NEOADJUVANT CHEMOTHERAPY RESPONSE AMONG PATIENTS WITH LOCALLY ADVANCED BREAST CANCER AT TIKUR ANBESSA SPECIALIZED HOSPITAL (TASH), ADDIS ABABA, ETHIOPIA

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List of Abbreviations

AAU……. Addis Ababa University

AC …… Doxorubicin + Cyclophosphamide

AC – T ……. Doxorubicin + Cyclophosphamide + paclitaxel

AJCC ……. American Joint Committee on Cancer

cCR……... Complete Clinical Response

CHS ……. College of Health Science

ECOG …… Eastern Cooperative Oncology Group

ER/PR……. Estrogen Receptor/Progesterone Receptor

FNAC …… Fine Needle Aspiration Cytology

HER2 …… Human Epidermal growth factor Receptor 2

LABC …… Locally Advanced Breast Cancer

MRM…… Modified Radical Mastectomy

MDT……. Multidisciplinary Team

NACT…… Neoadjuvant Chemotherapy

OR…… Odds Ratio

pCR…… Pathologic Complete Response

PD …… Progressive Disease

PR …… Partial Response

RECIST ……... Response Evaluation Criteria in Solid Tumors

SD …… Stable Disease

TASH ……...Tikur Anbessa Specialized Hospital

Summary

Background: Breast cancer is the leading cause of cancer death among females globally. In sub-Saharan African countries, a high proportion of breast cancers are locally advanced breast cancer (LABC) or metastatic at the time of diagnosis. LABC is primarily treated by neoadjuvant chemotherapy (NACT) before surgery. There is no data on response rate and resectability of LABC after NACT in Ethiopia.

Objective: The objective of this study is to assess the rate of clinicopathologic response and rate of resectability of LABC after NACT at Tikur Anbessa Specialized Hospital (TASH), Ethiopia.

Methods: This is a retrospective study which assesses response and resectability of LABC after NACT at TASH from September 2017 G.C to August 2019 G.C. Patients who were evaluated at breast multidisciplinary team (MDT) clinic by Breast surgeon and Oncologist and decided to receive upfront chemotherapy to downstage the tumor were included in this study. Patients were given 4 cycles of NACT with AC (doxorubicin + cyclophosphamide) or 8 cycles of NACT with AC – T (4 cycles of AC + 4 cycles of paclitaxel). After chemotherapy patients were revaluated at MDT for modified radical mastectomy (MRM). Data were collected from patient charts and filled on, cleared for completeness, analyzed using SPSS 25 software.

Results: A total of 141 breast cancer patients were presented to the MDT. Of which 63 patients were decided to undergo upfront surgery and 78 patients to receive neoadjuvant therapy. Of the 78 patients who received neoadjuvant therapy only 51 patients were eligible for the study. The mean age of patients was 40.1 ± 9.96 SD years old (24-65). 11 patients (21.6 %) had complete clinical response (cCR), 31 patients (60.8 %) had clinical partial response (PR), 3 patients (5.9 %) had stable disease (SD) and 6 patients (11.8 %) had progressive disease (PD) after NACT. Forty-one patients (80.4 %) undergo mastectomy, 23 patients (56.1 %) had negative margins, 16 patients (39 %) had positive margins and in 2 patients (4.9 %) the surgical margin status was not mentioned. Only 4 patients (9.8 %) had complete pathologic response (pCR) after NACT. Patients who took AC – T (NACT) had a higher overall clinical response rate ($p = 0.099$) and cCR ($p = 0.037$) but not statistically significant compared to patients who took AC NACT. Older patients ($\geq$ 50 years old) with LABC had higher complete pathologic response but not statistically significant after NACT during pathologic assessment compared to patients below the age of 50 years ($p = 0.062$).

Conclusion: The study has shown administering neoadjuvant chemotherapy either with AC or AC – T has decreased the tumor size significantly to make it resectable with a clear margin. AC – T had a slightly higher overall response rate and complete clinical response rate.

Chapter One: Introduction

1.1. Background

Worldwide, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 25% of cancer cases and 15% of cancer deaths (1). It is increasing in less-developed countries, likely related to changes in lifestyle factors (1). Breast cancer has now become the most commonly diagnosed cancer in women in several sub-Saharan African countries including Ethiopia (2).

Patients in sub-Saharan Africa have poor breast cancer outcomes by the standards of high-income countries; an estimated 50%–80% of breast cancers are locally advanced breast cancer (LABC) or metastatic at the time of diagnosis. Various factors like lack of education and poor socio-economic status are possible factors behind LABC or metastatic breast cancer in sub-Saharan countries (3,4,5). Women with breast cancer in Africa have been reported to have an earlier age at presentation and a higher proportion of more aggressive subtypes than women of European descent (6). However, a study was done in Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia revealed that 43% - 65% of women present with the less aggressive, hormone-responsive luminal A and B breast cancer subtypes (7). Women with breast cancer in Ethiopia usually present late and are expected to have a very limited life span (8).

Patients who present with LABC require care from a multidisciplinary team (MDT) that includes radiologists, pathologists, surgical oncologists, medical oncologists, and radiation oncologists. LABC is most appropriately treated with multimodality therapy using systemic therapy (generally chemotherapy and, when appropriate, endocrine and human epidermal growth factor receptor 2 (HER2)-directed therapy), surgery, and radiation aimed at eradicating all disease in the locoregional area and preventing distant disease recurrence (9).

LABC can present as either operable or inoperable disease. In general, the disease is considered to be inoperable if an initial surgical procedure is unlikely to completely resect all gross disease with the achievement of negative surgical margins. The inoperable disease requires the administration of upfront systemic therapy (neoadjuvant therapy) usually in the form of

chemotherapy or in certain situations endocrine therapy to reduce tumor volume in order to facilitate definitive local therapy. Patients who have an operable disease at the time of presentation have the option of either receiving neoadjuvant chemotherapy or proceeding directly with definitive surgery followed by adjuvant systemic therapy at a later date (9).

Neoadjuvant therapy refers to the systemic treatment of breast cancer before definitive surgical therapy (ie, preoperative therapy). For most patients with hormone receptor-positive disease, we recommend chemotherapy in the neoadjuvant setting rather than endocrine therapy. Chemotherapy is associated with higher response rates in a shorter time period. For select patients with the hormone-positive disease, neoadjuvant endocrine therapy may be an appropriate option. For patients with HER2-positive breast cancer, a HER2-directed agent (eg, trastuzumab with or without pertuzumab) should be added to the chemotherapy regimen (10).

Randomized clinical trials have found no significant difference in long-term outcomes when systemic therapy is given before or after surgery (11,12). The introduction of neoadjuvant chemotherapy (NACT) in LABC has advantages like the initiation of early systemic therapy, delivery of drugs through intact vasculature, down-staging of tumors, which in turn makes inoperable tumors operable and renders tumors suitable for breast-conserving surgery. NACT also allow for an *in vivo* assessment of chemosensitivity, permitting a regimen change that would not otherwise be made with traditional post-operative adjuvant treatment (12,13,14)

The use of preoperative systemic therapy may provide important prognostic information based on response to therapy. Achieving a pathologic complete response(pCR) to neoadjuvant therapy is associated with favorable disease-free and overall survival in early-stage breast cancer. The correlation between pathologic response and long-term outcomes in patients with early-stage breast cancer is strongest for patients with triple-negative breast cancer, less so for HER2-postive disease, and least for hormone-positive disease (15,16,17).

