

**SURVIVAL OF BREAST CANCER PATIENTS  
TREATED AT TASH,  
ADDIS ABABA, ETHIOPIA**



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**A RESEARCH PAPER SUBMITTED TO ADDIS ABABA UNIVERSITY,  
COLLEGE OF HEALTH SCIENCES, ONCOLOGY DEPARTMENT IN  
PARTIAL FULLFILMENT OF THE REQUIRMENTS FOR THE  
DEGREE OF SPECIALITY IN CLINICAL ONCOLOGY**

ADDIS ABABA, ETHIOPIA

SEPTEMBER, 2019

**ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCES**  
**SCHOOL OF MEDICINE**  
**DEPARTMENT OF CLINICAL ONCOLOGY**

**CLINICOPATHOLOGY AND TREATMENT PATTERNS OF HEAD AND NECK  
CANCERS AT TIKUR ANBESSA SPECIALIZED HOSPITAL, RADIOTHERAPY  
CENTER, ADDIS ABABA, ETHIOPIA**

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## **ACKNOWLEDGEMENT**

I would like to thank the Oncology Department of Black Lion Hospital for granting me the opportunity and permission to conduct my studies. I am particularly grateful for the unwavering assistance and guidance given to me by Dr. Mathewos Assefa, without whose help I wouldn't have been able to complete this study.

I would like to express my deep gratitude to Dr. Eva Johanna Kantelhardt and Dr. Ahmedin Jemal for giving me their time and support during this study.

I also like to thank my friend Dr Ephrem Tafesse who assisted me during the data collection as well as my colleagues and the staff at the department for the aid they gave me in conducting this study.

Finally, I wish to acknowledge the help provided to me by Mr. Ivan Soldatovic in analyzing the data

## **List of Abbreviations**

AA	Addis Ababa
AAU	Addis Ababa University
CO-60	Cobalt-60
CT	chemotherapy
DFS	Disease free survival
DMFS	Distant metastasis free survival
ER	Estrogen Receptor
FNAC	Fine needle aspiration histology
HIC	High-income countries
HDI	Human developmental index
HMIS	Health management information system
MFS	Metastasis free survival
Gy	Gray, unit of radiation
IAEA	International Atomic Energy Agency
OS	Overall survival
PFS	Progression free survival
RT	Radiotherapy
TASH	Tikur Anbessa Specialized Hospital
TNM	Tumor, Lymph node, metastasis

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## Summary

**Background:** Breast cancer is a major public health problem with significant morbidity and mortality in women worldwide. Studies in Sub-Saharan Africa (SSA) have shown that the estimated 5-year survival in women with breast cancer is below 50%, which is significantly lower than those from developed countries. There is limited data on survival of patients treated for breast cancer in Ethiopia.

**Objective:** The aim of this study is to assess the five-year survival of breast cancer patients treated at Oncology Department of Tikur Anbessa Specialized Hospital (TASH).

**Methods:** This is a retrospective cohort study that assesses the survival of and contributing factors of patients that were evaluated and treated at TASH between September 2014 and August 2015 G.C. Data was extracted from patient file by data collectors under the supervision of the primary investigator using structured questionnaire. Patients and/or their relatives were contacted through phone call and for those patients who were not available over the phone, the last date of follow up was used to calculate overall survival (OS). The data was analyzed using SPSS 22 software.

**Results:** Out of a total of 249 patient charts collected based on HMIS data, 216 cases were found eligible for our study. On further evaluation of the 216 cases, only 181 patients were eligible for the final analysis as 35 patients had some data missing (error of date entry on excel) or were lost from follow up by more than 6 months and couldn't be contacted over the phone.

The mean age of presentation was 43 (SD) years. Most patients (38.1%) had a stage III disease at presentation followed by stage IV disease 31.5%. Only 4.4% of our patients were stage I.

The median survival was 27 months where the 5-year OS was 44.2%. Stage at diagnosis, duration before the initiation of Adjuvant chemotherapy, number of chemotherapy cycles, the use of hormonal therapy and its duration were significantly associated with survival.

**Conclusion/recommendation:** The outcome of stage III & IV patients in our study is very low by the western standards.

We should devise a policy to increase public awareness, so that we can get these patients at an earlier stage. In addition, we have to increase access to recent treatment modalities and expand the available cancer centers.

# 1. Introduction

## 1.1 Background and Literature Review

Cancer is the most common and the second commonest cause of death in developed and developing countries respectively (1). Breast cancer is a major public health issue in the world regardless of economic development (2). It accounted for 23% of the total new cancer cases and 458,400 total cancer deaths in women across the world during 2008 (2). In the recently updated GLOBOCAN 2018, 2.1 million new breast cancer cases are expected to be diagnosed in women representing 1 in 4 cancers in women. It is the commonest cancer in the majority of the world parts and a leading cause of death in more than 100 countries. This same report places the breast ca as the most frequently diagnosed cancer, as well as, the leading cause of cancer death in women of Ethiopia (3). Up to date survival data are key indicators of the overall effectiveness of health services in the management of patients with cancer (4). The incidence, mortality and survival rate of breast cancer has large variation across the world (3). This is assumed to be the result of several underlying conditions like age, ethnicity, diet, lifestyle and reproductive factors (5).

Worldwide, the 5-year overall survival probabilities for breast cancer ranged from around >85% in highly developed countries down to 13.6% in Algeria and 12% in The Gambia (6). In the United States, breast ca is second to lung ca as the most common cause of cancer related death in women (7). However, there has been a decrease in breast cancer mortality in the United States and most of the Western world, attributable to the increased use of screening policy and advancements in adjuvant therapies. In 2008, the CONCORD study reported 5-year population-based survival from 31 countries, including 22 registries in US (8). 5-year survival in North America was one of the highest in the world with a figure of 84%, but large survival differences were documented between white (84.7%) and black (70.9%) females in the US, which might be the result of socioeconomic differences (8). The second cycle of the CONCORD program (CONDORD 2) examined survival from 10 common cancers in 67 countries. CONCORD2 is the largest study of population-based cancer survival trends to date, evaluating trends in five-year survival for over 25 million individual patients diagnosed during the period between 1995 and 2009. Age standardized five-year survival from breast cancer increased in many countries

worldwide. In the United States of America, it increased from 86% between 1995 and 1999 to 88.6% between 2005 and 2009 (9).

Among European countries, five-year relative survival in women ranges from 67% in Lithuania to 87% in Iceland with an average of 82% for the continent (10). Mauritius, one of the HIC countries in Africa, had a survival rate of 87%. But the data from 3 other SSA countries were far inferior to what was seen in other parts of the world as the survival rates were 53.4% for South Africa, 13.6% for Mali and 11.9% for Gambia. Persistent international differences in survival include can possibly explained by difference in quality of data collection and registry practices, differences biology of cancers, policy of screening, stage at diagnosis and disparity in diagnostic tools and high-quality care. Because of these reasons, the data from Africa (Gambia, Algeria and Mali) were considered unreliable estimates (9).

Precise records of incidence rates are not available because of the lack of proper cancer registration in most African countries (11). Breast cancer is considered to be responsible for 25% of all cancers and 15% of all cancer related deaths in women all over the world (12). By 2030, it is projected that developing countries will account for more than 70% of the world's cancer incidence. Breast ca is the most commonly diagnosed malignancy in countries like south Africa (13). Just like the other parts of the world, breast cancer has the highest incidence of new cases and deaths in women of sub-Saharan Africa, accounting for 94,000 new cases and 48,000 deaths in 2012 (14). There was 1 breast ca related death for every 4 new breast ca diagnosis in women of HIC but the figure from SSA Africa shows mortality rate double of what was seen in HIC, reflecting the poor outcome of this disease in the region (13).

A recent population-based registry study from SSA that included 14 registries from 12 countries reported on 1-,3-,5-year survival based on stage, age and HDI. Relative Survival varied significantly in between the countries with a very low rate of 3-year survival at 21.6% and high 3-year survival of 84.5% recorded from Zimbabwe and Namibia respectively. And a 5-year survival that ranged from as low as 12.1% to the highest of 83.2% in Uganda and Mauritius respectively. In this report, of those with recorded stages, 64.9% of the patients were diagnosed in their late stage of the disease. For the entire study group, relative survival at 1-, 3- and 5- year

were 86.1%, 65.8% and 59%. The same study has given the 1- and 3-year relative survival figures for Ethiopia of 90.7% and 63.6% (15).

There is scarcity of Data from SSA because of lack of proper data registration (10) and computing the five year survival of these patients is difficult as there is a high rate of loss from follow up, as one study showed around 35% were lost from follow up at one center(16). In one study from a tertiary center in SSA, five years cumulative survival was 51.8 %, which was a bit higher than what is shown to be around 40% for low income countries (16). This is a low figure than the 70 % survival in African Americans or the 85% survival outcome observed in Caucasians from the United States (8). Most breast cancers from low income countries like the majority of SSA regions are detected at advanced stages compared to what is observed in HIC. The inadequate facilities for early diagnosis and the unavailability of optimal treatment options along with the advanced stage at diagnosis has led to a very low survival in LIC compared to most HICs (9). More than half of the studies from a recent systematic review, that included 83 studied from 17 SSA countries reported that 70% or more of breast cancer patients were TNM stages III and IV at diagnosis which could be explained by more biologically aggressive form of the disease, a consequence of long delays between onset of symptoms and diagnosis as a result of poor health seeking behaviour and lack of awareness, an absence of strategy for early detection programs, and poor facilities for timely diagnosis and treatment (17). There is a predominance of aggressive breast tumors like triple negative tumors in SSA as well as African Americans which might explain the poor survival rate (18). But a large metaanalysis which identified 80 studies with more than 17,000 breast patients concluded that there is an overestimation of triple negative tumors in the literatures, even though their study had a low rate of triple negative breast ca patients ( but still higher than white women with breast ca in the US), they still reported a high rate of variability and heterogeneity in various regions of Africa (19). Ethiopia, like most parts of sub Saharan Africa, has a scarcity of information concerning breast cancer survival. AstraZeneca Ltd. Pharmaceutical company along with Axios Foundation launched an independent project where they provided free hormonal therapy ( anastrozole & tamoxifen) to women with breast ca with ER positive disease or whose receptor status was unknown (from 2006-2010) at Addis Ababa university hospital, Radiotherapy center. A breast ca metastasis free survival rate cohort study of the 1,070 patients was reported. After a median

follow up of 23.1 months, the five-year MFS rate was found to be 72% for stage I & II patients and 33% for stage III patients. This study was one of the largest to report on the outcome of a large group of breast cancer patients not only in Ethiopia but also in the sub-Saharan region. The authors concluded that the actual OS for these patients to be higher than what was generally observed in the rest of Africa. But the OS data was not reported and all patients who didn't return for follow up were assumed to have died (20).

