

# Pattern of Recurrence in Early Breast Cancer at a Tertiary Center in Sub-Saharan Africa: A Retrospective Cohort Study

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## Summary

**Introduction:** There is limited data on the recurrence rates and factors that contribute to recurrence in women managed for early breast cancer in sub-Saharan Africa. This study conducted at a tertiary level facility aims to determine the recurrence rates in patients treated for early invasive breast cancer. **Methods:** This is a single institution retrospective cohort study of women (18–75 years) treated for early breast cancer from 2009 to 2017. Demographic data, tumor, and treatment-related factors were summarized using descriptive statistics. Survival analysis and Cox proportional hazard regression were performed, with computation of hazard ratios and their 95% confidence intervals. **Results:** A total of 239 patients with an initial diagnosis of early breast cancer were identified. The mean age at diagnosis was 51 years (*SD* 13). The most prevalent molecular subtype was estrogen receptor/progesterone receptor (ER/PR)+ at 76% with only 2.9% having human epidermal growth

factor receptor 2 (HER2) overexpressing breast cancer. The overall recurrence was 7.1% with a 1.6% case mortality. The overall 5-year and 10-year survival rate was 94% and 91%, respectively. **Conclusion:** Early breast cancer in our setting has a good overall survival and low recurrence rates that are comparable to that found in Western countries.

**Keywords:** Early breast cancer, Recurrence, Disease-free survival

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## Introduction

Breast cancer is the leading cancer among women in developing countries, with an exponential increase in incidence in sub-Saharan Africa over the past 10 years (1). Early breast cancer (ductal carcinoma in situ [DCIS], Stage I and II breast cancer) is curable, however, there is always a substantial risk of recurrence even after an extended duration post-definitive treatment (2). Recurrent breast cancer has been shown to portend a poorer prognosis and inferior quality of life among survivors (3).

Studies have demonstrated that the risk of recurrence in early breast cancer is 7–20%, with 50% of recurrences

occurring within the first 5 years (4, 5). Studies interrogating the impact of race and ancestry on breast cancer survival have demonstrated that women of African descent have poorer breast cancer-free survival (6). The risk factors associated with recurrence can be categorized as patient related, breast cancer molecular biology, and treatment-related factors. An important patient-related factor is ancestry, with women of African ancestry having an aggressive morphological subtype of breast cancer with higher rates of triple-negative breast cancer, and human epidermal growth factor receptor 2

(HER2)+ morphological subtypes, which correlate with a higher recurrence rate and a poorer prognosis (7, 8). Despite the advances in breast cancer management worldwide, a majority of breast cancer patients from sub-Saharan Africa grapple with a lack of access to healthcare services as a result of both socioeconomic and institutional factors (9). Comprehensive breast cancer treatment services are largely lacking in most sub-Saharan countries. Healthcare-related factors such as inadequate skill and lack of knowledge among healthcare providers in the management of breast cancer compound the lack of access to radiotherapy, appropriate chemotherapy, and adjuvant hormonal treatment (9). Factors such as omission of radiotherapy, delayed time to radiotherapy (>12 weeks) (10), and omission of adjuvant hormonal therapy have been shown to contribute to breast cancer recurrence (11). The objective of this study was to determine the recurrence rate and factors associated with recurrence in patients treated for DCIS and early invasive breast cancer in our institution in between 2009 and 2017.

## Methodology

### *Study design*

Single-institution retrospective cohort study on the recurrence patterns and factors associated with recurrence in women treated for early breast cancer.

### *Study population*

All women managed for early breast cancer (DCIS, Stage I and II breast cancer [staged as per the American Joint Committee on Cancer (AJCC TNM criteria 7th edition)] from 2009 to 2017) at a single tertiary institution were identified in the health information registry and theater records. The study was conducted in 2019 with all patients managed for early breast cancer for the period 2009–2017 included in the study. All women were managed and followed up as per the National Comprehensive Cancer Network (NCCN) Guidelines 2017.

### *Exclusion criteria*

Women with medical records with key missing information on initial treatment: diagnostic work-up and initial surgery.