In Ethiopia, there is no government hospital laboratory with immunohistochemistry for tumor receptor status except in a private setting. Even in the non – government laboratories, they send

the tissue sample to abroad for tumor receptor examination. So, most breast cancer patients do not know their tumor receptor status except for few patients who can afford it.

Despite that in Tikur Anbessa Specialization Hospital (TASH), Addis Ababa, Ethiopia, patients with LABC are approached via a multidisciplinary tumor board whether to treat them with upfront surgery or available neoadjuvant chemotherapy (NACT) depending on the stage or tumor resectability and no data is available regarding the rate of response, rate of resectability and long term outcome of breast cancer patients after NACT. Although this study is premature to report on the long-term outcome, it will try to provide insights about the rate of response and resectability of patients with LABC after NACT in TASH.

1.2. Statement of the Problem

Breast cancer is the most common and second leading cause cancer death in women globally. Patients with breast cancer can present with early, loco-regional, and metastatic disease at diagnosis. Neoadjuvant therapy is one of the treatment modalities for loco-regional disease.

According to the Addis Ababa cancer registry in TASH, Breast Cancer is the most common solid malignancy diagnosed. There is no nationwide screening for breast cancer including a high-risk group population and most of the patients present with advanced disease. Even though TASH is the only oncology center with a radiation therapy machine in the country, different centers across the country deliver available chemotherapy to breast cancer patients.

Most of the patients cannot afford breast tumor receptor status which is important in the management and prognosis of breast cancer patients, despite those patients with LABC in TASH are given available NACT based on multidisciplinary tumor board decisions. It is the author's observation that patients with LABC are being treated with NACT in TASH but there are no data regarding the rate of response and resectability of patients with LABC after NACT.

1.3. Significance of the Study

The study will be the first of its kind to report on the rate of response and resectability of patients with LABC in Ethiopia. Not only it can encourage other centers to exercise such treatment, but it can also be used to advocate for adopting standard treatment for patients with LABC in Ethiopia. It can initiate further researches and can be used as base line data. It will also direct policy makers on what aspects need to be improved.

Chapter Two: Literature review

Although chemotherapy was traditionally administered after surgery, preoperative systemic therapy, also referred to as neoadjuvant therapy, with either chemotherapy or endocrine therapy is increasingly also an option. Neoadjuvant systemic therapy is reserved for women with locally advanced breast cancer (LABC) to enhance the likelihood of negative surgical margins and used for downstaging, to increase the likelihood of breast conservation in select women who are not initially lumpectomy candidates. However, the absolute increase in the number of women ultimately treated with breast conservation after preoperative systemic therapy is small. (18)

Patients most likely to be converted to breast conservation therapy with neoadjuvant chemotherapy are those with unicentric, higher grade, *HER2*-positive, or triple-negative cancers because these cancers often respond dramatically to chemotherapy (19). Some chemotherapy regimens have activity in the preoperative setting. Those regimens recommended in the adjuvant setting may be considered in the preoperative setting (20).

Early prospective, randomized trials of patients with operable breast cancer demonstrated clinical response rates to neoadjuvant chemotherapy ranging from 50% to 85% and pathologic complete response (pCR) rates in the breast ranging from 15% to 40%, (21,22) whereas more recent trials that have focused on the triple-negative and HER2-positive subtypes report pCR rates that exceed 50% (23-26). With increasing response rates, the number of women initially felt to require mastectomy who become candidates for beast conservative surgery has increased from 25% to 30% to 40% to 45%; yet, many women still require or choose mastectomy (21,22,26).

In the landmark National Surgical Adjuvant Breast and bowel Project B – 18 (NSABP B – 18) trial done in the United States and Canada which randomized 1,523 patients with operable breast cancer to receive neoadjuvant doxorubicin and cyclophosphamide (AC) for 4 cycles followed by surgery versus surgery followed by 4 cycles of AC found that after NACT breast tumor size was reduced in 80% of patients; 36% had a complete clinical response (cCR). 26% of women with a cCR had a pCR. Clinical nodal response occurred in 89% of node-positive

patients: 73% had a cCR and 44% of those had a pCR. Although overall survival and recurrence rates are similar between the two groups, patients who achieved a pCR in the breast after neoadjuvant chemotherapy had improved DFS and OS compared to those who did not particularly in younger patients (27).

In another land mark trial NSABP B – 27 done in the United States and Canada which randomized 2,411 patients with operable breast cancer to receive either four cycles of preoperative AC followed by surgery (group I), or four cycles of AC followed by four cycles of docetaxel, followed by surgery (group II), or four cycles of AC followed by surgery and then four cycles of docetaxel (group III) found that compared to preoperative AC alone, preoperative AC followed by docetaxel increased the clinical complete response rate (40.1% *v* 63.6%; $P <$ .001), the overall clinical response rate (85.5% *v* 90.7%; $P <$ .001), the pathologic complete response rate (13.7% *v* 26.1%; $P <$ .001), and the proportion of patients with negative nodes (50.8% *v* 58.2%; $P <$ .001). The addition of preoperative or postoperative T after preoperative AC did not significantly affect OS, slightly improved DFS, and decreased the incidence of local recurrences (28).

In European Organization for Research and Treatment of Cancer trial (EORTC 10902 trial) done in Europe which randomized 648 non-metastatic breast cancer patients to receive four cycles of fluorouracil, epirubicin, and cyclophosphamide preoperatively and postoperatively found that 57 patients (23%) were down staged by the preoperative chemotherapy, whereas 14 patients (18%) underwent a mastectomy and not the planned breast-conserving therapy. The use of preoperative chemotherapy yields similar results in terms of PFS, OS, and locoregional control compared with conventional postoperative chemotherapy (22).

In studies done across the United States and Europe like NOAH trial, NeoSphere trial, BERENICE trial, and TRYPHAENA trial have shown that the combination of HER2 targeted therapy with chemotherapy preoperatively has increased the response rate for patients with HER2-positive breast cancer (23, 24,29,30).