A recently published article which assessed outcome of women with breast ca who were treated mostly with only surgery revealed a 2-year overall survival of 53%. 65% of the patients in this study were hormone receptor positive and would have benefited from endocrine therapy. The 2-year survival of hormone positive disease was 59% compared to just 40% in the hormone receptor negative patients. Most patients in this study presented with advanced disease and high-grade tumor as 57.3% of the patients had cT3 or cT4 disease and 68% of the patients had grade 3 tumors (21).

A retrospective cohort study analysed the survival data of stage IV breast ca patients treated at TASH between 2006-10. This study revealed an estimated mean survival of 11.7 months. Based on a bivariate analysis, patients with de novo metastatic disease had better outcome than those with a recurrent metastatic disease with mean and median survival of 14.6 months & 9.1 months compared to 10.2 months & 5.2 months respectively (22).

The previous studies performed on survival of breast cancer patients in Ethiopia are either limited to patients treated with either surgery alone or those patients who were treated with hormonal agents. Others have not properly linked survival with its contributing factors as such we don't have a holistic view of the situation. Whereas other studies have reported only MFS using data from the same center as ours, who were treated with surgery and chemotherapy regimen similar to ours. Without properly identifying the probable cause, we cannot make any changes to what is already being implemented. In this study, we will describe the tumor characteristics, the five-year survival, and prognostic factors of breast cancer patients treated oncology center TASH, Addis Ababa, Ethiopia that is the only radiotherapy center in the

country. Hopefully this will give us a good view of the contributing factors that are altering the outcome of our patients and this might help the policy makers in designing a plan.

## **1.2 Statement of the Problem and Rationale**

According to GLOBOCAN 2018, Breast Cancer is the most common solid cancer diagnosed in Ethiopian patients. For a country, with an estimated population of more than 100 million, the radiotherapy center in Tikur Anbassa Specialized Hospital (TASH) is the only radiotherapy facility in the country. Further, the center has only one functional Co-60 Teletherapy machine and one high dose rate (HDR) Brachytherapy machine dedicated for gynecologic malignancies. So, it is difficult to deliver surgery, chemotherapy and radiotherapy in a timely fashion.

There is only limited data about the survival of breast cancer patients in Ethiopia. Thus, Proper investigation of the outcomes pertaining to breast cancer in Ethiopian population will help in determining the results of the current management and what needs to be improved. It will also direct policy makers on what aspects to focus on. After assessing the shortcomings of the current management methods, it will also direct future treatments to be tailored specifically for the Ethiopian population. Moreover, protocols that specifically concern the population can be setup based on such studies.

## **2. Research Questions**

- 1) What is the five-year survival probability of breast cancer patients at Addis Ababa Tikur Anbessa University hospital?
- 2) What are the factors associated with better survival rate in breast cancer patients treated at TASH?

## **3. Objectives**

### **3.1 General objectives**

- The overall aim of this study is to assess the five-year survival probability of breast cancer patients seen at Tikur Anbassa specialized hospital oncology center, AAU, Ethiopia

### **3.2 Specific objectives**

- To determine the five-year survival probability of breast cancer patients
- To assess contributing factors (like stage, age, sex and address) for survival
- To assess impact of hormonal therapy, chemotherapy and radiotherapy on outcome

## **4. Methods and Materials**

### **4.1 Study Area and Setting**

The study was conducted at Tikur Anbassa Specialized Hospital Radiotherapy center. Established 25 years back with the help of International Atomic Energy Agency (IAEA), the center currently has two Cobalt-60 Teletherapy units. One out of order since the past few years and one HDR Brachytherapy unit dedicated for gynecologic malignancies. Six full time consultant oncologists, four medical physicists and seven radiotherapists are currently working in the center. The center has started training clinical oncology residents in 2013 and currently 28 residents are enrolled. Activities include inpatient admission for chemotherapy and outpatient clinics for new patient evaluation and follow-ups. With a recently opened branch nearby the department has now 35 beds for chemotherapy admissions.

Upon initial presentation, patients will have a thorough physical examination after a proper history is taken. Laboratory blood work and metastatic work up through at least chest x ray and abdominopelvic ultrasound are required before initiation of any treatment.

Using the above information patients were staged using the 7<sup>th</sup> AJCC guidelines.

In our center patients are advised to undergo MRM as long as they present with an operable non metastatic disease. Those patients who present with advanced but non metastatic disease will initially receive neoadjuvant chemo before the MRM.

Depending on the stage adjuvant/palliative chemotherapy  $\pm$  endocrine therapy (for ER+ or whose receptor status is unknown) will be offered.

Radiotherapy is used depending on the stage of presentation and pathology report.

## **4.2 Study Design**

This is a retrospective cohort study that evaluated the five-year survival of breast cancer patients that were seen from September 2014 to August 2015 GC.

## **4.3 Source Population**

All the breast cancer patients that were registered at the oncology department of Tikur Anbassa hospital between September 2014 to August 2015 GC are included.

## **4.4 Study Population**

All cases of histopathology confirmed breast cancer patients seen in Tikur Anbassa Specialized Hospital Radiotherapy center and whose files were available during the study period.

## **4.5 Inclusion Criteria**

- Pathologically confirmed disease at presentation
- Patients of any stage

## **4.6 Exclusion Criteria**

- No available phone number listed on the patient medical record chart for contacting the patient or his relative
- If the socioeconomic status was not properly documented as per the questionnaire

## **4.7 Sampling Procedure**

HMIS logbook was used to identify all cases of breast cancer that were documented after evaluation at the oncology department. And every case that fulfills the inclusion criteria was included in the study.

## **4.8 Operational Definitions**

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

**T stage** – refers to the size of the tumor at presentation

**N stage** – refers to either clinical lymph node stage or based on the pathologic report of the submitted specimen

**Nx** – if the submitted or reported lymph nodes are less than the standard (10)

**Metastatic disease (M1)** - the presence of the disease outside of the primary breast and regional lymph nodes

**Five-year survival** – will be assessed using phone calls and if that's not working the last date of follow up will be used to determine the survival (Death from any cause is used to interpret the survival)

**Retreatment** – the need for treating the patient after completion of the primary adjuvant or palliative treatment for either local recurrences or distant metastasis

**Radiotherapy** – the use of photon energy (in our case, Co60) for adjuvant/recurrence treatment to the intact breast or chest wall and regional lymph nodes

**Hormonal therapy** – the manipulation of the endocrine function using either estrogen modulators or Aromatase inhibitors as a primary, adjuvant or palliative treatment

**Lost from follow up** – if patients did not have a follow up data on their medical charts for more than 6 months and were not reachable over the phone (the patients or their relatives).

#### **4.9 Variables**

##### **Dependent Variables**

Survival at 5 year

##### **Independent variables**

- Age
- Pathology (histology and grade)
- TNM stage
- Interval between surgery and adjuvant treatment
- Use of Hormonal treatment
- Duration of Hormonal therapy
- Number of chemotherapy cycles

#### **4.10 Data Collection Tools and Procedures**

Medical record charts were collected based on the HMIS record and all the cards that were not in accordance with the inclusion criteria were returned by the primary investigator/supervisor. The supervisor discussed the goal and purpose of the study as well as the questionnaire with the other data collectors. The data collectors filled sample/pilot charts together, so there was common understanding as well as interpretation of the parameters and data. There were regular meetings

with primary investigator/supervisor and data collectors concerning the process. Every patient (or their relatives) were contacted over the phone at the end of data collection to confirm their alive/dead status.

#### **4.11 Data Management and Quality Assurance**

The principal investigator gave training on the relevance of the study and standard operating procedures to the data collectors; and had followed closely the data collection procedures and kept hard copy of the completed forms in a protected place.

#### **4.12 Data Analysis**

The collected data was transferred to excel and subsequently entered into and analyzed using SPSS version 22. The main findings were described by using frequencies, percentages, and summary statistics.

We ran multivariable analysis with P value < 0.05 taken as significant outcome. And survival was calculated by Kaplan Meier method.

#### **4.13 Ethical Consideration**

Ethical clearance was obtained from the department of oncology at Addis Ababa University College of Health Sciences (AAU CHS).

#### **4.14 Dissemination of Results**

The study finding will be submitted to the department of oncology and AAU CHS. Publication of the result on scientific journals will be considered through peer review and presentation on different meetings/conferences.

## 5. Results

### 5.1 Socio Demographic Characteristics of the Patients

A total of 249 patient with a pathologically confirmed diagnosis of breast cancer were identified from HMIS data, of which 216 cases were eligible for this study. Of these 216 patients, women accounted for 201 (93.1%) of the cases and 15(6.9%) were men.