### *Data analysis and presentation*

Mean, median, and ranges were used to summarize the demographics, age at diagnosis, parity, quantity of alcohol intake, pack years of cigarette smoking, tumor size, and tumor margins. Race, level of education, menopausal status, contraception use, and family history of breast cancer were analyzed and summarized in frequencies and percentages.

Logistic regression model was used to identify the factors associated with recurrence (age, menopausal status, cigarette smoking, alcohol intake, parity, contraception use, receptor status, tumor grade, and family history of breast cancer, tumor size, tumor margins, and number of involved lymph nodes, type of surgery, chemotherapy, and hormonal treatment). Select variables for the multivariate regression model were selected using chi square  $p < 0.05$  or Fischer's exact test  $p < 0.05$  for categorical data and linear logistic regression  $p < 0.05$  for continuous data. Any variable with  $p$  value  $< 0.05$  was a plausible candidate for the multivariate model.

Survival analysis was performed using Kaplan–Meier curves comparing patients based on the major recurrence determinants (stage, receptor status, hormonal treatment), corresponding median survival times, and log rank tests. Cox proportional hazard regression was performed to compute the hazard ratios and their 95% confidence intervals.

### *Ethical consideration*

Approval was sought from the Research and Ethics Committee 2018/REC—108V1. All data sheets were coded by non-traceable serial numbers and the information obtained was treated with confidentiality and was only used for the intended purpose.

## Results

A total of 270 women managed for early breast cancer were identified from the hospital registry, with only 239

having complete records and were amenable for inclusion into the study.

#### *Age at diagnosis*

The mean age of the patients was 51.2 years ( $SD = 13.1$ ), while the median age was 50.0 years (IQR = 18) (Figure 1).

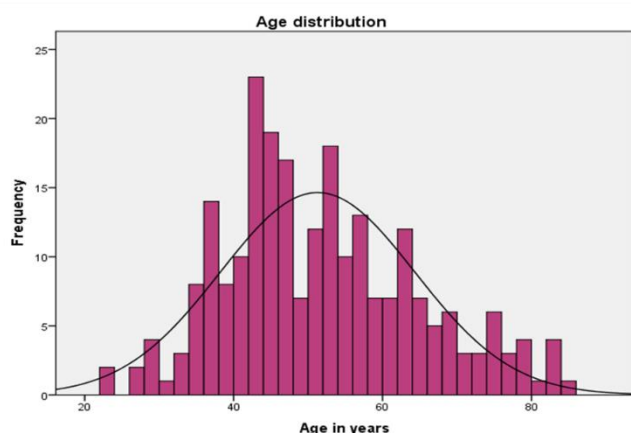


Figure 1. Age distribution

In this study, we note that 194 (81.3%) of the patients were of African ancestry, 36 (15%) were of Asian origin, and 9 (3.8%) were Caucasians. Out of 124 (44%) women with a documented level of education, 105 women (85%) had attained a tertiary level of education, 15 women (12%) had attained secondary school education, and only 3 women (2.4%) had attained a primary level of education.

Of the total 239 patients, 107 women (44.6%) were premenopausal, while 132 (55.4%) were postmenopausal. The parity ranged from 0 to 8, with 69 patients (28.9%) reporting contraceptive use within the past 5 years. Of these, 43 (69%) reported the use of combined oral contraceptive pills, and 26 (31%) reported the use of hormone-based injectable, intrauterine devices, and implants.

Only 19 (7.9%) of the patients in this series reported a family history of breast cancer. A total of 27 patients (12%) reported the use of alcohol with a low to moderate intake, with only 4 patients (1.6%) reporting cigarette use.

#### *Clinical characteristics*

A total of 27 patients (11.3%) had DCIS, 41 (17.2%) had Stage I breast cancer, and 171 (71.5%) had Stage II breast cancer. A total of 234 women (98%) had a breast mass at presentation; 206 (86%) presented with a breast mass only, while only 4.6% presented with nipple discharge. Only 0.4% were asymptomatic and were diagnosed on screening mammography.

#### *Histopathological characteristics*

The majority of the patients who presented with invasive ductal carcinoma (110 [51.8%]) had a DCIS component, with the most common architectural type being comedo/solid type. Lymphovascular invasion was present in 119 (49.8%) of all specimens, with a 99% prevalence in specimens with invasive breast cancer (Table 1).