There are little data on the response of breast cancer to NACT in low-resources developing African countries. In a single-center retrospective descriptive study done in Nigeria by Olukayode Adeolu Arowolo et al there were 350 cases of breast cancer seen during the study period (1982–2005), of which 62 patients (17%) had NACT (doxorubicin, cyclophosphamide, and 5-fluorouracil) for LABC. Of the 62 patients who completed three cycles of chemotherapy, the overall response rate was 51.8%, with complete clinical response seen in 4 patients (6.6%) and partial clinical response seen in 28 patients (45.2%). Twenty-one patients (33.9%) had no clinical response while three patients (4.8%) had progressive disease. Of the 41 patients who had six cycles of chemotherapy, complete clinical response was observed in 9 patients (21.9%) and partial clinical response in 12 patients (29.3%). There were no cases of complete pathological response. The study concluded that there was a poor overall clinical response rate to NACT in the Black population studied. Late presentation with large tumor mass may be accountable for this. (31)

In another study done in Nigeria by SNC Anyanwu et al 33 patients seen in the breast clinic from July, 2006 to March 2007 were recruited into the study. Patients received doxorubicin, 5-fluoro-uracil and cyclophosphamide by intravenous bolus or infusional injection on a three-weekly regimen. only 28 completed the treatment modality. One patient (3.6%) exhibited complete clinical response, 25 patients (89%) had a partial response and 2 had no response. The study concluded that Neo-adjuvant chemotherapy using anthracycline-based regimens is efficacious and safe in reducing tumor bulk in locally advanced breast cancers. (32)

In another prospective study done in Nigeria by Ochonma Amobi Egwuonwu et al which includes 114 patients of which the 31 patients who completed the four cycles of NACT (cyclophosphamide, Doxorubucin, and 5-Fluorouracil) 23 (74.2%) patients had more than 30% reduction in primary tumor size and 8 (25.8%) patients had no response. The response according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) methodology was 12.9% for a complete clinical response, 61.3% for partial response, and 25.8% for no response. Significant clinical response was seen in 74.2% of patients ($P < 0.0001$) (one-sample t-test). (33)

A study that was done in Johannesburg, South Africa by Paul Ruff et al which includes 554 non-metastatic breast cancer patients of which 195 received NACT (4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of paclitaxel (AC-T) or 6 cycles of 5-fluorouracil, doxorubicin, and cyclophosphamide) between 2009 to 2011. Of patients receiving NACT, 125 (64.1%) were evaluable for clinical response. Eighty (64.0%) patients had a clinically significant response; 19 (15.2%) patients had stable disease, and 26 (20.8%) patients had progressive disease. Multivariate analysis showed age <40 years and disease stage to be independently associated with the receipt of NACT. (34)

In TASH, Addis Ababa, Ethiopia new patients with locoregional breast cancer are evaluated on multidisciplinary tumor board bases for management decisions and most patients present with LABC. NACT is one of the treatment modalities. Even though patients with LABC have been given NACT as one of the treatment modalities, there is no data available on the rate of response and resectability of patients with LABC in TASH and other parts of the country. So, this study is the first study to provide on the rate of clinical and pathologic response and the rate of resectability of patients with LABC after NACT in Ethiopia.

Chapter Three: Objectives

3.1. General Objective

- To assess the rate of response and resectability of patients with LABC after NACT in TASH Oncology Center, Addis Ababa, Ethiopia

3.2. Specific Objectives

- To assess the **rate of clinical response** of patients with LABC after NACT
- To assess the **rate of pathological response** of patients with LABC after NACT
- To determine the rate of **R_0 resectability** of patients with LABC after NACT

Chapter Four: Methods and Materials

4.1. Study Area and Setting

The study was conducted in TASH, in the oncology center, Addis Ababa, Ethiopia. The oncology center was established in 1990 G.C. It has one functional cobalt 60 radiotherapy unit, one high dose rate brachytherapy unit, and recently installed one CT simulator and one Linear Accelerator Machine (LINAC). It has also more than 30 beds for in-patient chemotherapy admissions as well as beds for day care chemotherapy administration in the nearby branch health center. The most commonly administered chemotherapy in the day care is for breast cancer. The center had started training in clinical oncology in 2013 and is the only center providing clinical oncology residency training programs in the country.

4.2. Study Design

This is a retrospective cohort study that assessed response rate and resectability of LABC after NACT among patients treated between September 2017 G.C to August 2019 G.C.

4.3. Source Population

All new non-metastatic breast cancer patients that were seen in TASH oncology department by the multidisciplinary breast tumor board team from September 2017 G.C to August 2019 G.C.

4.4. Study Population

All cases of histopathology confirmed LABC patients that took NACT with at least 4 cycles of AC (Doxorubicin + cyclophosphamide) or 8 cycles of AC – T (Doxorubicin +cyclophosphamide + paclitaxel) at the TASH oncology department during the study period were the study population.

4.5. Inclusion Criteria

- All biopsy-proven LABC that took NACT with at least 4 cycles of AC or 8 cycles of AC – T

4.6. Exclusion Criteria

- If patients took less than 4 cycles of NACT
- If patients taking other types of NACT
- If patients took neoadjuvant endocrine therapy

4.7. Sampling Procedure

Health management information system and breast multidisciplinary team logbooks were used to identify all new cases of non – metastatic breast cancer that were documented after evaluation at the oncology department. And every case that fulfills the inclusion criteria were included in the study.

4.8. Data Collection Tools and Procedures

Medical record charts were collected based on the health information management system and breast multidisciplinary team logbooks and all the cards that were not following the inclusion criteria were returned by the primary investigator/supervisor. A structured questionnaire or Checklists was adapted from reviews of different standard literature and was used for data collection. The data collection format was filled and collected by a trained physician/data collector. Supervision was made by the investigator for its completeness and consistency.

4.9. Variables

Dependent variables

- Clinical response after NACT
- Pathologic response after NACT
- Rate of resectability after NACT

Independent variables

- Age
- Region
- Histologic type
- Histologic grade
- TNM stage
- Performance status (ECOG 0 – 4)
- Type of NACT

4.10. Operational Definitions

Eastern Cooperative Oncology Group (ECOG) performance status – is a performance scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

T stage – refers to the size of the tumor at presentation based on American Joint Committee on Cancer (AJCC) cancer staging 8th edition.

N stage – refers to clinical lymph node stage at presentation based on AJCC cancer staging 8th edition.

Average tumor size refers to the average of the two-dimensional measurement of the tumor.

Neoadjuvant chemotherapy (NACT) – refers to the administration of chemotherapy before definitive treatment i.e either before surgery or radiotherapy.

Clinical complete response (cCR) – refers to the disappearance of all target lesions on examination after NACT based on RECIST 1.1 criteria

Clinical partial response (PR) – refers to at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters based on RECIST 1.1 criteria

Progressive disease (PD) – refers to at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study or the appearance of one or more new lesions based on RECIST 1.1 criteria.

Stable disease (SD) – refers to neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on the study based on RECIST 1.1 criteria.

Overall clinical response refers to complete clinical response and partial clinical response

Pathologic Complete Response (pCR) – refers to no sign of cancer in tissue samples removed during surgery after NACT.

Modified radical mastectomy (MRM) – refers to the removal of the breast as well as a level I and/or II axillary dissection.

Simple mastectomy – refers to the removal of the breast but not the axillary contents.

R_0 resectability refers to resection with a negative pathological margin.

4.11. Data Quality Control

To assure the quality of data the following measure was undertaken. The appropriately designed data collection instrument was used. The checklist or format was pretested and the Clarity of the language of checklists was checked. Every day the collected data was reviewed and checked for completeness and consistency.

4.12. Data Analysis Procedures

The collected data were coded, cleaned and entered into SPSS version 25 for analysis. The main findings were described by using frequencies, percentages, and summary statistics. Chi-square and t-test were used for comparison based on the type of variables. Logistic Regression Model was used to assess explanatory variables significantly associated with the outcome variable. The results are presented using tables and texts as based on the type of data.

4.13. Ethical Considerations

Ethical clearance was obtained from the Ethical Review Board of Addis Ababa University College of health science and permission to conduct the study was obtained from the oncology department. Information from patient records and logbooks was used only for the purpose of this research. Confidentiality of the information was assured and privacy was maintained.

