ADDIS ABABA UNIVERSITY

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Clinicopathological factors associated with locoregional breast cancer recurrence, a retrospective study.

For Partial Fulfillment of the Post Graduate Program in Pathology

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The undersigned agree to accept all responsibilities for the scientific and ethical conduct of the *research project* and for the provision of required progress reports as per terms and conditions of the guideline of post graduate studies coordination office in effect at the time after proposal defense is forwarded as the result of this application. I will provide timely progress report to my advisor and seek the necessary advice and approval from my primary advisor in the course of the research.

Name of the student: Hidaya Yahya Mohammed Signature: _____ Date:

Name of the primary advisor: Dr Yonas Girma Signature: _____ Date:

Acknowledgment

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Acronyms and abbreviations

DCIS- Ductal carcinoma in situ

ER- Estrogen receptor

HER-2- Human epidermal growth factor receptor 2

LRR- Locoregional recurrence

LVI- Lymphovascular invasion

PNI- Perineural invasion

PR- Progesterone receptor

TASH- Tikur Anbessa Specialized Hospital

ABSTRACT

Background

Breast cancer is the most common cancer in Ethiopia with an estimated incidence of 16,133 new cases and 9,061 deaths in 2020. Patients with breast cancer are frequently observed experiencing locoregional recurrences despite the many treatment options available. The purpose of this research was to determine the incidence and recurrence predictors among patients with breast cancer at Tikur Anbessa Specialized Hospital, Ethiopia.

Methods

An institution-based retrospective study was conducted from November to December, 2023. 258 patients who had surgical treatment for breast cancer from September 11,2017 to September, 10, 2020 were included in this study. Data were collected from the patients charts by using Kobo toolbox. The collected data was analyzed using SPSS version 26. Median time to recurrence was determined, and life tables were used to determine recurrence free survival time and the proportion of survival over a follow-up period. The assumptions of cox proportional hazard were checked, and variables were analyzed in bivariate and multivariable Cox proportional hazard model. Adjusted Hazard Ratio (AHR) with 95%CI was calculated for the significant predictive variables and statistical significance was declared at p-value<0.05.

Result

The incidence rate of breast cancer recurrence was 5.36 per 100 person-years (95%CI=3.85-7.07) follow-up. The median Recurrence Free Survival (RFS) time was 55 months (95CI%=41.73-68.26). The proportion of RFS at 12, 24 and 60 months were 92.5%, 81.4% and 41.7% months respectively. Histologic grade 3 (AHR=3.22, 95% CI (1.37, 7.6)), and lymph node involvement (AHR=1.175, 95%CI, (1.11,1.27)) were independent predictors for increased risk of breast cancer recurrence.

Conclusion

There is high incidence of locoregional recurrence in breast cancer patients. Applicable pathological variables including histologic grade and lymph node positivity may predict the likelihood of a breast cancer recurrence and should be emphasized in breast cancer care.

1- Introduction

1.1 Background

Breast cancer is the most common cancer among women worldwide, affecting millions of lives every year. As of 2020, female breast cancer has exceeded lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million (11.7%) new cases and about 685,000 deaths, with large geographical variations observed between countries and world regions(1). Among women, breast cancer accounts for 1 in 4 cancer cases and for 1 in 6 cancer deaths. The burden of breast cancer varies across regions, with the highest incidence rates in high income countries, and the lowest rates in Africa and Asia. However, breast cancer incidence is increasing rapidly in low- and middle-income countries, where limited resources and late diagnosis often result in poor outcomes. Some of the most rapid increases are occurring in sub-Saharan Africa but often have low survival rates largely due to late-stage presentation(2)

In Africa, breast cancer is the most common cancer among women followed by cervical cancer, accounting for 16.8% of all new cases and 12.1% of all cancer deaths in 2020(3). Breast cancer patients in Africa tend to present at younger ages and with more aggressive tumors than in other regions(4).

Ethiopia is showing significant improvement in communicable disease but the landscape of disease is undergoing change with rise in morbidity and mortality due to noninfectious disease like cardiovascular disease, cancer and etc. (5). Breast cancer is the most common cancer among women in Ethiopia, with an estimated 16,133 new cases and 9,061 deaths in 2020 (6). Patients tend to be diagnosed at younger age with a mean age at diagnosis of 45.8 years(4). Approximately 65% of women are diagnosed at advanced stage of the disease (stage III and stage IV), which is due to delayed diagnosis and treatment. Late presentation is related to use of traditional medicine before treatment, patient delay and diagnosis delay(7).

Breast cancer recurrence is the reappearance of cancer after a period of remission. It can recur locally (same breast or chest wall) , regionally (nearby lymph nodes) or may recur distantly in other organ and is a major challenge for breast cancer management and control. The risk of

recurrence depends on various clinicopathological factors, such as tumor size, grade, stage, lymph node status, hormone receptor status, human epidermal growth factor receptor 2 (HER2) status, and molecular subtype (8).

There is a scarcity of data on the recurrence rate and patterns of breast cancer in Ethiopia. Understanding the clinicopathological factors that influence breast cancer recurrence in Addis Ababa can help to identify high-risk patients, optimize treatment strategies, and improve patient outcomes. It is essential to identify high-risk patients who may benefit from more intensive surveillance and treatment strategies.

The research will investigate the clinicopathological factors associated with locoregional breast cancer recurrence among patients treated at Tikur Anbessa Specialized Hospital (TASH), a tertiary referral center in Addis Ababa University. TASH is one of the few hospitals in Ethiopia that provides comprehensive care for breast cancer patients, including surgery, chemotherapy, radiotherapy, hormonal therapy, and targeted therapy.

1.2. Statement of the problem

Breast cancer is a major public health problem that affects millions of women worldwide. It is the most common cancer and the leading cause of cancer death among women and the burden of breast cancer varies across regions (2). One of the main challenges in breast cancer management is the risk of recurrence, which is the reappearance of cancer after a period of remission.