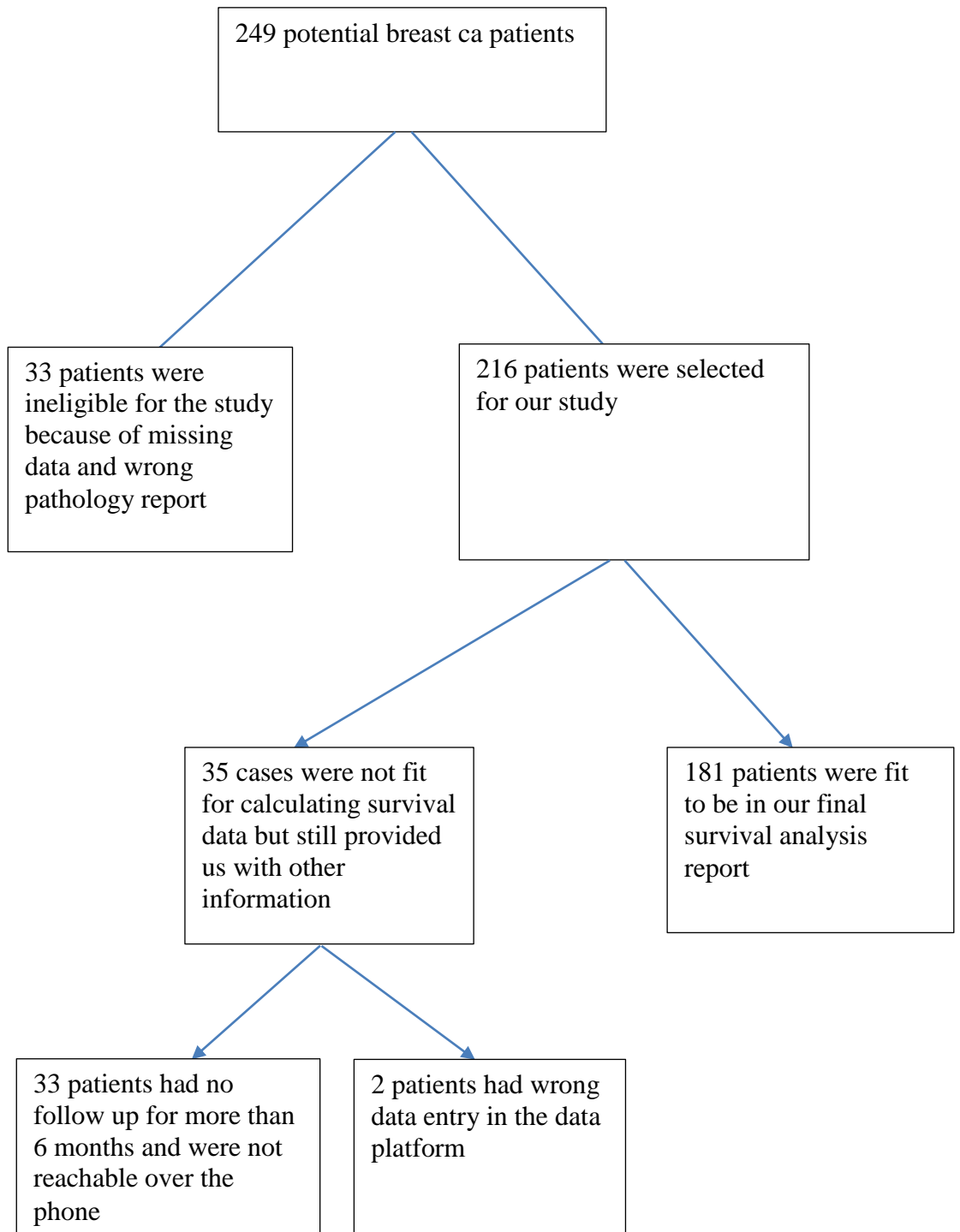
The mean age of patients was  $43.4 \pm 11.4$ SD years old and the commonest age group is age <40 accounting for 40.7% cases followed by age group of 40-50 years which accounted for 38 % of cases. 21.3% of the cases were above the age of 50 years. The youngest patient was 25 years old and the oldest patient was 85 years.

In terms of regional distribution 97 patients (44.9 % of the cases) were from Addis Ababa whereas the other cases were from outside of the capital city. (table 1)

Table 1: Distribution of patients by gender, address and age

<b>Address</b>	<b>Frequency</b>	<b>Percentage</b>
A.A	97	44.9
Oromia	50	23.1
Tigray	15	6.9
Snnpr	31	14.4
Amhara	19	8.8
Others	4	1.9
<b>Age category</b>		
Under 40 years old	88	40.7
40-50 years old	82	38
>50 years old	46	21.3

## Data flow diagram



## 5.2 Histopathology Characteristics

The commonest histology was ductal ca which had a 91.2% incidence followed by 2.8% cases of lobular ca. The rest of the cases (6%) constituted of other histology. (Table 2)

Moderately differentiated histology was seen in 48.1% of the patients followed by well differentiated type accounting for 29.2% of the cases and the remaining 22.7% of the patients had a poorly differentiated histology. (Table 2)

Table 2: Histology and grade distribution

<b>Histology</b>	Frequency	Percentage
Ductal/NOS	197	91.2
Lobular	6	2.8
Others	13	6.0
<b>Grade</b>		
Well differentiated	63	29.2
Moderately differentiated	104	48.1
Poorly differentiated	49	22.7

## 5.3 Stage Distribution

Based on the 7<sup>th</sup> AJCC staging for breast ca, the commonest stage of presentation was stage III and it accounted for 86(39.8%) of the cases followed by 66 cases (30.6%) of stage IV presentations. 56(25.9 %) of the patients had stage II disease and the least common stage was stage I (only 8 patients). So, 70.4% of the patients had locoregionally advanced or metastatic disease at presentation compared to 29.6% of cases diagnosed as stage I or II. (Figure 1)

Out of the 181 patients that were analyzed 38.1% of them were stage III at presentation, 31.5% were found to be stage IV, 26% were stage II and 8 (4.4%) of the patients were stage I on initial presentation based on the 7<sup>th</sup> AJCC stage classification. The combined number of stage I&II patients is 55 whereas 68.3% of patients presented with locally advanced or metastatic disease.

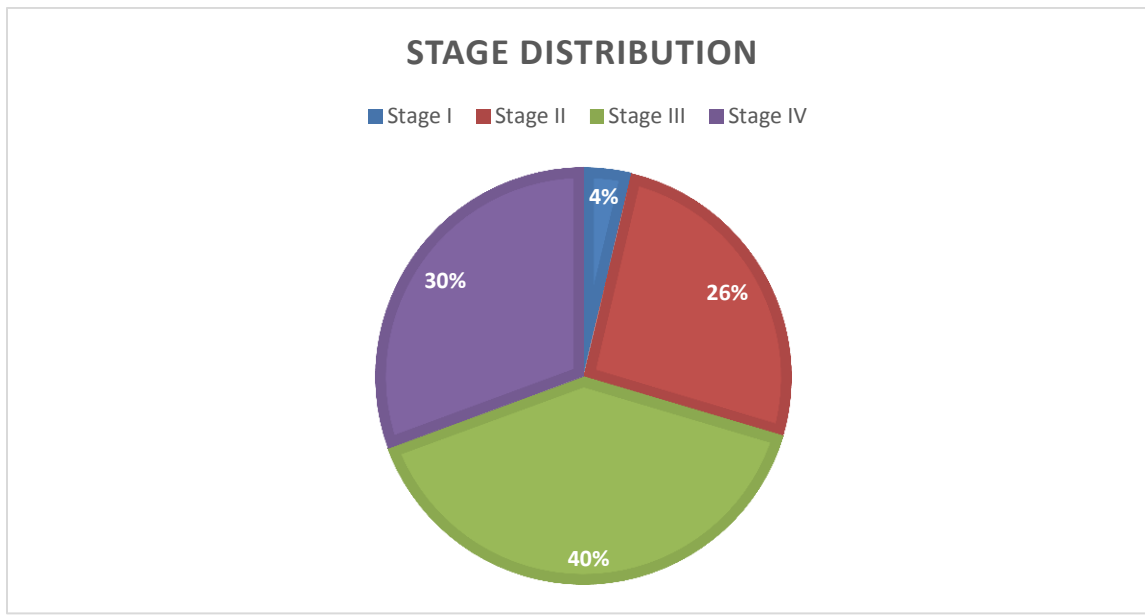


Figure 1: Stage distribution (n=216)

#### 5.4 Type of Treatment Given

From the total of 216 patients 171 had undergone surgery for their breasts of which 70.8 % of them took chemotherapy. Neoadjuvant chemotherapy was given to 7 patients before their surgery.

69.4% out of the 216 patients took 4-6 cycles of first line chemotherapy, 24 patients took one to three cycles and 3 patients took >6 cycles of chemotherapy. Whereas 18.1% of the patients had not received any type of chemotherapy for the totality of their follow up. (figure 2)

Out of the 132 patients who received adjuvant chemotherapy, 66 patients (50%) had a delay of 2-3 months, 43(32.6%) of the patients received the adjuvant treatment after more than 4 month of delay whereas 23(17.4%) of the patients were given chemotherapy within a month of the surgery. (Table 3) 19 patients out of 25 stage IV patients who already had MRM at presentation had taken palliative chemotherapy.

In the final analysis of the 181 eligible patients, 109 out of the 124 stage I-III patients took adjuvant chemotherapy whereas 41 out of 57 stage IV patients took palliative chemotherapy.

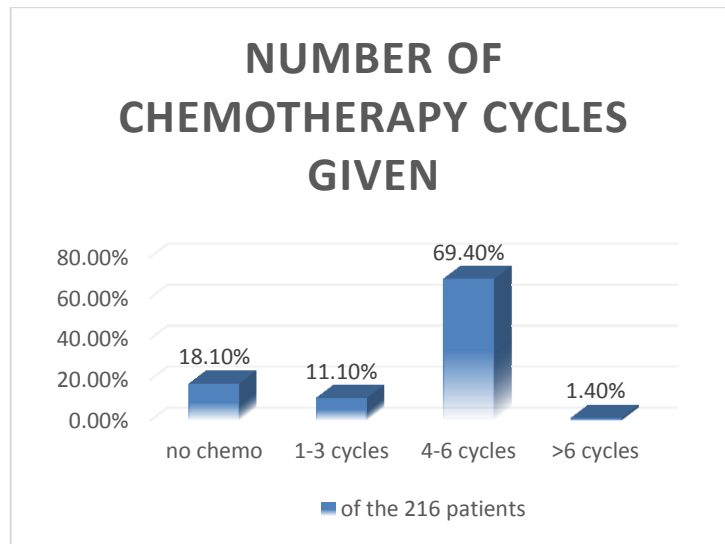


Figure 2: Number of chemotherapy cycles given

Table 3: Interval gap between surgery and adjuvant chemotherapy

Gap between surgery and adjuvant chemo	Frequency	Percentage
<1 months	23	17.4
2-4 months	66	50
>4 months	43	32.6
Total	132	100.0

Hormonal therapy was given to 43.1% of the patients while 123 patients didn't take any form of hormonal treatment at any time during their follow up. 74 out of the 93 patients took the hormonal therapy as part of their adjuvant treatment whereas 19 patients took it with a palliative intention. From the 93 patients who were on HT, 16.1% took it for no more than 6 months, 12.9% took it for 7-11 months, 16 patients received this form of treatment for 12-23 months and 53.8% took the treatment for more than 2 years. (figure 3)

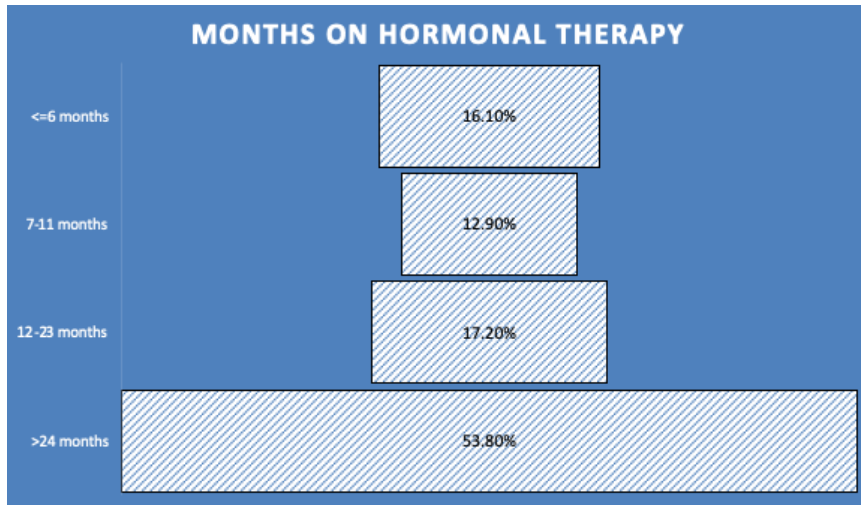


Figure 3: Months on HT

Only 47 patients received adjuvant radiotherapy. Three patients received the radiation within 6 months of the surgery, 15 patients received RT within 6-8 months of the surgery, 37.5% of the patients had a gap of 9-11 months and 25% of the patients were delayed for more than a year before they received the radiation.