4.14. Dissemination of the Result

This result will be submitted to the oncology department, Addis Ababa University, College of Health Science**.** Publication of the result in scientific journals will be considered through peer review and presentation at different meetings/conferences.

Chapter Five: Results

5.1. Sociodemographic Characteristics of Patients

A total of 141 new non-metastatic breast cancer patients were presented to the MDT during the study period as recorded on the breast MDT and health management information system logbooks. Of which 63 patients were decided to undergo upfront surgery and 78 patients to receive neoadjuvant therapy. Of the 78 patients who receive neoadjuvant therapy only 51 patients were eligible for the study and among the remaining 27 patients, 7 patients took less than 4 cycles of AC NACT, 6 patients took CMF (cyclophosphamide, methotrexate and 5-flourouracil) NACT, 6 patients disappeared after MDT decision was to give them NACT, 3 patients were given neoadjuvant hormonal therapy, and the chart was lost in 5 patients.

There were 50 female patients (98%) and 1 male patient (2%). The mean age of patients was 40.1 ± 9.96 SD years old with an age range from 24 years to 65 years. The majority of patients 84.3 % were below the age of 50 and the remaining 15.7% (8 patients) of the cases were $\geq$ 50 years old (table 1).

In terms regional distribution 23 patients (45.1 %) were from Addis Ababa, 16 patients (31.4 %) from Oromia, 6 patients (11.8 %) from SNNPR (Southern Nations, Nationalities, and Peoples' Region), 5 patients (9.8 %) from Amhara and 1 patient (2 %) from diredawa (table 1).

Table 1. Sociodemographic data

Gender	**No of patients**	**Percentage (%)**
Female	50	98
male	1	2
Age (years)		
≤ 49	43	84.3
≥ 50	8	15.7
Address		
Addis Ababa	23	45.1
Oromia	16	31.4
SNNPR	6	11.8
Amhara	5	9.8
Diredawa	1	2

5.2. Clinical Characteristics of Patients

Most of the patients presented with eastern cooperative oncology group (ECOG) performance status of 1 ((34 patients (66.7 %)), followed by ECOG 0 (13 patients (25.5 %)), and ECOG 2 (4 patients (7.8 %)) respectively (table 2).

Most of the patients presented with breast swelling of ≤ 1-year duration (66.7%). The remaining presented with breast swelling of > 1 year to 2 years (29.4 %), and > 2 years (3.9 %) respectively (table 2)

The majority 39.2 % (20 patients) had T_{4b} breast carcinoma followed by T_{4c} - 35.3 % (18 patients), T_3 - 11.8 % (6 patients), T_{4d} - 9.8 % (5 patients), and T_{4a} - 3.9% (2 patients) of the cases respectively (table 2).

The nodal status at presentation were N_2 in 39.2 % (20 patients), and N_1 in 33.3 % (17 patients), N_0 accounts for 21.6 % (11 patients) and N_3 for 5.9 % (3 patients) of the cases (table 4).

According to the 8th edition of the AJCC breast cancer staging system, most of the patients were stage IIIB 86.3 % (44 patients) followed by stage IIIA 7.8 % (4 patients) and stage IIIC 5.9 % (3 patients) respectively (Table 2).

Table 2. Clinical characteristics of patients

ECOG status	**No. of patients**	**Percentage (%)**
0	13	25.5
1	34	66.7
2	4	7.8
Duration of symptoms		
≤ 1 year	34	66.7
> 1 year to 2 years	15	29.4
> 2 years	2	3.9
Initial tumor status		
T_3	6	11.8
T_{4a}	2	3.9
T_{4b}	20	39.2
T_{4c}	18	35.3
T_{4d}	5	9.8
Initial nodal status		
N_0	11	21.6
N_1	17	33.3
N_2	20	39.2
N_3	3	5.9
Stage		
IIIA	4	7.8
IIIB	44	86.3
IIIC	3	5.9

5.3. Histopathologic Characteristics

The most common histologic type was ductal carcinoma accounting for 92.2 % (47 patients) of the cases, followed by mixed ductal and lobular carcinoma 3.9 % (2 patients), lobular carcinoma 2% (1 patient) and papillary carcinoma 2 % (1 patient) of the cases respectively (table 3).

In terms of the degree of differentiation about 47.1 % (24 patients) of the cases were poorly differentiated carcinoma, 39.2 % (20 patients) were moderately differentiated carcinoma and 13.7 % (7 patients) were well-differentiated carcinoma Table 3).

Only in 3 of the patients the ER/PR and HER2 status were determined and among them 2 of the patients had ER/PR + and HER2 - tumor receptor status and 1 of the patient had ER/PR - and HER2 - (triple-negative) tumor receptor status (Table 3).

Table 3. Histopathologic characteristics

Histologic type	**No of patients**	**Percentage (%)**
Ductal	47	92.1
Lobular	1	2
Mixed ductal and lobular	2	3.9
Papillary	1	2
Grade		
Well differentiated	7	13.7
Moderately differentiated	20	39.2
Poorly differentiated	24	47.1
Tumor receptor status		
ER/PR + and HER2 -	2	3.9
ER/PR – and HER -	1	2
Not determined	48	94.1

5.4. Type of NACT, Tumor Characteristic Before and after NACT

5.4.1. Type of NACT

In this study, among the 51 patients, 21 patients (41.2%) were given 4 cycles of AC (doxorubicin + cyclophosphamide) and 30 patients (58.8%) were given 8 cycles of AC – T (4 cycles of AC + 4 cycles of paclitaxel). (table 4).

Table 4. Type of NACT

Type of NACT	Number of patients	Percentage (%)	Dose mg/m2
AC	21	41.2	A = 60, C = 600
AC – T	30	58.8	A = 60, C = 600, T = 175

AC = doxorubicin + cyclophosphamide, AC – T = AC + paclitaxel, given every 3 weeks

5.4.2. Tumor characteristics Before and After NACT

During the MDT evaluation most of the patients (48 patients) were unresectable LABC ($T_3N_{2-3}M_0$, $T_4N_{0-3}M_0$) accounting for 94.1 % of the cases and the remaining 3 patients (5.9 %) were resectable LABC ($T_3N_1M_0$) before administering NACT (table 5).

In this study at presentation 44 patients (86.3%) had tumor size > 5cm and 7 patients (13.7%) had tumor size $\leq$ 5cm, with minimum tumor size of 4cm, maximum tumor size of 22.5cm and average tumor size of 8.57cm ± 3.61 SD.

At presentation 25 patients (49 %) had fixity to the chest wall, 19 patients (37.3 %) had ulcerated breast lesions, and 40 patients (78.4 %) had clinically palpable lymph nodes. (table 5)

At the end of NACT (AC or AC – T) 43 patients (84.3 %) were labeled as resectable during MDT evaluation (3 patients remained resectable before and after NACT + 40 patients were deemed resectable from the 48 patients who were unresectable before NACT, but 2 patients

refused surgery) and 8 patients (15.7 %) were unresectable after NACT (6 patients (11.8 %) received 2nd line chemotherapy due to disease progression, 1 patient (2 %) had no breast tissue left for surgery due to complete clinical response, 1 patient (2 %) had stable disease) (table 5).

