) had clinical stage IIIa disease at presentation [30, 14, 31, 32]. Considering hormonal status and cPR prior studies shows patient with triple negative and Her2 positive have higher cPR. A Study in USA shows rates of pCR in both the breast and axilla were 38.2% in triple-negative, 45.4% in HER2-positive, and 11.4% in hormone-receptor-positive, HER2-negative disease ($P<$ 0.0001). However, in our study only seven patients were hormonal status determined and for all patients with cpr hormonal status determination were not done [10].

**Strengths and Limitations of The Study**

**Strengths**

- This is the first study to describe Pathological complete response and clinical responses in locally advanced breast cancer patients receiving NAC
- The study was conducted at TASH which was the Preferred referral hospital in the country were patient came from all part of Ethiopia and may represent the majority of the society of the country at large.
- I took all patients in the study time to increase the sample size which increases the representativeness of the results.

**Limitations**

- Although we chose longer study time the number of patient small which decrease the power of the result.
- Most of study participant hormonal status not determined and we were unable to assess the association with hormonal status.

**Conclusions and Recommendation**

Neoadjuvant chemotherapy can achieve a high clinical response, and there is also complete pathological response in some patients with locally advanced breast cancer. Although the entire patients in our study undergone MRM it was possible to do Breast Conserving Surgery (BCS) in some of the patient after NACT. We recommend further research to find Predictors for response. All patient should have core needle biopsies with hormone status determination before starting NACT because for those patients with cPR it is impossible to do after surgery this not only affect our prediction to response NACT but also future adjuvant hormonal treatment of the patient. Further study to determine the contribution of response to NACT to survival should be done.

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