#### *Management*

Of the 239 patients reviewed, 98 (41%) received breast-conserving surgery (BCS), while 141 (59%) had a mastectomy  $\pm$  axillary lymph node dissection/sentinel lymph node biopsy (ALND/SLNB). Of the 27 patients diagnosed with DCIS, only 5 (19%) had BCS, with the rest getting a mastectomy. All the patients had negative margins on pathological assessment.

A total of 96 (40.2%) patients received adjuvant radiotherapy after surgery. Of the 98 patients who had BCS, only 71 (72%) received radiotherapy in our facility. Of the 54 (22.6%) patients who started radiotherapy after 12 weeks, 45 had BCS for invasive breast cancer with 42 of these receiving adjuvant chemotherapy prior to radiotherapy. Only three patients had a delay in initiation of radiotherapy beyond 12 weeks.

Of the 202 patients with hormone receptor-positive breast cancer, 164 (81%) received adjuvant hormonal therapy, with 78% of them reporting compliance to the therapy. The mean duration of hormonal treatment in this study was 3.1 years ( $SD 1.9$ ). Of the 27 patients with HER2+ positive breast cancer, only 17 (63%) received Herceptin.

# PATTERN OF RECURRENCE IN EARLY BREAST CANCER

Table 1. Table summarizing patient and tumor characteristics

RECURRENCE	YES	NO	TOTAL	p VALUE
Age at diagnosis				
21–30	3 (16.7)	6 (2.7)	9 (3.8)	0.003
31–40	5 (27.8)	33 (14.9)	38 (15.9)	0.152
41–50	7 (38.9)	70 (31.7)	77 (32.2)	0.529
51–60	0 (0.0)	60 (27.1)	60 (25.1)	0.011
61–70	2 (11.1)	28 (12.7)	30 (12.6)	0.839
71–80	0 (0.0)	20 (9.0)	20 (8.4)	0.181
81–90	1 (5.6)	4 (1.8)	5 (2.1)	0.273
Alcohol intake				
Yes	0 (0.0)	25 (11.4)	25 (10.5)	0.131
No	18 (100.0)	195 (88.6)	213 (89.5)	
Family history				
Yes	0 (0.0)	19 (8.6)	19 (7.9)	0.195
No	18 (100.0)	202 (91.4)	220 (92.1)	
Type of treatment received				
Breast conserving surgery	11 (61.1)	87 (39.4)	98 (41)	0.071
Mastectomy	7 (38.9)	134 (60.6)	141 (59)	
Adjuvant hormonal therapy				
Yes	10 (55.6)	157 (71.4)	167 (70.2)	0.159
No	8 (44.4)	63 (28.6)	71 (29.8)	
Adjuvant chemotherapy				
Yes	11 (61.1)	126 (57.0)	137 (57.3)	0.735
No	7 (38.9)	95 (43.0)	102 (42.7)	
Tumor grade				
Grade 1	0 (0.0)	24 (11)	24 (10.2)	0.162
Grade 2	8 (50.0)	122 (55.7)	130 (55.3)	0.658
Grade 3	8 (50.0)	73 (33.3)	81 (34.5)	0.176
Lymphovascular invasion				
Yes	10 (55.6)	109 (49.3)	119 (49.8)	0.494
No	8 (44.4)	112 (50.7)	120 (50.2)	
Tumor size				
Mean ± SD	27.5 ± 7.9	26.2 ± 14.1		0.703
Tumor receptors				
ER + PR + /PR+	14 (77.8)	168 (76.4)	182 (76.5)	0.892
ER + PR + HER2+	0 (0.0)	20 (9.1)	20 (8.4)	0.181
HER2+	0 (0.0)	7 (3.2)	7 (2.9)	0.442
Triple-negative	4 (22.2)	25 (11.4)	29 (12.2)	0.176
Duration from surgery to radiotherapy (days)				
Mean ± SD	202.3 ± 202.0	133.8 ± 209.2		0.406
Reported compliance to hormonal therapy				
Yes	10 (90.9)	124 (76.5)	134 (77.5)	0.270
No	1 (9.1)	7 (4.3)	10 (4.6)	0.466
LTFU	0 (0.0)	31 (19.1)	31 (17.9)	0.109
Radiotherapy				
Yes	7 (38.9)	91 (41.2)	98 (41.0)	0.850
No	11 (61.1)	130 (58.8)	141 (59.0)	
Lymph node status (# of nodes)				
0	9 (50.0)	143 (65.6)	152 (64.4)	0.184
1	5 (27.8)	37 (17.0)	42 (17.8)	0.249
2	1 (5.6)	21 (9.6)	22 (9.3)	0.567
3	3 (16.7)	17 (7.8)	20 (8.5)	0.194