After NACT 11 patients (21.6 %) had no palpable mass on the breast. The remaining patients had an average tumor size of 3.52cm ± 2.59 SD and a maximum tumor size of 10cm. After NACT 5 patients (9.8%) had fixity to the chest wall, 12 patients (23.5 %) had ulceration and 13 patients (25.5 %) had clinically palpable lymph nodes (t=Table 5).

Table 5. Tumor Characteristics Before and After NACT

Characteristics	**Before NACT**		**After NACT**	
	No of patients	**Percentage (%)**	**No of patients**	**Percentage (%)**
Unresectable	48	94.1	8	15.7
Fixity to the chest wall	25	49	5	9.8
ulceration	19	37.3	12	23.5
Clinically palpable nodes	40	78.4	13	25.5
Average tumor size	8.57cm		3.52cm	

5.5. Clinical Response, Type of Treatment After NACT, Pathologic Response and Rate of R_0 Resectability

5.5.1. Clinical Response after NACT

According to Response Evaluation Criteria in Solid Tumors (RECIST 1.1), 11 patients (21.6 %) had complete clinical response (cCR), 31 patients (60.8 %) had clinical partial response (PR), 3 patients (5.9 %) had stable disease (SD) and 6 patients (11.8 %) had progressive disease (PD) after NACT (AC or AC – T) (table 6).

Among the 40 patients (78.4%) who had initially clinically palpable nodes, 27 patients (67.5%) had clinically complete nodal response and the remaining 13 patients (32.5 %) had still palpable lymph nodes after NACT

Based on the type of NACT, among the 30 patients who took AC – T, 9 patients (17.7 %) had cCR, 18 patients (35.3 %) had PR and 3 patients (5.9 %) had SD. Among the patients who took AC, 2 patients (3.9 %) had cCR, 13 patients (25.5 %) had PR and 6 patients (11.8 %) had progressive disease (table 7).

5.5.2. Type of Treatment After NACT

Based on MDT evaluation after NACT 41 patients (80.3 %) had surgery, 6 patients (11.8 %) received 2^{nd} line chemotherapy due to disease progression, 2 patients (3.9 %) refused surgery and later received 2^{nd} line chemotherapy due to disease progression, 1 patient (2 %) received radiotherapy because there was no breast tissue left for surgery due to complete clinical response, 1 patient (2 %) received hormonal therapy due to the response rate was stable disease and inoperable with tumor receptor of ER/PR+ and HER2- (Table 6).

For the patients who undergo surgery 40 patients (78.3 %) had modified radical mastectomy and 1 patient (2 %) had a simple mastectomy (Table 6).

5.5.3. Pathologic Response

The tumor pathology assessment among the 41 patients whose pathology specimen was submitted to pathology after surgery showed that only 4 patients (9.8 %) had complete pathologic response (pCR) after NACT. After MRM 48.8% (20 patients) of the nodal specimen were negative for secondary deposit and 20 patients (48.8 %) had positive lymph node disease. Among the patients who had negative nodes 8 patients (19.5 %) had initially clinical N_0 nodal status and the remaining had clinically palpable nodes ($N_1/N_2/N_3$) and among the patients who had pathological positive lymph node disease 2 patients (4.8 %) had initially N_0 nodal status (table 6).

Based on the type of NACT, Among the 26 patients who took AC – T and undergo surgery, the tumor pathologic assessment showed that only 3 patients (7.3 %) had complete pathologic response and in the nodal specimen assessment 9 patients (22 %) had no secondary deposits in the nodes and 16 patients (39.1 %) had a positive nodal disease. Among the patients who had negative nodes 3 patients (7.3 %) had initially N_0 nodal status and among the patients who had pathologic positive lymph node disease 1 patient had initially N_0 nodal status. Among the 15 patients who took AC, only 1 patient (2.4 %) had complete pathologic response and in pathologic nodal response assessment 11 patients (26.8 %) had no secondary deposits in the nodes and 4 patients (9.7 %) had a positive nodal disease. Among the patients who had negative nodes 5 patients (12.2 %) had initially N_0 nodal status and among the patients who had positive lymph node disease 1 patient had initially N_0 nodal status (table 7).

5.5.4. Surgical Margin Status After Surgery / Rate of R_0 Resectability

For the 41 patients who undergo surgery and pathologic assessment, 23 patients (56.1 %) had negative margins, 16 patients (39 %) had positive margins and in 2 patients (4.9 %) the surgical margin was not mentioned in the pathologic assessment. Among the patients who had positive surgical margins after surgery, 6 patients (14.6 %) had positive deepest surgical margin only, 5 patients (12.2 %) had positive both deepest and radial surgical margins, 4 patients (9.8 %)

had positive radial surgical margin only and in 1 patient (2.4 %) the deepest surgical margin was positive but the radial surgical margin was not mentioned (Table 6).

Based on the type of NACT, among 26 patients who took 8 cycles of NACT and undergo surgery, 14 patients (34.1 %) had negative margins, 10 patients (24.4 %) had positive margins and in 2 patients (4.9 %) the margin was not mentioned. For the patients who had positive surgical margins 5 patients (12.2 %) had both radial and deepest margins positive, 3 patients (7.3 %) had positive deepest margin only and 2 patients (4.9 %) had positive radial margin only. Among the 15 patients who took 4 cycles of NACT and undergo surgery 9 patients (22 %) had a negative margin and 6 patients (14.6 %) had positive margins. For the patients who had a positive margin, 3 patients (7.3 %) had a positive deepest margin only, 2 patients (4.9 %) had a positive radial margin only and 1 patient (2.4 %) had a positive deepest margin but not mentioned radial margin (Table 7).

Table 6. Response, type of treatment, and surgical margin status after NACT

Clinical response	**No of patients**	**Percentage (%)**
cCR	11	21.6
PR	31	60.8
SD	3	5.9
PD	6	11.8
Type of treatment after NACT		
Surgery	41	80.3
2nd line chemotherapy for PD	6	11.8
Refused surgery and later received 2nd line chemotherapy for PD	2	3.9
Radiotherapy for cCR	1	2
hormonal therapy for SD	1	2
Type of surgery		
MRM	40	78.4
Simple mastectomy	1	2
Complete pathologic response		
Yes	4	9.8
No	37	90.2
Pathologic nodal response		
Negative lymph nodes	20	48.8
Positive lymph nodes	20	48.8
Surgical margin status		
Negative	23	56.1
Positive	16	39
Not mentioned	2	4.9

cCR- complete clinical response, PR- clinical partial response, SD- clinical stable disease, PD – clinical progressive disease, MRM- modified radical mastectomy

Table 7. Response and surgical margin status based on the type of NACT

Clinical response	**AC**		**AC – T**	
	No of patients	**Percentage (%)**	**No of patients**	**Percentage (%)**
cCR	2	3.9	9	17.7
PR	13	25.5	18	35.3
SD			3	5.9
PD	6	11.8		
Complete pathologic response				
yes	1	2.4	3	7.3
No	14	34.1	23	56.1
Pathologic nodal response				
Negative lymph nodes	11	26.8	9	22
Positive lymph nodes	4	9.7	16	39.1
Surgical margin status				
Negative	9	22	14	34.1
Positive	6	14.6	10	24.4
Not mentioned			2	4.9

cCR- complete clinical response, PR- clinical partial response, SD- clinical stable disease, PD – clinical progressive disease

5.6. Effect of NACT on Tumor Characteristics and Response to Neoadjuvant

In this study, the mean tumor size before NACT was (m=8.57cm) and after NACT (m = 3.52 cm), had greater tumor size before NACT than after NACT ($t(50) = 8.919$, $p < 0.001$).