13.9% of the patients have taken palliative RT for various indications at some point in their treatment.

## 5.5 Treatment Outcome

After analyzing the 216 patients, 35 cases were dropped because of incomplete data and/or loss from follow up for more than 6 months and were not reachable over the phone. Less than 20% of the patients were lost from follow up, so the chances of reaching to a biased conclusion was low. The median follow up period for the entire group was 19 months. The median survival for the 181 patients is 27 months (95% CI 18.3-35.7), with a 5-year OS rate of 44.2%. (figure 4)

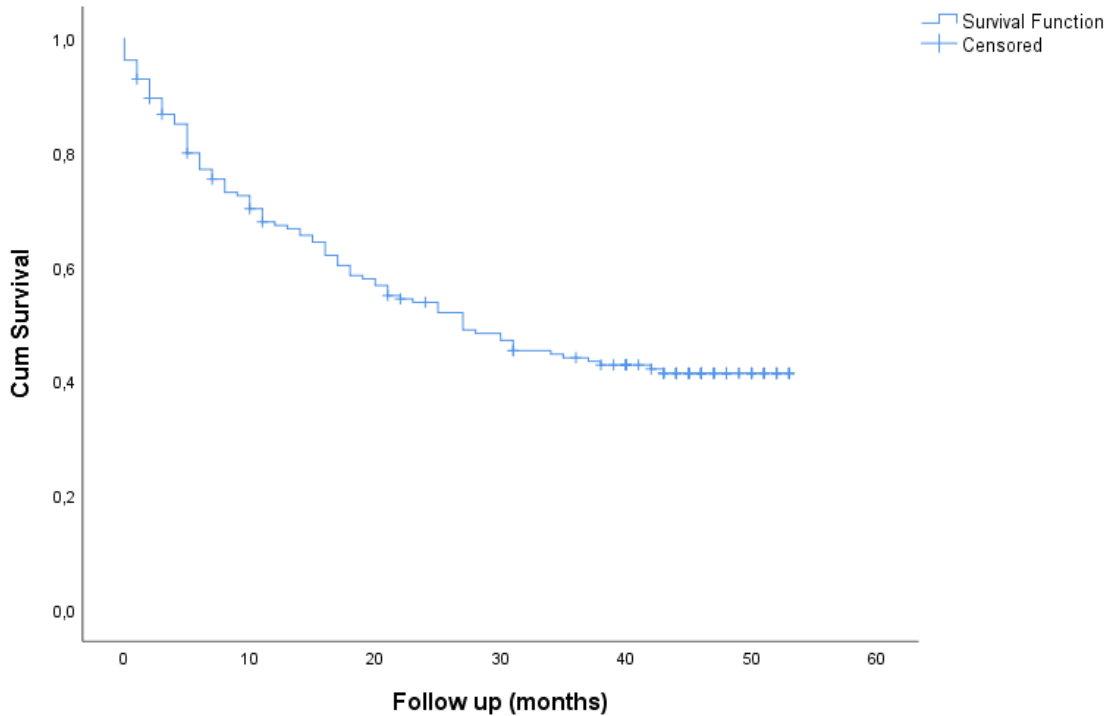


Figure 4: Overall survival of Breast ca patients

There was statistically significant difference in survival between the different stages, with the five-year survival rate being 100% for stage I patients, 87.2 % for stage II, patients and 42 % for stage III patients while only 3.5% stage IV patients were alive (Log Rank test  $p < 0.001$ ). (figure 5)

Table 4: Mean survival for stage II, III, & IV disease

Stage	Mean	95% Confidence Interval	
2	48,298	44,566	52,030
3	29,377	24,328	34,425
4	12,851	9,691	16,011

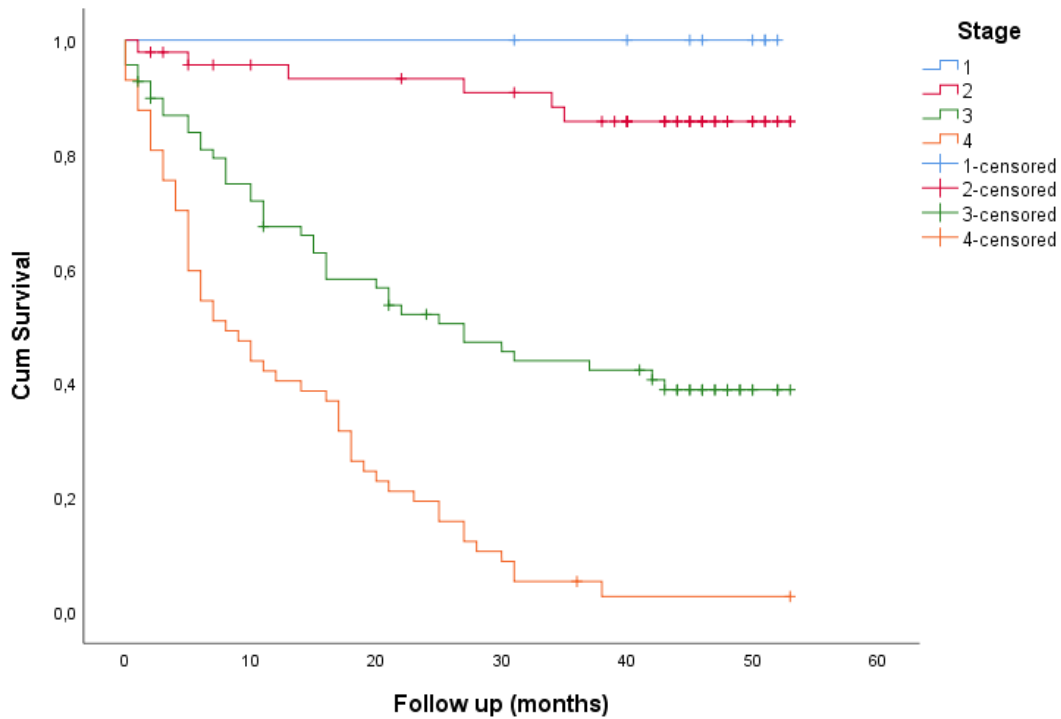


Figure 5: Overall Survival based on stage

When assessing Stage I&II patients as one group, they had a 5-year OS rate of 89.1% with a mean survival of 49 months. In contrast, when assessing combined stage III&IV patients, they had an 5 year OS rate of 24.8% with a mean survival of 21.7 months. Significant difference between the two groups was seen (Log Rank test  $p < 0.001$ ). (figure 6, table 5)

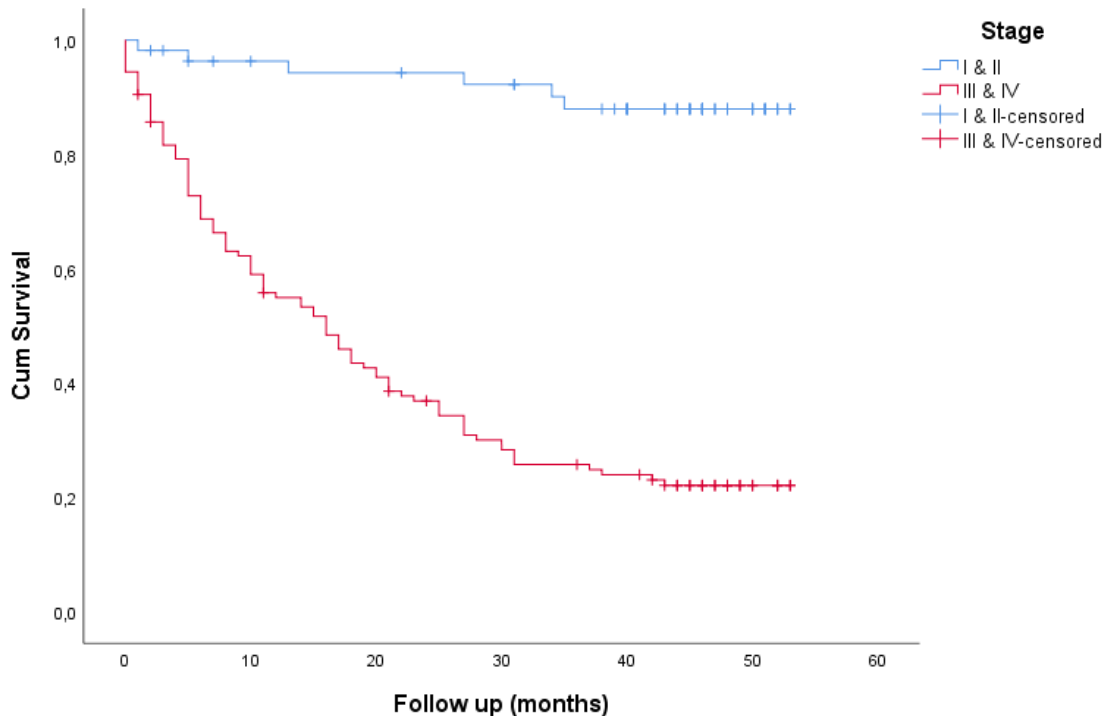


Figure 6: OS based on Stage I, II vs III, IV disease

**Table 5: Mean survival for stage I &II vs III, & IV disease**

Stage	Mean	95% Confidence Interval	
		Lower	Upper
I & II	49,019	45,825	52,214
III & IV	21,719	18,311	25,128

Out of the 181 patients who were eligible for analysis 87 of them took hormonal therapy (HT) for a various duration while 51.9% were not on HT. The 5-year OS was 64.4% for those who were on Hormonal therapy while only 25.5% five-year OS was attained for those patients who didn't take any kind of HT. The mean survival for those who didn't take any HT was 18.8 months whereas those patients who were on HT had a mean survival of 41.1 months (log rank  $p < 0.001$ ). (Figure 7)

The total months of HT intake was significantly (corrected p value of 0.008) associated with a difference in mean and median survival of 52.2 months and not reached vs 24. Months and 19 months respectively for those patients who were on HT for 24+ months and 7-11 months. (table 6)

The effect of HT on survival might be flawed because of lead time bias as those who died early might have been on HT for a short duration. We can't also exclude the inclusion of only favorable group of patients in the longer duration arm.