Approximately 70% of breast cancer patients in most high-income countries are diagnosed in stages I and II, whereas only 20%-50% patients in the majority of low- and middle-income countries are diagnosed in these earlier stages. One of the factors is the delay between symptom discovery and start of treatment. Majority of breast cancer patient in low-income countries have a median time interval of 3-8months from onset of symptom till the initiation of treatment, while patients in high income countries have an interval of 30-48 days(9). Study from Ethiopia showed that majority of percent of the patients were diagnosed at advanced stage of the disease (44% stage III and 20% stage IV), with only 36% of the patients diagnosed at early-stage (5% stage I and 31% stage II)(7).

The late stage presentation and low survival of breast cancer patients in Sub-Saharan Africa results in number of maternal orphans due to breast cancer death which results in intergenerational consequences(10). Recurrence is associated with reduced survival and quality of life, as well as increased costs and psychological distress. The risk of recurrence depends on various clinicopathological factors, such as tumor size, grade, stage, lymph node status, hormone receptor status, human epidermal growth factor receptor 2 (HER2) status, and molecular subtype.

Locoregional recurrence (LRR) is the most common type of recurrence in breast cancer patients who undergo surgery. LRR can occur in the same breast or chest wall (local recurrence) or in the nearby lymph nodes (regional recurrence).

Each breast cancer pathology report contains a number of variables that aid in predicting and determining prognosis. Clinical teams can make more customized therapy choices for each patient with breast cancer using these factors. With the addition of hormonal state, traditional pathologic criteria such as favorable histologic subtype, size, lymph node status, and Nottingham grade are significant determinants that are clinically meaningful in decision-making. Neoadjuvant therapy response, tumor-infiltrating lymphocytes (TILs), the tumor's germline BRCA status, PIK3CA mutation status, and PDL-1 mutation status are also employed to ascertain further potential therapeutic possibilities(11).

As locoregional breast cancer recurrence can have a significant impact on patient outcomes, understanding the clinicopathological factors associated with locoregional recurrence is crucial to improve patients' outcomes and advancing our understanding of the disease. This study is the very first study that assesses factors associated with breast cancer recurrence by Pathology department in Addis Ababa, Ethiopia. The study wants to evaluate additional pathological parameters not studied previously like lymphovascular, perineural invasion and presence of DCIS in relation with locoregional breast cancer recurrence.

1.3. Significance of the study

Breast cancer recurrence, which can take the form of metastasis, a second primary breast cancer, or locoregional recurrence, is a significant cause of mortality and morbidity among breast cancer survivors. The majority of risk factors for recurrence are pathological factors, including tumor

grade, lymph node status, margin status, perineural invasion, and hormonal status. This indicates that the pathological report provided by the pathology department is of utmost significance in determining the prognosis of breast cancer patients.

However, there is limited data on the clinicopathology of breast cancer recurrence in Ethiopia, Addis Ababa university, TASH, the largest referral center for cancer care in the country. By integrating previously unstudied variables such HER-2 status, perineural and lymphovascular invasion, the current study aims to provide comprehensive and up-to-date information on the clinicopathological parameters linked to breast cancer recurrence in Tikur Anbessa Specialized Hospital, Addis Ababa.

Studying the clinicopathologic factors that are associated with breast cancer recurrence is important for improving the management and outcomes of patients with recurrent breast cancer. It can also help identify patients who are at high risk of recurrence and provide them with tailored surveillance and preventive interventions.

2. Literature review

Breast cancer recurrence is a major challenge for breast cancer management and control. Recurrence can occur locally, regionally, or distantly, and can affect the quality of life and survival of breast cancer patients. Breast cancer is the most common and leading cause of cancer death among women in Ethiopia(6). Majority of breast cancer patients in Ethiopia are diagnosed at advanced stages which negatively affects their prognosis and survival(7). In Ethiopia, cancer deaths accounts for approximately 11% of the adult deaths with 67% deaths occurring before the age of 65 accounting for considerable number of premature deaths. Among women the leading cause of death is breast cancer(12).

Incidence of breast cancer recurrence differs across different country. Study done in Iran showed 20.2% patients developed locoregional recurrence followed over 12 years(13), whereas 6.72% in Egypt (14) and 5.1% breast cancer patients in South Korea developed local breast recurrence(15). E3 cohort study done in France have reported 6.9% locoregional breast cancer recurrence and 12.25% distant metastasis after patients were followed for 18 years(8). Retrospective cohort study done in 2014 at TASH, showed that 26.6% of patients developed distant metastasis(16) whereas study in 2018(17), reported that 6.5% of breast cancer patients developed locoregional recurrence with a median time of 60.33 months(17). Locoregional recurrence was 6.7 per 100 person years among breast cancer patients treated at Hawassa, Ethiopia(18).

There are several clinical and pathological factors identified as risk for locoregional breast cancer recurrence. Study in Emory hospital found that 20% of under 40 breast cancer patients developed locoregional recurrence in comparison to only 7% of above 75 breast cancer patients stating that age is associated with locoregional recurrence(19). Similarly research in Iran(13), USA (20), Trinidad(21) and Hawassa Ethiopia(18) have reported that age is a predictor of recurrence were younger breast cancer patients are found to have higher rate of locoregional recurrence and poorer outcome.

Majority of the factors that are associated with breast cancer recurrence are pertaining to the pathological factors including tumor size, tumor grade, nodal status, marginal status and molecular subtype. The molecular classification of breast cancer based on the expression of ER,

PR, HER2, and Ki67 has been widely accepted as a prognostic and predictive tool for breast cancer management. The molecular subtypes have different biological characteristics, clinical behaviors, treatment responses, and outcomes. Generally, Luminal A subtype has the best prognosis and triple negative breast cancer (TNBC) has the worst prognosis among the molecular subtypes(22). Majority of breast cancer patients in Ethiopia are Luminal A type (40%) whereas only 10% are HER2 enriched. But studies in TASH has shown that younger patients were found to be Luminal type B whereas older patients were Luminal type A(23).