There was very strong evidence of relationship between fixity to chest wall before NACT and after NACT (chi-square = 12.675 df = 1, $p < 0.001$). There was very strong evidence of a relationship between ulceration before NACT and after NACT (chi-square = 4.798, df = 1, $p = 0.02$). There was also very strong evidence of relationship between clinically palpable lymph nodes before and after NACT (chi-square = 19.875, df = 1, $p < 0.001$). (Table 8)

Table 8. **Effect of NACT on Tumor Characteristics**

Tumor characteristics	**Before NACT (%)**	**After NACT (%)**	**Pearson chi-square**	**df**	**p-value**	**Odds ratio**
Fixity to chest wall	49	9.8	12.675	1	< 0.001	0.113
ulceration	37.3	23.5	4.798	1	0.02	0.518
Clinically palpable nodes	78.4	25.5	19.875	1	< 0.001	0.094

5.7. Predictors of Clinical Response

Using binary logistic regression, patients with ulcerated breast lesions before NACT were slightly less likely to have overall clinical response ($p = 0.056$, OR = 4.46, for no response). Patients who took AC – T (NACT) had slightly significant overall clinical response compared to patients who took AC NACT ($p = 0.099$, OR = 3.6). There was no relationship between age and clinical response after NACT ($p = 0.68$, OR = 1.6, for younger patients). Initial clinical tumor

size didn't predict the degree of response after NACT (p = 0.644, OR = 2.1, for small-size tumors). There was no relationship between initial clinical nodal status and over all clinical response in patients who took NACT (p = 0.414, OR = 0.4 with, for positive node patients) (table 9).

Using multinomial logistic regression, patients with skin ulceration before NACT were significantly less likely to have partial response after NACT (p = 0.05, OR = 0.205) and for complete clinical response (p = 0.185, OR = 0.286). Patients who took AC – T (NACT) had slightly significant complete clinical response compared to patients who to AC NACT (p = 0.037, OR = 9) and for partial response (p = 0.20). Patients with T_3 had statistically significant complete clinical response (p = < 0.001) compare to no response. Patients with N_1 had also statistically significant complete clinical response (p = < 0.001) compare to partial or no response. Well-differentiated tumors had statistically significant complete clinical response (p = < 0.001) compare to no response. Age was not a predictor of complete clinical response (p = 0.217) and partial response (p = 0.900). Initial tumor size didn't predict the rate of complete clinical response (p = 0.35) and partial response (p = 0.673). Initially clinically palpable nodes didn't predict the rate of complete clinical response (p = 0.662) and partial response (p = 0.368).

5.8. Predictors of Pathologic Response

In the 41 patients who undergo surgery and pathologic assessment, using binary logistic regression for predictors showed that older patients (≥ 50 years old) with LABC had higher complete pathologic response but not statistically significant after NACT during pathologic assessment compared to patients below the age of 50 years (p = 0.062, OR = 8.25). Initial tumor size and nodal status didn't predict the rate of complete pathologic response after NACT (p = 0.999). Type of NACT didn't predict the rate of complete pathologic response after NACT (p = 0.617, OR = 0.548 AC – T for no pCR). Complete clinical response didn't predict the rate of pCR after NACT (p = 0.998) (table 9).

For pathologic nodal response assessment, patients with initially clinically palpable nodes were slightly less likely to had negative nodes after NACT in the pathologic assessment ($p = 0.034$, OR = 6.33). Well differentiated and moderately differentiated tumors were slightly less likely to had negative nodes after NACT in the pathologic assessment than poorly differentiated tumors ($p = 0.099$, OR = 5 and $p = 0.094$, OR = 3.33 respectively). Type of NACT didn't predict the rate of negative nodes after NACT in the pathologic assessment ($p = 0.256$, OR = 2.2 for positive nodes) (table 9).

5.9. Predictors of Surgical Margin Status/R_0 Resectability

For the 39 patients for whom surgical margin was mentioned in the pathologic report, using binary logistic regression for predictors showed that patients with fixity to chest wall before NACT had a slightly significant positive surgical margin after NACT ($p = 0.092$, OR =3.12 for positive margin). Patients with ulceration before NACT ($p = 0.032$, OR = 4.63), clinically palpable nodes after NACT ($p = 0.024$, OR = 13.2) and ulceration after NACT ($p = 0.013$, OR = 17.1) had also a statistically significant positive margin during the pathologic assessment. Type of NACT ($p = 0.918$), initial tumor size ($p = 0.678$) and fixity to chest wall after NACT ($p = 0.999$) didn't predict the surgical margin status (table 9).

Table 9: Predictors of Response and Surgical Margin Status

Predictors of overall clinical response		
Positive predictors	**Negative predictors**	**No effect**
AC – T (NACT) (p = 0.099, OR = 3.6) for overall response and (p =0.037, OR=9) for complete clinical response	Ulceration before NACT (p = 0.056, OR = 4.46) for overall response and (p = 0.05) for partial response	Age (p = 0.68)
		Tumor size (p = 0.644)
		Nodal status (p = 0.414)
Predictors of pathologic response for pCR		
Positive predictors		**No effect**
Age ≥ 50 year ((p = 0.062, OR = 8.25)		Initial tumor size and nodal status (p = 0.999).
		Type of NACT (p = 0.617)
		Complete clinical response (p = 0.998)
Predictors of pathologic nodal response for negative nodes		
Negative predictors		**No effect**
Initially clinically palpable nodes assessment (p = 0.034, OR = 6.33)		Type of NACT (p = 0.256)
Well differentiated tumor (p = 0.099, OR = 5)		
Moderately differentiated tumor (p = 0.094, OR = 3.33)		
Predictors of positive surgical margin status		
Positive predictors		**No effect**
Fixity to chest wall before NACT (p = 0.092, OR =3.12)		Type of NACT (p = 0.918)
Ulceration before NACT (p = 0.032, OR = 4.63)		initial tumor size (p = 0.678)
Clinically palpable nodes after NACT (P = 0.024, OR = 13.2)		fixity to chest wall after NACT (p = 0.999)
Ulceration after NACT (p = 0.013, OR = 17.1)		

Chapter Six: Discussion

In this study, the mean tumor size of patients with locally advanced breast cancer at presentation was 8.57cm with the range of 4cm up to 22.5cm size and about 86.3% patients had tumor size > 5cm. This is slightly lower than patients in other SubSaharan countries like in Nigeria about 90.3% of the patients had tumor size greater than 5cm with the range of 3cm up to 22cm size and median of 10cm in study done by Olukayode Adeolu Arowolo et al (31). In study done by Ochonma Amobi Egwuonwu et al the mean tumor size at presentation was 11.5 cm (range 5-25 cm) (33). The mean tumor size was 4.5 cm and about 45% of the cases had tumor size > 4cm in the NSABP B-27 trial and about 13% of the patients had tumor size > 5 cm in the NSABP B-18 trial done in the united states and Canada (27, 28).