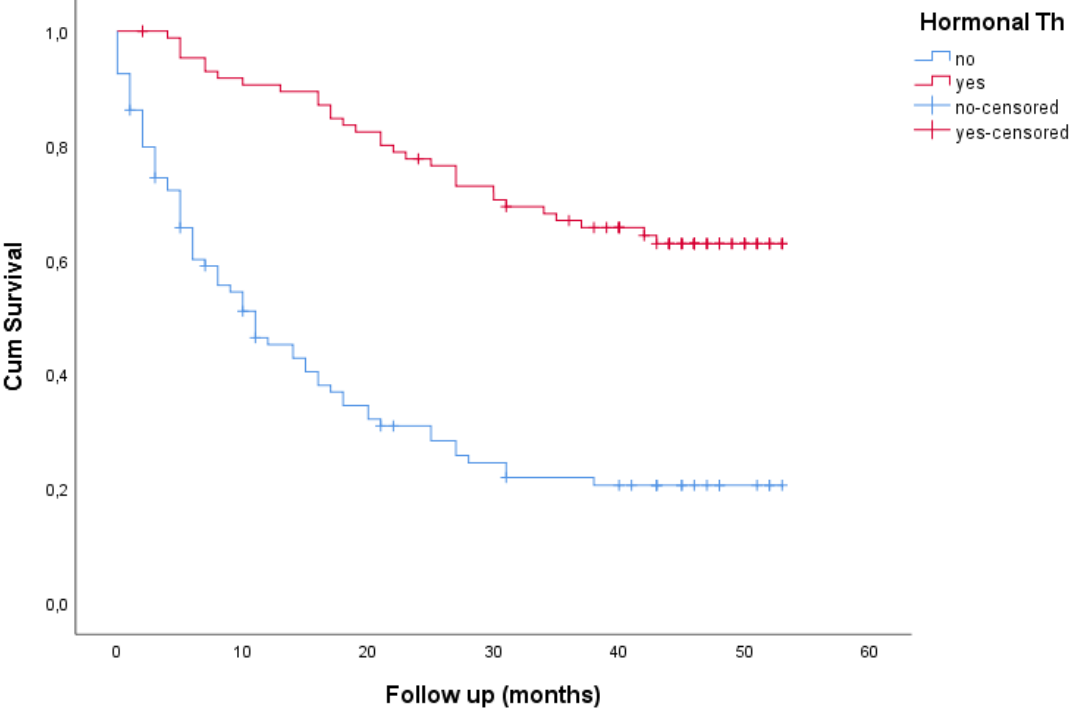


Figure 7: The impact of HT on Overall Survival

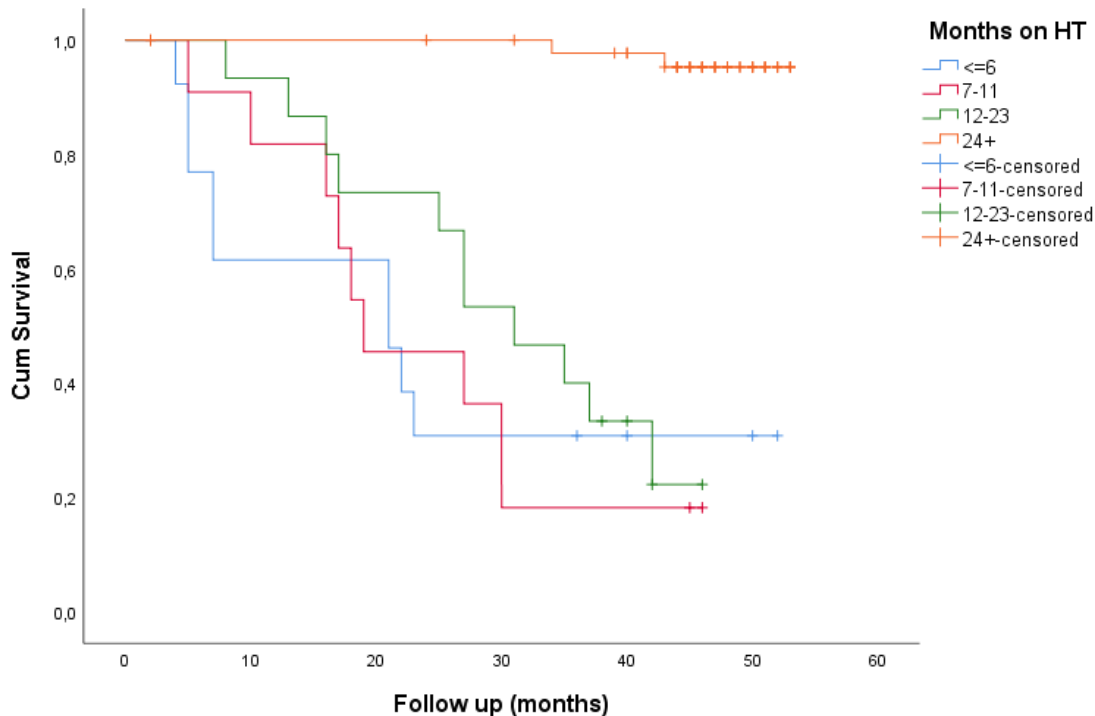


Figure 8: Relation of the total duration of HT and OS

Table 6: Mean and median survival based on months on HT

Use of HT	Mean	95% Confidence Interval		Median	95% Confidence Interval	
		Lower	Upper		Lower	Upper
no HT	18.863	14.830	22.896	11.000	6.148	15.852
<=6	24.846	14.347	35.346	21.000	3.385	38.615
7-11	24.000	16.483	31.517	19.000	8.211	29.789
12-23	30.622	24.281	36.964	31.000	21.532	40.468
24+	52.324	51.372	53.275	.	.	.

The impact of delay on initiation of adjuvant Chemotherapy on OS was also assessed. Out of the 108 patients who received adjuvant chemotherapy, 17 patients took chemo within a month of their surgery, 58 patients took treatment between 2 and 3 months after surgery and 33 patients had a delay of 4 or more months before they received any additional treatment after their surgery. Their OS rate was 82.4 %, 77.6% and 42.4 %. (Figure 9)

The influence of selection bias on the outcome of these patients can't be ruled out as some of the patients might have deteriorated or died while on chemotherapy because of poor performance status.

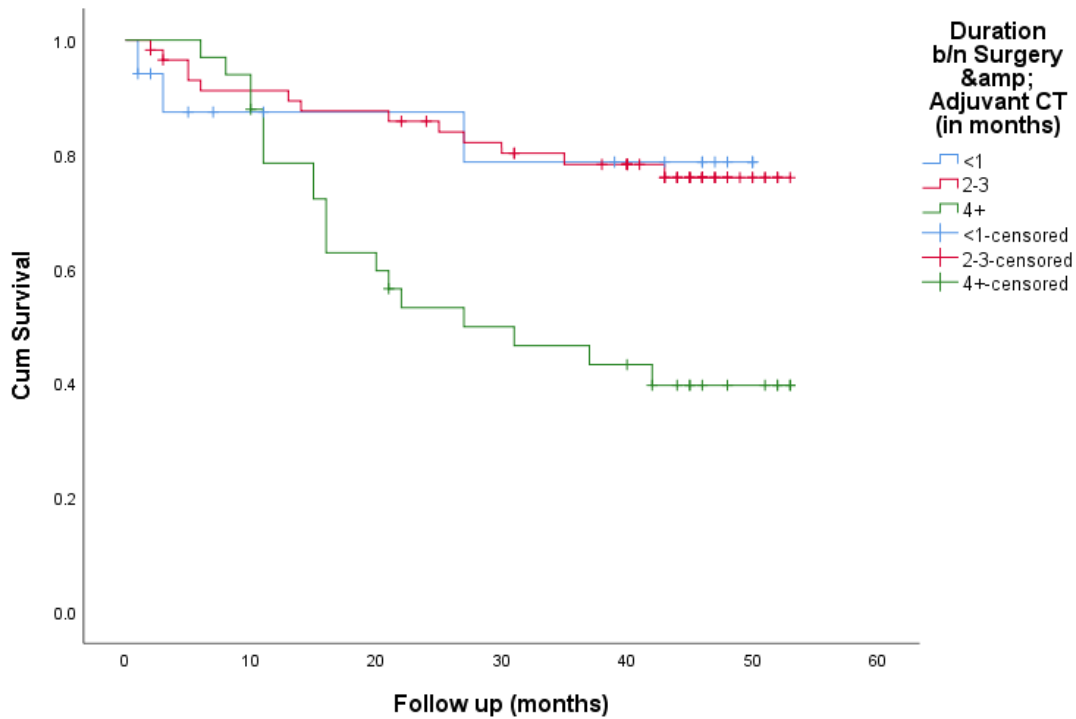


Figure 9: Impact of delay in initiating adjuvant chemotherapy on overall survival

<i>Pairwise Comparisons Log Rank (Mantel-Cox)</i>		
Duration b/n Surgery & Adjuvant CT (in months)	p value	
	<1	2-3
2-3	.995	
4+	.063	.001

Out of the 181 patients, 31 patients didn't receive any chemotherapy while 19 patients took 1-3 cycles of chemotherapy and 131 patients were given 4 or more cycles of chemotherapy.