The French E3N prospective cohort study that was initiated in 1990 investigated factors associated with breast cancer recurrence in 4926 breast cancer patients followed over a period of 18 years. They found that 2.7% of the patients developed recurrence and have identified that patients with pathologic report of high grade carcinoma, large tumor size (>2cm), axillary nodal involvement, and negative estrogen and progesterone receptors were at a higher risk of recurrence or death(8). According to another study, non-luminal-A subtypes, younger age , and nodal involvement was associated with LR. The 8-year risk of LR was 2.8 % for node-negative patients and 5.2 % for node-positive patients(20).

A study done in Trinidad showed that stage of breast cancer, lymph node status, ER and PR positivity and molecular subtype were associated with breast cancer recurrence with Five-year overall survival and recurrence-free survival rates of 74.3% and 56.4%, respectively(21). This is supported with the finding in Ireland which showed that histologic grade, HER2 positivity and receiving targeted therapy predicted shorted tumor recurrence whereas breast cancer patients with ER and PR positivity, invasive lobular carcinoma and receiving endocrine therapy predicted longer tumor recurrence(24).

Although incidence of breast cancer in sub-Saharan Africa is relatively low compared to developed country, survival from the disease in this region is poor, mortality rates are as high as in high-income countries. Stage at diagnosis is a major contributing factor to poor survival from breast cancer. In sub-Saharan Africa majority of breast cancer patient with late stage (stage III/IV)(10) which could be due to use of traditional medicine before treatment, patient delay and diagnosis delay(7).

In addition to nodal status and size of tumor, study in Egypt has found that presence of lymphovascular invasion (LVI) and extensive intraductal component were risk factors for loco-regional recurrence (LRR) (14). Study in Korea has shown that Similarly Zhong et al, has found that early-stage breast cancer patients with LVI-positive had poorer overall survival, disease free survival and increased risk of locoregional recurrence than those LVI-negative patients (25). Furthermore, Narayan P. et al has found perineural invasion as an important prognostic marker for breast cancer recurrence(26). This shows that tumor DCIS component lymphovascular invasion and perineural invasion are important prognostic factors in breast cancer recurrence.

Study in Korea has shown that hormone receptor negativity and not taking radiation therapy were associated with locoregional breast cancer recurrence(15).

There are few studies done on risk of locoregional recurrence in Ethiopia. Shiferaw et al has conducted retrospective follow up study in 2018 among breast cancer patients at TASH by analyzing 518 breast cancer patients. Mean age at diagnosis was 44 years. Predictors of recurrence were negative estrogen receptor, high histologic grade, positive lymph node status, clinical staging III, and involved deep surgical margin(17).

Another study on breast cancer recurrence in Addis Ababa was conducted by Hadgu et al., assessing the molecular subtypes and clinicopathological features of 114 breast cancer patients who experienced recurrence between 2012 and 2015 at TASH. The most common molecular subtypes were luminal A (40%) followed by luminal B (26%). HER2-enriched and triple-negative accounted for 10% and 23% respectively. But contrary to previous literatures, the study did not find any significant differences in tumor grade, histology, and stage between the molecular subtypes(23).

A study done in Hawassa hospital, Ethiopia by Teshome reported that incidence of recurrence was 6.5 per 100 person years. Locoregional breast cancer recurrence was associated with younger age, clinical stage III, two or more lymph nodes involvement, histologic grade III, and the presence of preexisting comorbidity(18).

Although hormonal positivity especially ER positivity is reported to have good prognostic value with lower locoregional recurrence risk, it is only true for the first 5 years. International Breast Study Group clinical trials I to V have found that during the first 5 years, patients with ER positive breast cancer patients had a lower annualized hazard compared with those with ER negative disease (9.9% v 11.5%; P = .01). However, beyond 5 years, patients with ER-positive disease had higher hazards(27).

In contrary to all above researches, study in Iran showed no significant association between age, weight, tumor size, nodal status, stage, grade and histology of tumor and locoregional breast cancer recurrence(13).

3- Objective of the study

3.1. General objective of the study

-To assess clinicopathological factors that are associated with locoregional breast cancer recurrence in Addis Ababa University, Tikur Anbessa Specialized Hospital.

3.2. Specific objective of the study

-To assess incidence of locoregional recurrence among breast cancer patients diagnosed from 2017-2020

-To determine clinical and pathological factors associated with locoregional breast cancer recurrence in breast cancer patients diagnosed from 2017-2020

4- Materials and Methods

4.1 Study area

Ethiopia is found in Eastern Horn of Africa, with a population a of more than 110 million. The study will be conducted in Department of Pathology, College of health Sciences, TASH, Addis Ababa University, Addis Ababa Ethiopia. It is the largest referral as well as the main teaching hospital in the country.

Department of Pathology, in TAH, Addis Ababa, Ethiopia is the oldest pathology department in Ethiopia which is established in 1965. Currently the department has Seventeen Senior Pathologists with a rank of Assistant Professor to Associate Professors, twelve Residents, six Histotechnologists and Four lab assistants. The department provides hematology, cytopathology, surgical pathology and neonatal autopsy services. Biopsy specimens received in 10% formalin will undergo routine tissue processing and stained with Hematoxylin and eosin stain.

4.2 Study design and period

Hospital based retrospective study was done between November 2023-December 2023.

4.3. Source population

All histopathological confirmed female breast cancer patients treated at the oncology unit, TASH, Addis Ababa University in the period of September,11,2017 till September,10,2020.

4.4 Study population

All histopathological confirmed female breast cancer patients treated at the oncology unit, TASH, Addis Ababa University in the period September,11,2017 till September,10,2020 fulfilling the inclusion criteria.

4.5 Inclusion criteria

- All female breast cancer patients with primary confirmed invasive breast cancer report from September,11,2017 till September,10,2020.

4.6. Exclusion criteria

- Those patients with missing resection biopsy report.
- Patients with bilateral breast cancer at initial diagnosis.
- Patients who had metastatic breast cancer (stage IV) at initial diagnosis of breast cancer.