In this study, about 94.1 % of the cases presented to multidisciplinary tumor board with inoperable breast cancer (T_3N_2/N_3M_0 or $T_4N_{0-1}M_0$). In the study done by Ochonma Amobi Egwuonwu et al about 87.1% of the cases had inoperable breast cancer at presentation (33), but in the NSABP B-18 and NSABP B-27 trails all patients presented with operable breast cancer ($T_{1-3}N_{0-1}M_0$) (27,28).

About 78.4% of the patients had clinically palpable nodes in our study. This is slightly lower than patients in Nigeria about 88.7% of patients had clinically palpable nodes in a study done by Olukayode Adeolu Arowolo et al (31). In the NSABP B-18 trial and NSABP B-27 trial, about 26% and 30% of the patients had clinically positive nodes respectively (27, 28).

The type of neoadjuvant chemotherapy we used in our study was either doxorubicin and cyclophosphamide or doxorubicin and cyclophosphamide followed by paclitaxel. In the NSABP B-18 trial they used only doxorubicin and cyclophosphamide and in the NSABP B-27 trial the type of neoadjuvant chemotherapy was either doxorubicin and cyclophosphamide or doxorubicin and cyclophosphamide followed by docetaxel (27, 28). In most of the studies done in Africa the type of neoadjuvant chemotherapy they used was another anthracycline based regimen (in most of them doxorubicin,5-flourouracil and cyclophosphamide) (31, 32, 33, 34).

In this study, the overall response rate (complete and partial clinical response) was 82.4% with complete clinical response of 21.6% and among the patients who had clinically palpable nodes the complete clinical nodal response was 67.5% and the mean tumor size was decreased from 8.57 cm to 3.52 cm after NACT t(50) = 8.919, p </= 0.001. The response rate is higher than the study done by Olukayode Adeolu Arowolo et al in which the overall response rate was 51.8%, with complete clinical response seen in 6.6% of patients (31), and by Ochonma Amobi Egwuonwu et al in which the overall response rate was 74.2% with complete clinical response of 12.9% with the mean tumor size decreased from 11.5cm to 7.5cm after NACT (33). This can be explained by the chemotherapy regimen used, tumor biology, and larger tumor size at presentation in the case of the study done by Arowolo and Egwuonwu. But the response was comparable to the NSABP B-18 trial in which the overall response rate was 79% with a complete clinical response of 35% and 73% had complete clinical nodal response among the patients who had initially clinically palpable nodes (27). In the NSABP B-27 the overall clinical response rate at the time of surgery for those in the AC + docetaxel group (90.7%) was statistically significantly higher than for those in AC group (85.5%; $P < .001$) and the complete clinical response rate was statistically significant in the AC + docetaxel group compared to AC group (63.3% Vs 40.1%; $P < .001$) (28). In our study, patients who took AC – T (NACT) have slightly significant overall clinical response and complete clinical response compared to patients who took AC (NACT) (p = 0.099, OR = 3.6) and (p = 0.037, OR = 9) respectively.

In our study, among the patients who undergo surgery and pathologic assessment only 9.8 % of the patients had complete pathologic response and 48.8 % of the patients had negative nodes in the pathologic assessment, but 19.5 % of them had clinically non-palpable nodes at the initial presentation. We also found that older patients (≥ 50 years old) with LABC had higher complete pathologic response but not statistically significant after NACT during pathologic assessment compared to patients below the age of 50 years (p = 0.062, OR = 8.25). This is higher than the study done by Olukayode Adeolu Arowolo et al as there were no cases of complete pathologic response (31). The pCR is lower than the NSABP B-18 trial in which 26 % of the patients had complete pathologic response and 44 % of the patients had complete pathologic nodal response (27), this is due to the early stage of disease at presentation. In the NSABP B-27 trial, preoperative AC followed by docetaxel improves the pathologic complete response and the

proportion of negative nodes than AC with (26.1 vs 13.7 %; $p < .001$) and (58.2 % vs 50.8%; $p < .001$) respectively (28). However, in this study type of NACT didn't predict the rate of complete pathologic response after NACT ($p = 0.617$, OR = 0.548 AC – T for no pCR) and the rate of pathologic nodal response ($p = 0.256$, OR = 2.2 AC – T for no response).

In this study for the patients who undergo surgery and pathologic assessment, 56.1 % patients had negative margins, 39 % patients had positive margins and in 4.9 % of patients the surgical margin was not mentioned in the pathologic assessment. It also showed that patients with fixity to the chest wall and ulceration before NACT had a slightly significant positive surgical margin after NACT ($p = 0.092$, OR =3.12 and $p = 0.032$, OR = 4.63 for positive margin respectively). Patients with clinically palpable nodes after NACT ($P = 0.024$, OR = 13.2) and ulceration after NACT ($p = 0.013$, OR = 17.1) had also a slightly significant positive margin during the pathologic assessment.

Chapter Seven: Conclusion and Recommendations

7.1. Conclusion

The study has shown that administering neoadjuvant chemotherapy either with AC or AC – T has decreased the tumor size significantly to make it resectable with clear margin and patients who took AC – T had slightly higher overall response rate and complete clinical response rate.

7.2. Recommendations

The principal investigator recommends that it is recommended to give neoadjuvant chemotherapy with AC – T for patients with operable or inoperable locally advanced breast cancer. Large scale study with baseline information on tumor biology is recommended.

7.3. Limitations of the Study

- This is a retrospective study which is less powerful than a prospective study.
- In almost all of our patients the tumor receptor status was not determined which is an important predictor of response.
- Difficult to assess the rate of complete pathologic nodal response as some patients had inadequate lymph node resection or evaluation for pathologic assessment.

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ANNEXES

Annex I. Data Extraction Tools

1. Demographic Data

Serial No.	Variable	Category
101	MRN	
102	Sex	1.Female 2. Male
103	Age (years)	
104	Region	1. Addis ababa 2. Amhara 3. oromia 4. Tigray 5. SNNPR 6. Gambela 7. BenishangulGumuz 8. Harar 9. Diredawa 10. Somalia 11. Afar

2.Disease Characteristics

Serial No.	variable	Category
201	ECOG	1. ECOG 0 2. ECOG 1 3. ECOG 2 4. ECOG 3 5. ECOG 4

202	Duration of symptoms	1. </= 3 months 2. >3 to 6 months 3. >6 to 12 months 4. > 12 months to 2 yrs 5. > 2 yrs
203	Initial average tumor size in cm	
204	Skin changes before NACT	1. Yes 2. No
205	Fixity to chest wall before NACT	1. Yes 2. No
206	Ulceration before NACT	1. Yes 2. No
207	Initial Tumor status (T)	1. T1 2. T2 3. T3 4. T4a 5. T4b 6. T4c 7. T4d
208	Initially clinically palpable nodes	1. Yes 2. No
209	Initial Nodal status (N)	1. N0 2. N1 3. N2 4. N3