The OS was 16.1% for those patients who didn't even receive a single cycle of chemotherapy while it was 15.8% for those who took 1-3 cycles of chemotherapy and patients who took 4 or more cycles had a superior OS in comparison to the other 2 groups ( $p=0.017$ ). (figure 10)

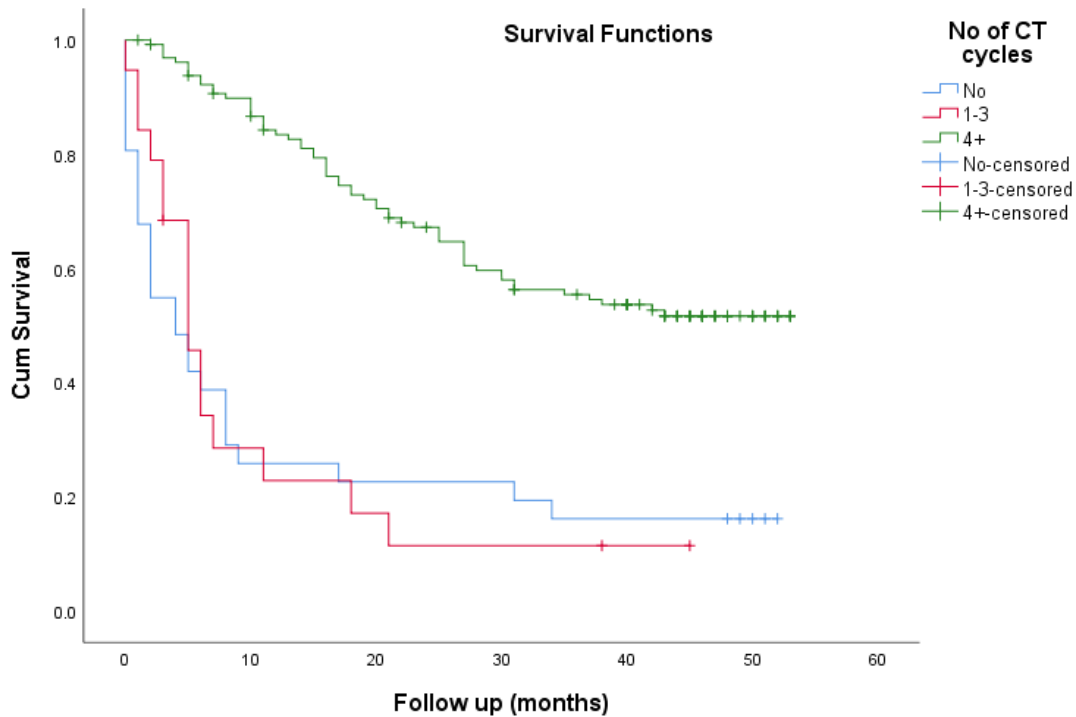


Figure 10: OS based on number of chemotherapies administered

Table 7: Number of chemotherapy with mean and median survival outcome

Number of CT cycles	Mean	95% Confidence Interval		Median	95% Confidence Interval	
No	13.258	6.661	19.855	4.000	1.273	6.727
1-3	10.732	4.503	16.962	5.000	2.987	7.013
4+	36.241	32.926	39.556	.	.	.

Age groups didn't show statistically survival difference. patients above the age of 50 had a 5-year survival of 51.2%, while those patients between the ages 40 &50 and under 40 years had a five-year survival of 44.9% & 39.4% respectively. (figure 11)

Table 8: Mean and medians for survival time based on age categories

<i>Means and Medians for Survival Time</i>						
Age	Mean	95% Confidence Interval		Median	95% Confidence Interval	
<40	29,534	24,704	27,000		19,117	34,883
40-50	28,703	23,431	27,000		16,728	37,272
>50	31,854	25,019	.		.	.

No significant difference between groups (Log Rank test p=0.620).

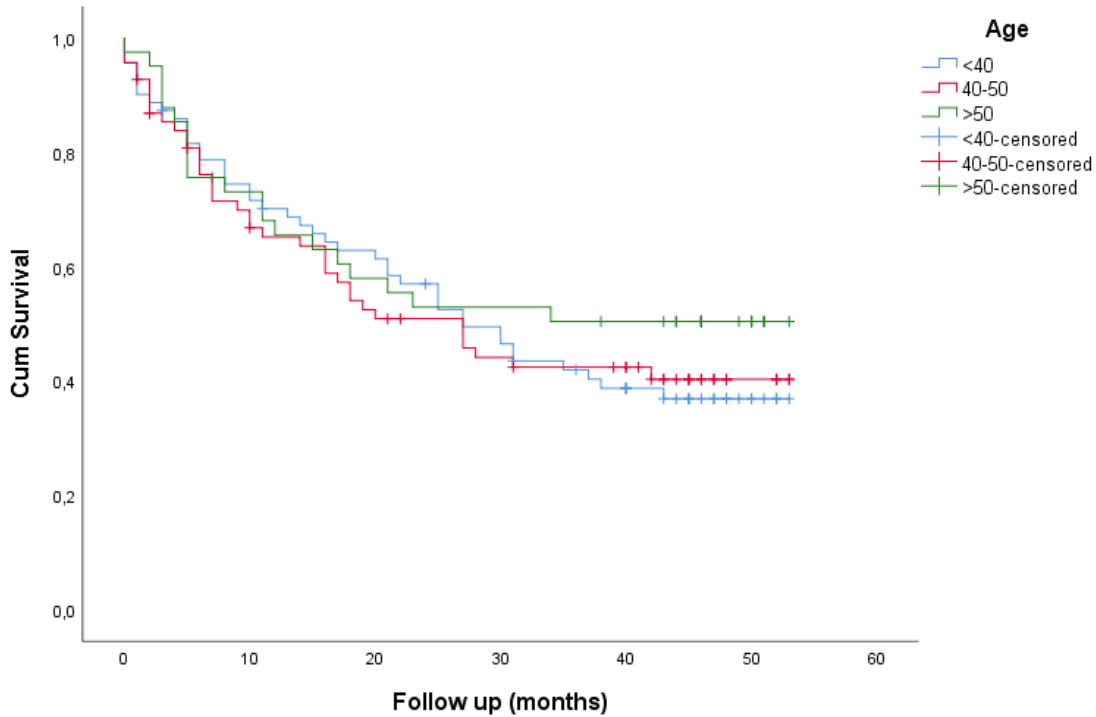


Figure 11: OS based on Age

According to the analysis of our patient’s data, Age has no impact on OS or disease parameters like Stage, Histology, Grade and Recurrence patterns. (table 9)

Table 9: Age in correlation with Stage, Histology, Grade and Recurrence

		Age						p value
		<40		40-50		>50		
		N	%	N	%	N	%	
Stage	1	4	4.5%	1	1.2%	3	6.5%	0.353
	2	19	21.6%	20	24.4%	17	37.0%	
	3	39	44.3%	35	42.7%	12	26.1%	
	4	26	29.5%	26	31.7%	14	30.4%	
Stage	I & II	23	26.1%	21	25.6%	20	43.5%	0.068
	III & IV	65	73.9%	61	74.4%	26	56.5%	
Histology	ductal	81	92.0%	77	93.9%	39	84.8%	0.203
	other	7	8.0%	5	6.1%	7	15.2%	
Grade	1	21	23.9%	27	33.3%	14	30.4%	0.152
	2	42	47.7%	39	48.1%	23	50.0%	
	3	25	28.4%	15	18.5%	9	19.6%	
Recurrence	no	66	75.0%	65	79.3%	38	82.6%	0.574
	yes	22	25.0%	17	20.7%	8	17.4%	

From the 181 eligible patients 81 of them presented with moderately differentiated tumors, 30.5 % had well differentiated disease and 44 patients had grade 3 disease. OS was found to be 48.1%, 47.3% and 34.1 % respectively with  $p=0.302$ . (figure 12)

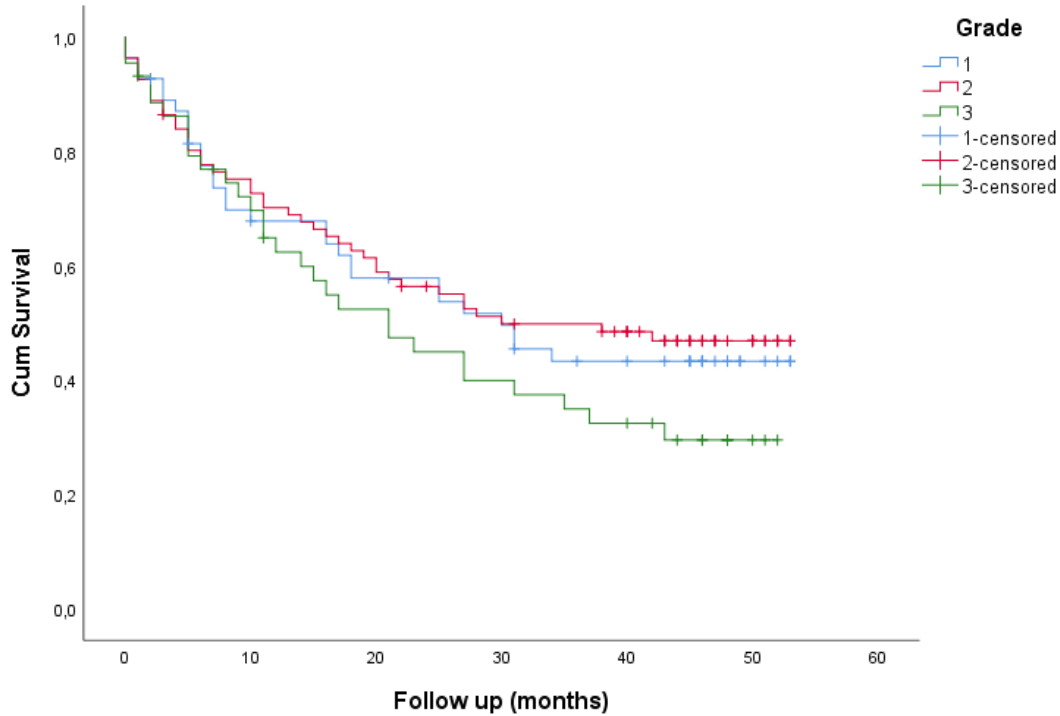


Figure 12: OS by Grade

Table 10: Mean and Median survival time based on Grade

Grade	Mean	95% Confidence Interval		Median	95% Confidence Interval	
Grade 1	30,378	24,552	36,203	30,000	14,875	45,125
Grade 2	31,594	26,841	36,346	30,000	.	.
Grade 3	25,836	19,857	31,814	21,000	11,223	30,777

OS was 43.9% for ductal ca while it was 47.1 % for the others. Median survival was 27 months for ductal ca (including Ductal ca NOS) and 34 months for the others category. No significant difference between groups as Log Rank test was  $p=0.495$ . (Figure 13)