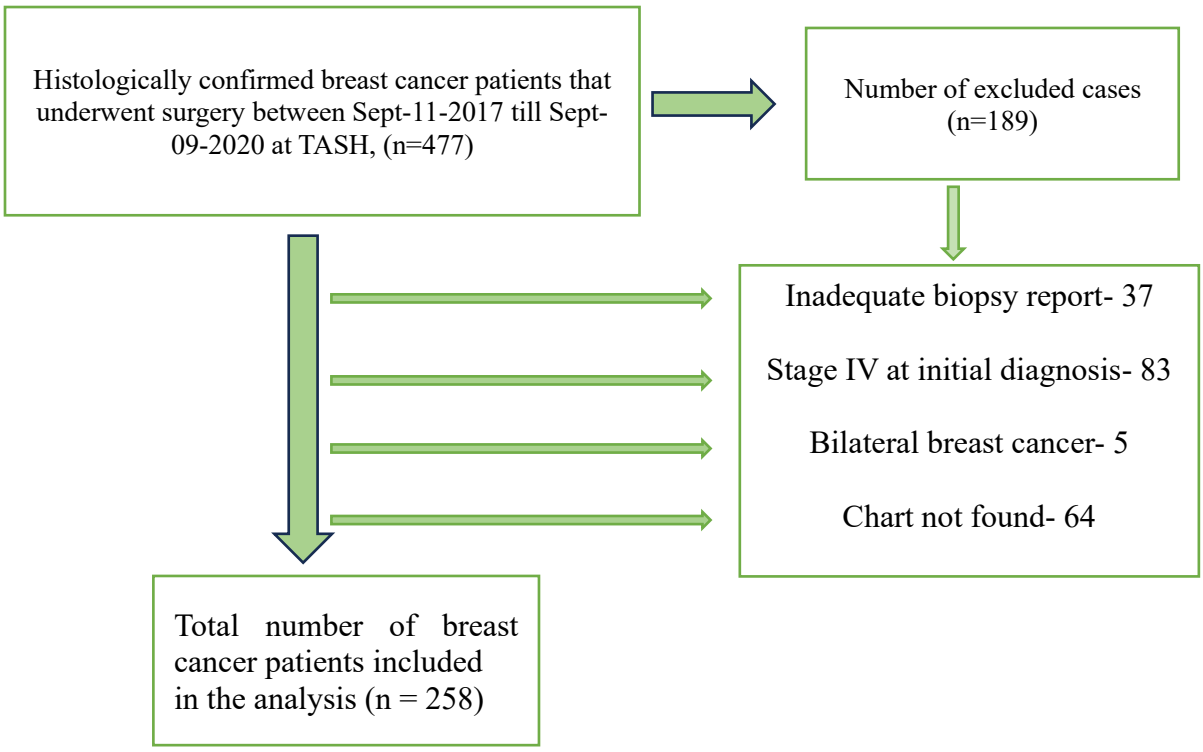
4.5. Sample size determination

All female breast cancer patients fulfilling the criteria during the study time were included.

4.6.Sampling technique

All female breast cancer patients who attended the oncology unit from September,11,2017 till September,10,2020 were included and chart was reviewed for each patients.

Figure 1: Flow diagram showing the sampling procedure of breast cancer patients those underwent breast surgery at TASH, Addis Ababa, 2023



4.7.Data Collection and tools

The starting point for the study was the first date of breast cancer diagnosis to the date of recurrence, the date of death, the date of lost follow- up (censored), or end of the study (until Dec, 30, 2023), whichever comes first. Their recurrence status will be biopsy or FNAC proven reports. Clinicopathological data's will be extracted from the hard copy of initial breast cancer report using extraction sheet. Factors is determined by using reviewed literatures.

4.8.Study variables

4.8.1. Dependent variable (Out-come variable)

The outcome variable- Locoregional breast cancer recurrence

***Time variable*-** Time to recurrence of breast cancer

4.8.2. Independent variable

Sociodemographic factors- Age and residence.

Clinical and treatment related factors- Duration of lesion, comorbidity, treatment type, chemotherapy, endocrine therapy and radiotherapy usage.

Pathological factors- Tumor grade, tumor stage, tumor size, lymph node status, ER, PR and HER-2 status, LVI and PNI.

4.9. Operational definition

Locoregional recurrence (event)- Biopsy or FNAC confirmed recurrence of breast cancer in the ipsilateral breast or chest wall or ipsilateral axillary lymphnode after surgery.

Time to recurrence- Time from the date of breast surgery to the date of recurrence

Censored: Patients whose status was unknown, including lost on follow up or patients who did not develop recurrence at the end of the follow-up period

Recurrence Free Survival (RFS): time interval from date of surgery for breast cancer to date of LRR or last date of follow-up, whichever comes first.

4.12. Data analysis

Data was entered into KOBO template and cleaned using frequencies and crosstabs on SPSS. The cleaned dataset was analyzed using SPSS version 26. Data analysis had two steps. First, descriptive analysis was done. The incidence density rate was calculated for the entire study period. Kaplan–Meier curves were plotted and compared using log rank tests.

Second, bivariate cox regression analysis was performed to evaluate the crude association of variables with time to recurrence, and those variables with p-value < 0.25 in bivariate analysis were entered into final multivariable Cox proportional hazard model. Finally, Adjusted Hazard ratios (AHRs), with 95% CIs was used to determine the independent effect of each explanatory variable on recurrence of breast cancer. Multicollinearity was checked by analyzing variance inflation factor with the cut-off value of <10, and all variables have displayed no collinearity. Finally, the statistical significance was declared at p-value <0.05.

4.13. Ethical considerations

Institutional ethical permission was sought from the ethical and Publication Committee of pathology department before data collection. Confidentiality was assured by avoiding writing names on the checklist. Only the data collectors had access to the patient's record.

4.14. Result dissemination plan

The result of this study will be presented to Pathology department, Addis Ababa University. And copy of the study publication will be distributed to Addis Ababa University main campus library archive.

5- Result

5.1. Socio-demographic characteristics of the study participants

A total of 258 study participants were included in the study. The median age at breast cancer diagnosis was 40 years (IQR:35-48). Out of the 258-study participant, 181(70.2%) were married, 150(58.1%) were diagnosed at age 40 and below of which 213(82.6%) were premenopausal. The median duration of symptom is 6 months (IQR: 3-12). Majority of the patients treated at TASH were from rural area 133(51.6%) (Table 1).