210	Stage	1. IIB 2. IIIA 3. IIIB 4.IIIC
211	Histologic type	1. Ductal 2. Lobular 3. Mixed ductal/lobular 4. Tubular 5. Mucinous 6. Medullary 7. Papillary 8. Metaplastic 9. Other types
212	Grade	1. well differentiated 2. moderately differentiated 3. poorly differentiated
213	Tumor receptor status	1. Not determined 2. ER/PR + and HER2 – 3. ER/PR + AND HER2 + 4. ER/ PR – AND HER2 + 5. Triple negative

214	Staging investigation done before and after NACT with complete blood count, liver and renal function test, chest x-ray, and abdominopelvic ultrasound	1. Yes 2. No
215	Echocardiography	1. Yes 2. No
216	Bone scan	1. Yes 2. No
217	Resectable before NACT	1. Yes 2. No

Treatment related

Serial No.	Variable	Category
301	Type of NACT	1. 4 cycles of AC 2. 8 cycles of AC – T (4 cycles AC + 4 cycles T)
302	Dose A=60mg/m2, C=600mg/m2, T=175mg/m2 given every 3 weeks	1. Yes 2. No
303	Tumor size in cm after 4 cycles of AC	
304	Tumor size in cm after 8 cycles of AC – T	
305	Skin changes after NACT	1. Yes 2. No
306	Fixity to chest wall after NACT	1. Yes 2. No
307	Ulceration after NACT	1. Yes 2. No
308	Clinically palpable LN after 4 cycles of AC	1. Yes 2. No
309	Clinically palpable LN after 8 cycles of AC - T	1.Yes 2. No
310	Clinical response after 4 cycles of AC	1. clinical complete response (cCR) 2. clinical partial response (PR)

		3. Stable disease (SD) 4. progressive disease (PD)
311	Clinical response after 8 cycles of AC – T	1. cCR 3. SD 2. PR 4.PD
312	Reason for continuation of 8 cycles of AC - T	1. cCR 3. SD 2. PR 4. PD
313	Subsequent treatment after 1st line NACT	1. Surgery 2. Radiotherapy 3. 2nd line chemotherapy 4. Hormonal therapy
314	Resectable after NACT	1. Yes 2. No
315	Type of surgery	1.Modified Radical Mastectomy (MRM) 2. Simple Mastectomy
316	Surgical margin after surgery	1. Negative 2. Positive 3. Margin not mentioned
317	If the surgical margin is positive which margin is positive	1. Deepest margin only 2. Radial margin only 3. Deepest margin but not mentioned radial margin 4. Radial margin but not mentioned deepest margin 5. Both margins
318	Complete Pathologic Response (pCR) after 4 cycles of AC or 8 cycles of AC – T	1. Yes 2. No
319	Complete pathologic nodal response after 4 cycles of AC or 8 cycles of AC – T	1. Yes 2. No

Annex II. ECOG Performance Status

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Annex III: AJCC 8th Edition Breast Cancer Staging

American Joint Committee on Cancer (AJCC)
TNM Staging System For Breast Cancer

Primary Tumor (T) The T category of the primary tumor is defined by the same criteria regardless of whether it is based on clinical or pathological criteria, or both. The T category is based primarily on the size of the invasive component of the cancer. The maximum size of a tumor focus is used as an estimate of disease volume. The largest contiguous dimension of a tumor focus is used, and small satellite foci of noncontiguous tumor are not added to the size. The cellular fibrous reaction to invasive tumor cells is generally included in the measurement of a tumor prior to treatment; however, the dense fibrosis observed following neoadjuvant treatment is generally not included in the pathological measurement because its extent may overestimate the residual tumor volume. The clinical size of a primary tumor (T) can be measured based on clinical findings (physical examination and imaging modalities, such as mammography, ultrasound, and MR imaging) and pathological findings (gross and microscopic measurements). Clinical tumor size (cT) should be based on the clinical findings that are judged to be most accurate for a particular case, although it may still be somewhat inaccurate because the entent of some breast cancers is not always apparent with current imaging techniques and because tumors are composed of varying proportions of noninvasive and invasive disease, which these techniques are currently unable to distinguish. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification the size should be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 4.9 mm is reported as 5 mm, or a size of 2.04 cm is reported as 2.0 cm (20 mm). The exception to this rounding rule is for a breast tumor sized between 1.0 and1.4 mm. These sizes are rounded up to 2 mm, because rounding down would result in the cancer's being categorized as microinvasive carcinoma (T1mi) defined as a size of 1.0 mm or less.

Table 1. **Definitions for T, N, M**

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)*	Ductal carcinoma *in situ*
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement >1.0-1.9 mm to 2 mm)
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/ or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macrosopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma

*Note: Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition.

Continued

Table 1. **Definitions for T, N, M (continued)**

Regional Lymph Nodes (N)

Clinical (cN)

cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; *or* in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; *or* in ipsilateral internal mammary lymph node(s) with level I, II axillary lymph node metastases; *or* metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively.
*The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.
**cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Pathologic (pN)

pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cells clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined.
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes

Continued

Table 1. **Definitions for T, N, M (continued)**

Pathologic (pN)

pN3	Metastases in 10 or more axillary lymph nodes; *or* in infraclavicular (level III axillary) lymph nodes; *or* positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive level I, II axillary lymph nodes; *or* in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; *or* in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); *or* metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); *or* pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes

Distant Metastasis (M)

M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

Table 2. **AJCC Anatomic Stage Groups**

The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available.
Cancer registries in the U.S. must use the Clinical and Pathological Prognostic Stage Group tables for case reporting.

Stage 0	Tis	N0	M0	**Stage IIIA**	T0	N2	M0
Stage IA	T1	N0	M0		T1	N2	M0
Stage IB	T0	N1mi	M0		T2	N2	M0
	T1	N1mi	M0		T3	N1	M0
Stage IIA	T0	N1	M0		T3	N2	M0
	T1	N1	M0	**Stage IIIB**	T4	N0	M0
	T2	N0	M0		T4	N1	M0
Stage IIB	T2	N1	M0		T4	N2	M0
	T3	N0	M0	**Stage IIIC**	Any T	N3	M0
				Stage IV	Any T	Any N	M1

Notes:
1. T1 includes T1mi.
2. T0 and T1 tumors with nodal micrometastases (N1mi) are staged as Stage IB.
3. T2, T3, and T4 tumors with nodal micrometastases (N1mi) are staged using the N1 category.
4. M0 includes M0(i+).
5. The designation pM0 is not valid; any M0 is clinical.
6. If a patient presents with M1 disease prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
7. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence of disease progression, and provided the patient has not received neoadjuvant therapy.
8. Staging following neoadjuvant therapy is designated with "yc" or "yp" prefix to the T and N classification. There is no anatomic stage group assigned if there is a complete pathological response (pCR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

Continued

Annex IV. Assurance of Principal Investigator

I, the undersigned Clinical Oncology Resident agree to accept responsibility for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the research and publications office of the Addis Ababa University.

Name of the Investigator: Dr. Desta Mulu (4th Year Clinical Oncology Resident)

Signature_____ Date_____/_____/_____

Approval of the Primary Advisor

Advisor Name: Dr. Mathewos Assefa (MD, Internist, FC Rad Onc (SA))

Signature_____ Date _____/_____/_____