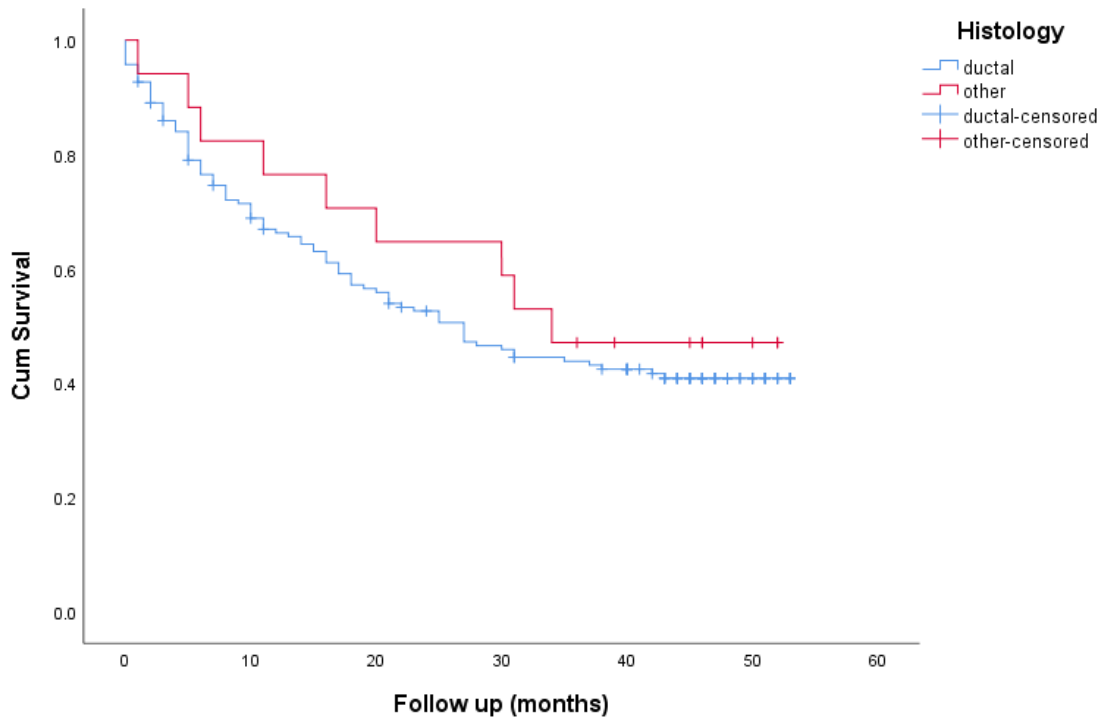


Figure 13: OS based on Ductal (including NOS) histology vs others

Out of 124 Stage I-III breast ca patients 80 patients didn't receive adjuvant RT while 44 patients took radiotherapy. Based on the analysis RT was not found to alter the OS or median survival.

Delay between surgery and adjuvant RT was also analyzed and there was no difference in terms of outcome when the time gap before radiotherapy was checked but there was an OS and median survival trend between the no RT and those patients who received RT within 8 months of their surgery but the p value was 0.089. (Figure 14)

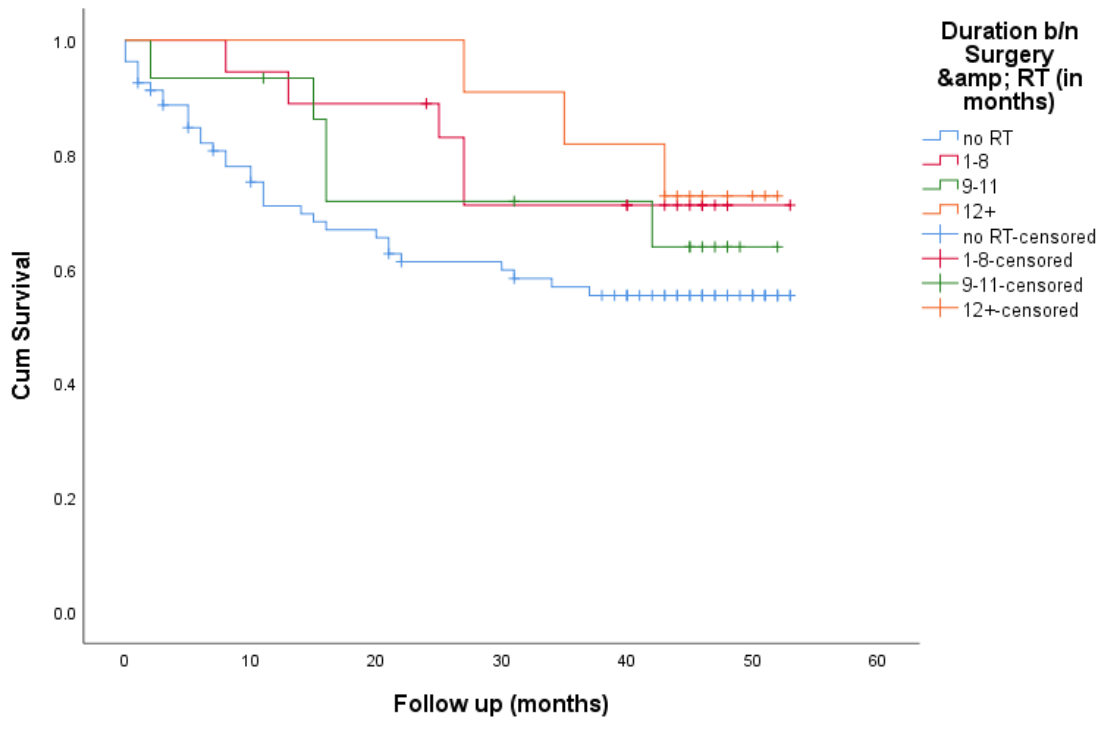


Figure 14: The impact of Radiotherapy on OS

## 6. Discussions

The results from this retrospective study show that the median survival for breast cancer is 27 months while the 5-year overall survival for the entire patients' group was 44.2 %. Factors that are found to be significantly associated with survival are stage of the disease, hormonal therapy and timing of adjuvant chemotherapy and number of chemotherapies cycles the patients took.

The survival in this study is lower than that of the report from CONCORD 2008 which reported 5-year relative survival ranging from 80% or more in north America, Australia, Finland, Japan and Sweden to 60% or less in Slovakia and Brazil but slightly better than that of 38.8 % in Algeria (8). The recently published CONCORD-3 report for women diagnosed between 2010-14 showed an increment in 5-year net survival which approached 90 % in north America, while 85% or better survival has been reported from 25 countries. 12 countries (3 from south and central America; 5 Asian countries and turkey) as well as 4 European countries reported an 80-84% survival. A 70-79% survival range has been seen from 12 countries (23). Overall survival data was reported from our neighboring country, Sudan, which reported on 64 patients, as having a median overall survival of 40 months and a 5-year survival probability of 38% and like our patients, the majority of patients presented with stage III & IV disease. This study also suffered from variable follow up period in between the patients and number of the patients that were studied (24). Our data shows a lower 5-year survival rate of 44.2% compared to other African countries in the recent retrospective study by Joko-Fru et al where they reported overall age standardized relative survival of 66.3% at 5 year. They also documented disparity not only between different countries but also in different registries within the same country. The 5-year survival varied from 5.3% in Kyandondo, Uganda to 93.7% in Mauritius (15).

One explanation for the lower rate of survival in African countries could be because of tumor biology as a result of race (25). In 5 consecutive trials assessing adjuvant treatment for breast ca, coordinated by the SWOG, adjusted for age, hormonal receptors, number of involved LNs, and tumor size, black patients had worse outcome than the other patients with regard to disease-free, overall, and cause-specific survival (25). This finding is supported by a cohort of 205,736 breast ca patients who joined the SEER registry between 1990 and 2000, after adjusting for gender histology, age receptor status and residential area, white women had substantially better survival than black women (26). This higher mortality rate among African Americans, despite having a

lower incidence rate than non-Hispanic whites, was attributed both to a diagnosis at a more advanced stage and to poorer stage-specific survival. For example, the 5-year relative survival for breast cancer in the regional stage is 74% in blacks compared to 86% for white women who are diagnosed at a similar stage (27). But 74% survival in blacks from America is still significantly better than our figure of 62.9% (for stage I-III patients) and even lower for regionally advanced (stage III) disease so other factors must also have a role in the difference of outcomes seen.

The mean age of our patients was 43 years and the commonest age group is age <40. There was mean survival difference of 3 months and a 12% five year survival difference in between those who were older than 50 years and in those between the age of 40 & 50, in favor of the older age group, but it was not statistically significant and as such, age has no prognostic implication in our analysis. According to a study done by Fregene and Newman, African women are on average diagnosed 10 years earlier than women from the west. They were also more likely to be diagnosed at a more advanced stage and thus tended to have a higher mortality too (28). The age distribution seen in our study as well as other SSA might be due to the younger age demography of this region (22). Age was also not a prognostic factor for survival after adjusting for stage and HDI in the population-based registry study by Joko-Fru et al. (15).

The lower rate of survival for our patients can be explained by the more advanced stage presentation in our population as 38.1% of the patients were stage III at presentation, & 31.5% were found to be stage IV with the combined proportion of 68.3% of patients presenting with locally advanced or metastatic disease. Stage was a significant prognostic factor in our study as it was discussed in the results part. Stage III & IV patients were > 3 times more likely to die at 5 years than stage I & II patients. The combined 5-year OS for stage I-III is 62.5% vs 3.5 for metastatic patients.

Similar to our finding, most patients in developing countries present with advanced stage, although there are only a few available data on stage at presentation, they indicate that a really high proportion of cases within the developing world area are detected in late stages (29). In a prospective cohort study from Ethiopia conducted in the same center as this retrospective study, involving 1,070 patients, a metastatic free 2-year survival of 72 % in stage I & II patients and

32% probability in stage III patients was documented. This in the authors opinion pointed to a more favorable outcome in their cohort compared to OS reports from other parts of Africa. This study also reported a high proportion of patients had a stage III disease (70% of stage I, II, III patients) (20). In our study stage III patients accounted for 55.6% of non-metastatic patients which might suggest an improvement of earlier presentation to the hospital than at the time this cohort was conducted. In another study from our center where 573 women with metastatic disease were analyzed for survival, a mean survival of 11.7 month was obtained (22) which is more or less similar to our report of 12.8 months mean survival.

A study from Sudan has reported that 64% of the patients presented with stage III & IV disease and the 5-year OS was 38% (28), which had similar stage and survival distribution to our study. A study from a tertiary center in Uganda revealed a 5-year overall survival of 56% for their entire patient group, 39% for advanced stage and with, a relatively good outcome, for early stage disease of 74%. In this study 51 % of the patients had stage III disease, metastatic disease was seen in 26.3% and the rest of the patients were discovered to have early disease (30). This study reaffirms the need for diagnosing patients at an earlier stage than what is observed with the current trend in Africa.

A retrospective analysis from Egypt had confirmed that stage III was the commonest stage presentation in their study accounting for 46.7% followed by stage II disease (39.5%) and the third commonest stage was stage IV with 10.5% incidence (31). This study suggests that there is a better chance of patients being diagnosed before the disease was metastatic in certain parts of Africa. And stage by stage comparison of survival for stage III and stage IV disease from this study was also better than ours. The reason for this is unknown but younger mean age in our study, delay in initiation of the treatment, lack of treatment adherence and tumor biology might be responsible for this discrepancy.