5.2. Baseline clinicopathologic and treatment characteristics of the study participants

Moderately differentiated (grade II) was the most common histologic grade accounting to 97(37.6%) of patients and 242(93.8%) were of Invasive breast carcinoma, no special type (NST). Only 36 (14%) of patients had preexisting comorbidity at the time of diagnosis. More than half of patients, 138(53.5%), were in clinical stage III cases whereas 107 (41.5%) were stage II and only 13(5%) were stage I at time of diagnosis. At least one or more lymph node positivity was seen in 169(65.1%) of patients and 195(46.4%) cases had tumor size of 2.5 to 5cm at a time of diagnosis (Table 1). All patients had Modified radical mastectomy (MRM) out of which, 26(10.1%) of patient underwent lumpectomy prior to MRM. Approximately all patients have received adjuvant chemotherapy 253(98.1%) and 220(85.3%) of patients were on hormonal therapy (Table 2).

Only 47(18.2%) of breast cancer patient had ER and PR status determined and 32(12.4%) had their Her2 status determined. Similarly, LVI and PNI status was commented in the biopsy report of 68 (26.36%) and 20(7.8%) of patients respectively (Table 3).

Table 1: Sociodemographic and Clinicopathological characteristics of breast cancer patients who had surgical treatment in TASH, Ethiopia (n=258)

Variable	Category	Frequency (%)	Percentage
Age	<=40	150	58.1%
	>40	108	41.9%
Residence	Urban	125	48.4%
	Rural	133	51.6%
Marital status	Married	181	70.2%
	Other	77	29.8%
Preexisting comorbidity	No	222	86%
	Yes	36	14%
Histologic grade [a]	Grade 1	53	20.5%
	Grade 2	97	37.6%
	Grade 3	92	35.7%
	Not applicable	16	6.2%
Histologic type	Invasive carcinoma, NST	242	93.8%
	Other	16	6.2%
Axillary nodal involvement	Negative	90	34.9%
	Positive	169	65.1%
N-stage [b]	N0	90	34.9%
	N1	58	22.5%
	N2	78	30.2%
	N3	32	12.4%
T-stage [b]	T1	38	14.7%
	T2	141	54.74%
	T3	50	19.4%
	T4	29	11.2%
Stage [b]	Stage 1	13	5%
	Stage 2	107	41.5%
	Stage 3	138	53.5%
Surgical margin status	Free	225	87.2%
	Involved	33	12.4%
Total		258	100%

a. Nottingham
b. Based on 8th edition AJCC cancer staging manual

Table 2: Treatment characteristics of breast cancer patients who had surgical treatment in TASH, Ethiopia, (n=258)

Variable	Category	Frequency (%)
Type of surgery	MRM	232(89.9%)
	Lumpectomy followed by MRM	26(10.1%)
Adjuvant chemotherapy	No	5(1.9%)
	Yes	253(98.1%)
Hormonal therapy	No	38(14.7%)
	Yes	220(85.3%)
Type of hormonal therapy	Tamoxifen	158(71.8%) *
	Anastrozole	62(28.2%) *
Radiotherapy	No	189(73.26%)
	Yes	69(29.74%)

*Calculated out of patients receiving Hormonal therapy(n=220)

Table 3: LVI, PNI and hormonal status of breast cancer patients who had surgical treatment in TASH, Ethiopia (n=258)

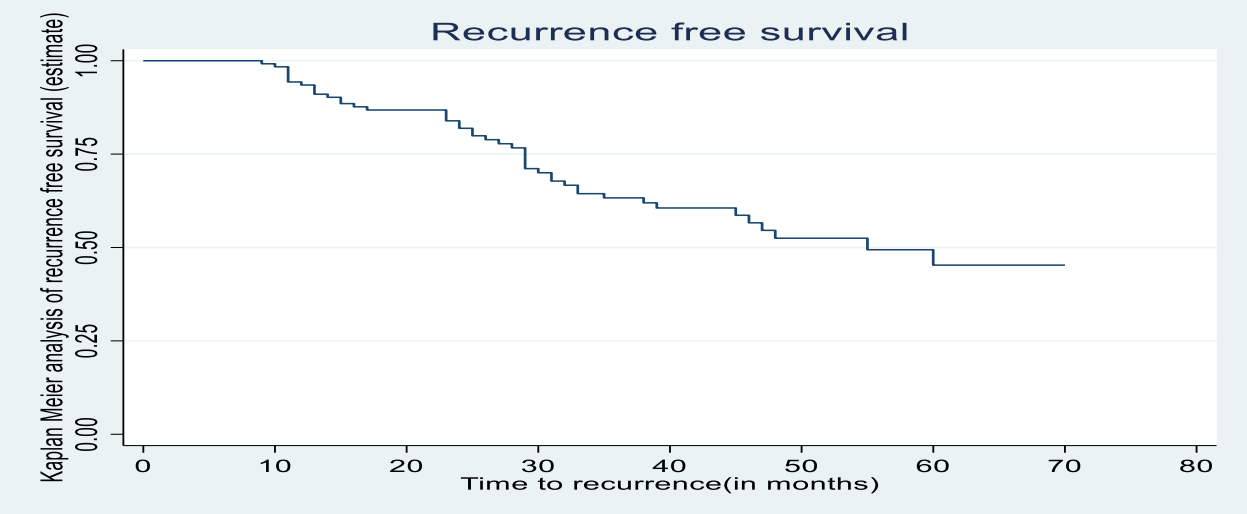
Variable	Category	Frequency (%)
Lymphovascular invasion	Not identified	27(10.5%)
	Present	41(15.9%)
	Not stated	190(73.6%)
Perineural invasion	Not identified	12(4.7%)
	Present	8(3.1%)
	Not stated	238(92.2%)
ER status	Negative	13(5%)
	Positive	34(13.2%)
	Not determined	211(81.8%)
PR status	Negative	23(8.9%)
	Positive	24(9.3%)
	Not determined	211(81.8%)
Her-2 status	Negative	21(8.1%)
	Indeterminate	6(2.3%)
	Positive	5(1.9%)
	Not determined	226(87.6%)
Total		258(100%)

5.3. Incidence of breast cancer recurrence

The overall incidence rate of locoregional breast cancer recurrence in the cohort during the 858 person-years of observation was 5.36 per 100 person-years (95%CI=3.85-7.07) follow-up. The median Recurrence Free Survival (RFS) time was 55 months (95 CI%= 41.73, 68.26). The estimated recurrence free survival was 92.5%, 81.4%, 60.4%, 50.5% and 41.7% at 12, 24, 36, 48 and 60 months, respectively (Figure 1).

Among the recurrences, 32(69.6%) of patients had involvement of ipsilateral chest wall whereas, 14(30.4%) had ipsilateral axillary lymph node recurrence over the course of the study period. Thirty sex (78.3%) of recurrences were confirmed using FNAC, 6(13%) by biopsy and 4(8.7%) were diagnosed using both FNAC and biopsy.

Figure 2: An overall Kaplan-Meier analysis of recurrence-free survival of breast cancer patients who had surgery at, TASH, Ethiopia, 2023



5.4. Recurrent free survival among different groups of breast cancer patients

The log-rank test was performed to test presence of any significant differences in time to recurrence among various levels of the categorical variables considered in the study. The Log rank (LR) test shown that patients with histological grade 3 had shorter median time to recurrence compared with those having grade 1 or 2 (p-value for LR=0.00). Similarly, the median recurrence time for those who were in clinical stage I and II at baseline was longer than that for patients with clinical stage (III) (p-value for LR=0.02). Patients with four or more lymph node involvement had shorted median time to recurrence as compared with those having less than four lymph node involvement (p-value for LR=0.04).

Figure 3: Kaplan-Meier recurrence free survival function among different groups of breast cancer patients by Histologic grade.

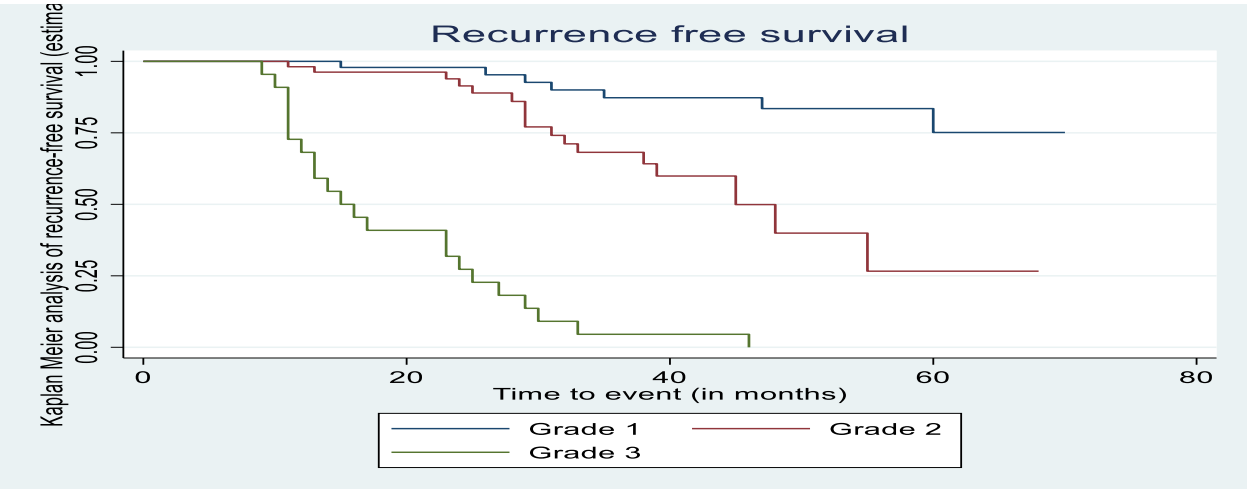


Figure 4: Kaplan-Meier recurrence free survival function among different groups of breast cancer patients by stage of cancer.

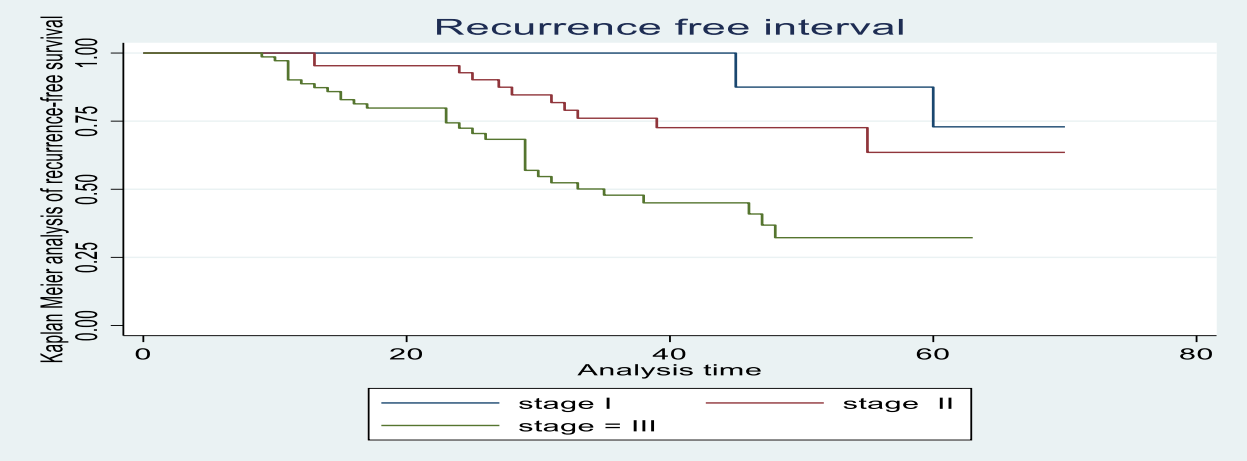
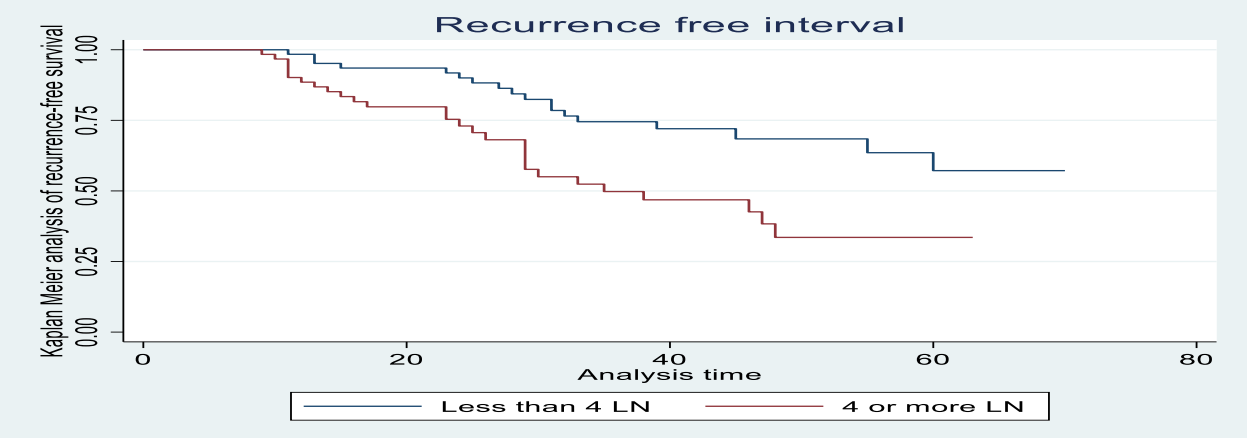