One of the significant prognostic factors in our analysis was time interval between surgery and adjuvant chemotherapy. The OS rate was almost 2 times higher in patients who were put on chemotherapy within a month of their surgery than those patients who had a delay of 4 or more months. This finding is supported by the report from a retrospective study of 2,594 patients from British Columbia cancer agency in which the overall survival was inferior when the patients

were started on chemotherapy after 12 weeks compared to those patients who received it within 12 weeks (32). Our study is also similar to a more recent publication from 2014 which utilized a large retrospective cohort of stage I-III breast ca patients diagnosed and treated between 1997-2011. It reported that patients with more advanced stage had worse outcome when adjuvant chemo was started 61 days or more after the date of surgery. In this study stage II patients had worse RFS and DRFS when chemo was delayed by more than 2 months with no difference in OS while stage III patients experienced inferior OS, DRFS and RFS when chemo was delayed by more than 61 days compared to those who were initiated within 30 days (33).

This is in contrast to a Spanish report (GEICAM) from the El Alamo project (15,400 patients between 1990-97). They analyzed 2,782 stage I-III breast ca patients in terms of adjuvant chemotherapy timing as <3 weeks, 3-6 weeks, 6-9 weeks and > 9 weeks showed that there was no significant difference in 5-year DFS or OS between the 4 arms (34).

Another significant factor for prognosis was number of adjuvant chemotherapy cycles, as those who managed to take more than 4 cycles had a mean survival of almost three times that of those who didn't take any chemotherapy. This wasn't surprising as there are abundant literatures which have shown survival benefit of chemotherapy. Our study suffers from its limitation of selection bias as patients who were able to survive longer are more likely to receive more cycles.

A metanalysis by the Early Breast trialists' Collaborative Group (EBCTCG) showed that the use of CMF or an anthracycline containing regimen produced an absolute benefit of 2-3% in 10-year survival for patients between 50-69 years and a 7-11% absolute benefit in those younger than 50 years. When CMF chemotherapy was directly compared to anthracycline containing regimens, the latter arm revealed a greater effect in terms of 5-year survival and recurrence rate (35).

A collaborative metanalysis of 194 unconfounded randomized trials (that utilized hormonal therapy and adjuvant chemotherapy that used several combination chemotherapies tamoxifen, ovarian suppression, FAC, FEC, & CMF) was done. None of the studies included taxanes, AI or trastuzumab. Anthracycline containing regimens, when given for 6 months, reduced annual death rate by 38% for those younger than 50 years and by about 20% for those patients between 50-69

years (36). The aforementioned metanalysis closely resemble the chemotherapy regimen that is commonly given per the study institution's guidelines (CMF, AC, FAC) and thus collaborates our finding.

Modern chemotherapy regimens yield a median survival of 2-3 years in stage IV patients with 5-20% of these patients having many years of prolonged survival. (37) As the more efficacious newer agents were never used during the treatment of the study population, we don't expect a survival magnitude of such range.

Hormonal therapy, as expected, had a significant role in improving survival. The OS was 64.4% versus 25.5 % in patients who were on hormonal therapy versus those who were not. Endocrine therapy was given to patients with ER+/PR+ disease and those whose receptor status was unknown. Our study also shows that duration of endocrine treatment correlates with survival benefit as those patients who took the treatment for 2 or more years had a mean survival double of those patients who took it for less than 11 months. As with the effect of number of chemotherapy cycles, the duration of HT suffers from selection bias as those patients with favorable outcome are going to take it for longer duration than those who had poor prognosis from the start.

The metanalysis by EBCTCG showed that 5 years of adjuvant Tamoxifen reduces yearly death rate by 31% regardless of PR receptor status, age of the patient or other tumor parameters. It also demonstrated that, even though both adjuvant 1-2 years and 5 years of tamoxifen reduced recurrence and breast cancer death significantly in ER positive breast cancer patients and to a lesser extent in women with an unknown receptor status, 5 years of tamoxifen was more beneficial than just 1-2 years of the same treatment. The same metanalysis concluded that treatment with either FEC or FAC followed by adjuvant 5 years of tamoxifen was able to reduce mortality by 45% in women between the age of 50 & 69 and by 57% for women younger than 50 years of age (36). In our study even shorter duration of endocrine therapy was associated with survival benefit but the survival benefit was increased by longer duration of use.

Previous studies from Ethiopia are different in the receptor status as one study showed that out of 352 patients whose receptor status was analyzed only 31% of the patients had ER-ve/PR-ve disease while 69% of the patients had either or both ER and PR positive disease (38). Another study that included 114 breast ca patients determined that luminal A disease was the commonest molecular sub type and 65% of patients, in this study, had ER receptor positive disease and 43% PR positive disease with only 10% rate of HER2+ enriched disease and in total 66% of patients had luminal (type A & B ) disease (39). Even though receptor status was never confirmed for most of our patients, the survival benefit demonstrated with its use suggest a high rate of receptor expression in our study group.

In our study the use of post mastectomy radiotherapy didn't have a significant impact on survival. We haven't assessed the effects of RT on DFS and/or locoregional control rate. The lack of impact from radiotherapy, on survival, can be explained by the short duration of our study. Most of the previous prospective studies and metaanalyses demonstrated its survival benefit after prolonged follow up. The 20 years follow up result of the British Columbia trial showed that when radiotherapy was added to chemotherapy (vs chemotherapy alone); there was a statistical significant benefit in improving locoregional recurrence, systemic relapse free survival, breast ca free survival, event free survival, breast ca specific survival and OS (unlike the results from the 15 years follow up which hadn't demonstrated a statically significant OS benefit) (40).

The Danish breast cancer cooperative 82b trial demonstrated significant benefit of CMF + PMRT in terms of locoregional recurrence reduction, increment of DFS and OS at 10 years, over CMF alone, regardless of histologic grade, tumor size and number of involved LNs (41). In the future a prolonged follow up of patients who received radiotherapy from centers in Ethiopia might give us the estimated benefit of radiotherapy in Ethiopian population.

Histologic sub type didn't correlate with change in survival patterns in our study. Ductal ca NOS has a median survival of 27 months whereas the other histology groups as a whole had a 34 months median survival, but this difference was not statistically significant.

The lack of difference in outcome has already been reported by a prospective cohort from the same center (20).

Pathologic grade was also found to have no influence on survival as grade 3 tumors had 21 months of median survival while grade 1 & 2 had 30 months of median survival. But this difference wasn't found to be significant on the log rank test.

The limitation of our study is that there is a possibility of selection bias in determining the prognostic values of number of chemotherapy cycles as well as duration of hormonal therapy, since patients with favorable outcome from the start are going to receive more chemotherapy cycles and longer duration of endocrine treatment.

We didn't also assess the molecular patterns (receptor status, HER2+ and Ki67index) as it wasn't available for the majority of the patients. This makes it even harder to conclude any benefit of hormonal therapy in our study population. These parameters would have also helped us to differentiate the prognosis of patients regardless of HT and would have also suggested which patients would have potentially benefitted from anti-HER2 treatments.

Another limitation we saw in hindsight is that we haven't assessed the adequacy of the surgery or completeness of pathology report as these issues are expected to have a large impact in terms of outcome even in patients with the same stage of disease.

## **7. Conclusion and Recommendation**

### **7.1 Conclusions**

Median survival for the entire population is 27 months with a 5-year survival rate of 44.2%. 62.9 % of the patients with non-metastatic disease have 5-year survival compared to 3.5% survival in stage IV patients. Based on our analysis significant associations were made between OS and stage at diagnosis, delay between surgery and adjuvant chemotherapy, use of chemotherapy, total number of chemotherapy cycles administered, use of hormonal therapy and its duration.

### **7.2 Recommendations**

Since stage at presentation has been the most significant factor in determining OS, every effort should be made to diagnose breast ca patients at an earlier stage through early detection.

The survival rate in parts of the world where breast cancer awareness is high and/or screening modalities are used, most patients are diagnosed at an earlier stage and survival is excellent.

We have to expand oncology care in Ethiopia by expanding the facilities as well as interdisciplinary communications through multidisciplinary meetings as timing of adjuvant treatment was seen to impact the outcome of our patients.

The use of molecular profiling in routine clinical practice might yield a better understanding of breast cancer biology and it might decrease costs and toxicity by avoiding unnecessary prolonged endocrine treatment in those women with receptor negative disease.

Finally, we have to expand the availability of the chemotherapy options, newer endocrine agents and targeted therapies in managing breast ca in all stages of the disease.

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## 8. Annexes

### 8.1 Data abstraction tools

#### 1. Demographic data

Ser. no	Item	
101	Card number	
102	Phone number	
	Sex	1. M    2. F
103	Age (years )	
104	Address (Region)	1. A.A 2. Outside of A.A

#### 2. Disease and treatment characteristics

201	Clinical Stage	1. I 2. II 3. III 4. IV
202	Pathologic Stage	
203	ECOG Performance (0-4)	
204	Date of FNAC/BIOPSY/REFERRAL	
205	Duration of time between surgery and first presentation to Oncology department in	
206	Histology	1. Ductal 2. Lobular 3. Medullary 4. Mucinous 5. Papillary 6. Tubular 7. Squamous 8. Adenoid cystic 9. Cribriform 10. Undifferentiate 11. NOS
207	Grade	1. well differentiated 2. moderately differentiated 3. poorly differentiated

208	Family history	1. Yes 2. No
209	Metastasis at presentation	1 Yes 2 No
210	Neoadjuvant Chemotherapy	1. Yes 2. No
211	Neoadjuvant radiotherapy	1. Yes 2. No
212	Duration between surgery and adjuvant chemotherapy (in months)	
213	Number of chemotherapy cycles (in number)	
214	Adjuvant Radiotherapy	1. Yes 2. No
215	Duration between surgery and radiotherapy (in months)	
216	Palliative radiotherapy (+/-)	1. Yes 2. No
217	Hormonal therapy (+/-)	1. Yes 2. No
218	Months on hormonal therapy	

#### 5. Survival data

501	Current Status	1 Alive without recurrence 2 Alive with local recurrence 3 Alive with distant metastasis 4 Dead
502	Site of recurrence	1-Chest wall 2-Axilla, 3-Other site
503	Second line chemotherapy	1. Yes 2. No
504	Time of last follow up (months after initial presentation)	
505	Months the patient is/was alive after the date of histologic confirmation (phone interview)	