Figure 5: Kaplan-Meier recurrence free survival function among different groups of breast cancer patients by Lymph node status.



5.5- Factors associated with breast cancer recurrence

Independent variables were determined based on the literature review. These includes age at diagnosis, comorbidity, histologic grade, T-stage, lymph node status, stage of breast cancer, hormonal therapy and radiotherapy. Hormonal status, LVI and PNI were not included in the regression analysis since it is missing in majority of the patients.

Bivariate analysis at 0.25 level of significance was run to select variables to be fit into the multivariable ordinal logistic regression model and from which; lymph node status, histologic grade, clinical stage and hormonal status were included. On multivariable ordinal logistic regression model, after adjusting for other covariates, only histologic grade and lymph node status were found to be significantly associated with risk of breast cancer recurrence (Table 4).

Patients with histologic grade 3 were 3.22 times at more risk to develop breast cancer recurrence compared to patients with grade 1 histology (AHR=3.22 (1.37, 7.6), p-value <0.008, 95%CI). Patients with histologic grade 2 were 2.5 times at more risk to develop breast cancer recurrence compared to patients with grade 1 histology (AHR=2.544(1.032, 6.269), p-value <0.04, 95%CI). Likewise, lymph node involvement was associated with increased risk of breast cancer recurrence. With each increase in lymph node positivity the risk of developing breast cancer recurrence increases by 1.175 (AHR=1.175(1.1,1.25), p-value <0.001, 95% CI).

Table 4-Proportional Cox Hazard regression analysis of predictors associated with breast cancer recurrence in breast cancer patients, TASH, Ethiopia.

Variable	Crude Hazard ratio (CHR)(95% CI)	*p*-value	Adjusted Hazard ration (AHR) (95% CI)	*p*-value
Number of Positive Lymph nodes	1.17(1.14,1.23)	0.00	1.175 (1.103, 1.257)	**0.00****
Histologic grade				
Grade 1	1			
Grade 2	1.81(0.79, 4.35)	0.189	2.544 (1.03, 6.27)	**0.04****
Grade 3	2.93(1.25, 6.87)	0.013	3.224 (1.36, 7.6)	**0.008****
Stage of breast cancer				
Stage I/II	1			
Stage III	3.044(1.56, 5.8)	0.001	1.08 (0.49,2.43)	0.85
Use of hormonal therapy				
No	1			
Yes	0.457 (0.21,0.995)	0.047	0.523 (0.238, 1.146)	0.105
*Statistically significant				

6- Discussion

The study has found that majority of breast cancer patients are diagnosed at stage III accounting for 138(53.5%) with only 13(5%) of patients diagnosed at stage I with an incidence rate of breast cancer recurrence of 5.46 per 100-person years. The median age of breast cancer diagnosis is 40 years, with median duration of symptom of 6 months. Patients with high grade histology, high clinical stage and positive lymph node status had an overall earlier breast cancer recurrence. The most significant factor associated with development of breast cancer recurrence were higher histological grade and lymph node status.

According to this study the median age of breast cancer in our set up is 40 years which is less than majority of higher income countries including France, Ireland and Trinidad. Additionally, most patients are diagnosed at clinical stage III accounting for more than half of patients, in contrary to other developed countries(10). Even in comparison to our neighbor Egypt, a study showed that the median age of diagnosis is 52 years with 80% of patients diagnosed at stage I and II (14). This shows that there is huge gap in our patients' awareness regarding breast cancer and as majority of breast cancer patients are diagnosed at advanced stages it negatively affects their prognosis and survival.

Breast cancer recurrence incidence rate of 5.46 per 100-person years is less than study done in Egypt (6.7%) but comparable to France (4.9%) and South Korea (5.1%). Although it is similar with previous literatures in Ethiopia including, Addis Ababa (6.5)(17) and Hawassa (6.7%)(18), the current study is only regarding locoregional breast cancer recurrence excluding distant metastasis. This shows that sizeable number of patients are at risk of locoregional breast cancer recurrence despite the variable treatment options.

The median Recurrence Free Survival (RFS) time was 55 month which is comparable to previous researches in Addis Ababa (60 month)(17) but higher than Hawassa (48 months)(18). In this retrospective follow-up study, the 5-year RFS rates was 41.7%. This value is much lower than those reported in studies conducted in Iran (82.5)(13) and Trinidad (74.3)(21). This difference might be attributed to fact that TASH is the major referral centers in which breast cancer patients are referred across the whole country for treatment. Additionally, the access of care, inadequate early screening and treatment of patients especially access to radiotherapy and appropriate

endocrine therapies affect the overall RFS.

The study has identified that patients with higher histological grade at higher risk of breast cancer recurrence as compared with lower histologic grade. This is in consistent with previous studies (8,17,18,21). Similarly, lymph node status was significantly associated with breast cancer recurrence, thus as the number of positive lymph node increases the risk of breast cancer recurrence increases as well. This is in concordance with previous researches in ((8,14,17–19,21). Thus, the likelihood of a breast cancer recurrence in the future is significantly influenced by pathological characteristics especially the histological grade and lymph node status.

Clinical stage of patients was not associated with breast cancer recurrence in the current study. This might be due to most patients treated at TASH were stage III at time of diagnosis. Likewise, hormonal therapy had no significant association, this is partly attributed to the initiation of hormonal therapies to all breast cancer patients despite having no hormonal status determined. But on future, determination of hormonal status and usage of hormonal therapy appropriately will likely give an insight on whether there is difference in recurrence risk. Additionally, no significant association was found between age, comorbidity and risk of breast cancer recurrence.

Important factors such as hormonal status, LIV and PNI were not included in the regression analysis to check for recurrence risk since it was not determined for majority of the patients.

7-Strength and limitation of the study

Despite being single-center study, the study is representative since TASH is the primary referral center for cancer patient across the country. To minimize sampling bias, all breast cancer patients fulfilling the inclusion criteria over the 3year period were included. But there might be selection bias as breast cases with incomplete pathologic report were excluded. It was not possible to incorporate hormonal status, LVI, or PNI in the regression analysis due to a lack of data.

8-Conclusion and recommendations

8.1- Conclusion

Risk factors for loco-regional recurrence play an important role in the decision for the treatment of breast cancer. This decision-making can be optimized if patients at high risk for loco-regional recurrence can be identified. Histological grade and lymph node positivity is significantly associated with breast cancer recurrence. Assessing the histological grade appropriately and harvesting as much lymph node as possible to rule out any metastasis is crucial as it has significant value in determining breast cancer recurrence risk.

8.2- Recommendations

There is inconsistency in pathologic reporting of breast cancer resection specimens. Important prognostic factors such as LVI, PNI are not commented routinely on majority of the patients. This will affect risk stratification of patients as wells and the data for further research. Thus, having agreed upon reporting formats to be applied by all pathologists in the country is highly recommended.

Additionally, hormonal status is also not determined for majority of patients as the service is not easily available in the setup. This has major constraint in determining hormonal therapy required for the patients. Incorporating hormonal status as routine practice in addition to histopathology is recommended for the better outcome of breast cancer patients.

For future researches, to avoid incomplete data, prospective follow up study with larger sample size is advised. Factors such as LVI, PNI and hormonal status should be considered in future studies.

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Annex: Data Extraction sheet

CODE_____ Medical Record Number (MRN)_____

PART I: SOCIODEMOGRAPHIC CHARACTERISTICS

1- Patient Age at diagnosis: _____Years

2- Marital Status 1. Single 2. Married 3. Widowed 4. Divorced

3- Place of residence 1. Urban _____

2. Rural _____

3. Unknown

PART II: CLINICO-PATHOLOGICAL CHARACTERISTICS

4- Pre-existing medical comorbidity at the time of diagnosis

1. Yes 2. No 3.Unknown

5- If there is pre-existing comorbidity, specify _____

6- Body mass index at the time of first diagnosis _____Kg/m^2

7- Date of diagnosis _____/_____/_____(DD/MM/YY)

8- Laterality 1. Left 2.right

9- Stage of cancer at diagnosis 1) I 2) II 3) III

10- Histological grade of breast cancer

1. Well Differentiated (Grade 1)
2. Moderately Differentiated (Grade 2)
3. Poorly Differentiated (Grade 3)
4. Not Determined

11- Histology type of breast cancer

1. Invasive Breast carcinoma, NST
2. Invasive Lobular carcinoma
3. Medullary carcinoma
4. Mucinous carcinoma
5. Mixed carcinoma
6. Other: _____

12- Surgical margin 1. Free 2. Involved

13- If positive margin. Specify the site _____

14- Lymphovascular invasion:

1. Not identified
2. Present
3. Not reported

15- Perineural invasion:

1. **Not identified**
2. **Present**
3. **Not reported**

16- Number of positive lymph nodes involved_____

17- N stage:

18- Tumor size in centimeter

1. T1<2cm
2. T2 2-5cm
3. T3 >5cm
4. T4

19- Estrogen receptor status- 1. Negative 2. Positive 3. Not determined

20- Progesterone receptor status 1. Negative 2. Positive 3.Not determined

21- HER-2 Status 1-Negative 2-Positive

PART III. TREATMENT-RELATED VARIABLES

22- Date of surgery _____/_____/_____(DD/MM/YY)

23- Duration of days from diagnosis to date of surgery (in days) _____(days)

24- Type of surgery

1. Modified radical mastectomy

2. Lumpectomy

3. Breast conservative surgery

25- Use of neoadjuvant chemotherapy 1. Yes 2. No

26- If yes to #25, Number of cycles _____

27- Use of adjuvant chemotherapy 1.Yes 2. No

28 If yes to #27, number of cycles _____

29 The regimen of chemotherapy used

1. AC (doxorubicin, cyclophosphamide)
2. Paclitaxel

3. AC + Paclitaxel

30 Use of hormone therapy? 1.Yes 2. No

31 If yes to #30, duration (months): _____

32 If yes to #30, regimen of hormone therapy used 1. Tamoxifen 2. Anastrozole

33 Date of last contact: ___/____/____ (DD/MM/YY)

34 The Status of the patient during last contact

1. Recurrence

2. Censored

35 Type of locoregional recurrence

1. Local recurrence (chest wall/ ipsilateral breast)

2. Regional recurrence (Lymph node)

36 For recurrent, date of recurrence ____/____/____ (DD/MM/YY)

Abstraction date: _____/_