Abbreviation: LTFU, lost to follow-up.

A total of 136 patients who received adjuvant chemotherapy, 7 (5.1%) had Stage I invasive breast cancer and 129 (94%) had Stage II invasive breast cancer.

Table 2. Clinical profile of patients and management of patients with recurrent breast cancer

TIME TO RECURRENCE	FREQUENCY
≤2 years	11
>2 years	6
Type of recurrence	
Locoregional recurrence	12
Metastatic recurrence	5
Receptors status	
ER+/ER + PR+/PR+	11
ER + PR + HER2+	1
HER2+	1
Triple-negative	2
Unknown	2
Detection of breast cancer recurrence	
Clinical breast examination	7
CT scan/ultrasound	4
MRI	2
Self-breast examination	4
Management of recurrent breast cancer	
Systemic chemotherapy only	2
Surgery only	1
Surgery and chemotherapy	9
Surgery, chemotherapy, and radiation	2
Surgery and radiation therapy	1
None	2
Type of surgery for recurrent breast cancer	
Bilateral salpingo-oophorectomy	1
Breast conserving surgery	1
Mastectomy	12
None	3
Outcome	
Alive	5
Deceased	4
Lost to follow-up	8

Abbreviations: *CT*, computed tomography; *ER*, estrogen receptor; *HER2*, human epidermal growth factor receptor 2; *MRI*, magnetic resonance imaging; *PR*, progesterone receptor.

### Recurrence

The overall recurrence rate for early breast cancer in this series is 7.1% (17), with one patient developing contralateral breast cancer. Of the 27 (7.4%) women with DCIS, 2 had locoregional recurrence with invasive breast cancer, 4.8% (2 out of 42 women) recurrence was in women with Stage I breast cancer, and 8.2% (14 out of 171 women) recurrence was in patients with Stage II breast cancer. The recurrence rate following BCS and mastectomy was 10% (10/98) and 5% (7/141), respectively (Table 1). A total of 70% (12/17) of the recurrences were locoregional, while 30% (5/17) were distant metastases. In this series, 83% of the total recurrences occurred within the first 5 years after treatment (Table 2). For hormone receptor-positive breast cancer, local recurrence occurred in 7/13 women, regional recurrence in 3/13, while metastatic recurrence occurred in 3/13 women. In triple-negative breast cancer, one recurrence was local, one was regional, and two were metastatic. (Table 1)

Eleven (61%) of the patients with recurrence had BCS, though this was not found to be statistically significant ( $p = 0.071$ ), five (45%) of whom did not undergo radiotherapy after surgery ( $p = 0.85$ ). Eight of the patients who had BCS experienced a locoregional recurrence, while three had metastatic breast cancer (Table 1).

Eleven (61%) patients had detection of recurrence either via a self-breast examination or a clinical breast exam, ratio at 4:7. The detections made on self-breast examination were in-between the scheduled clinical reviews. (Table 2)

In the univariate analysis model, there were no factors found attaining statistical significance, therefore a multivariate regression model was not generated.

### Survival analysis

The median duration of follow-up was 4.8 years (IQR 3.6–6.4) years. Kaplan–Meier curve for the overall survival (OS), stage-specific survival, receptor status, type of surgery, and adjuvant hormonal and chemotherapy were plotted (Figures 2 and 3). The overall 5-year survival rate was 94%, while the overall 10-year survival rate was 92.9% (Table 3).

The cox regression analysis and hazard ratios were used to explore the factors that influence survival (Table 4).

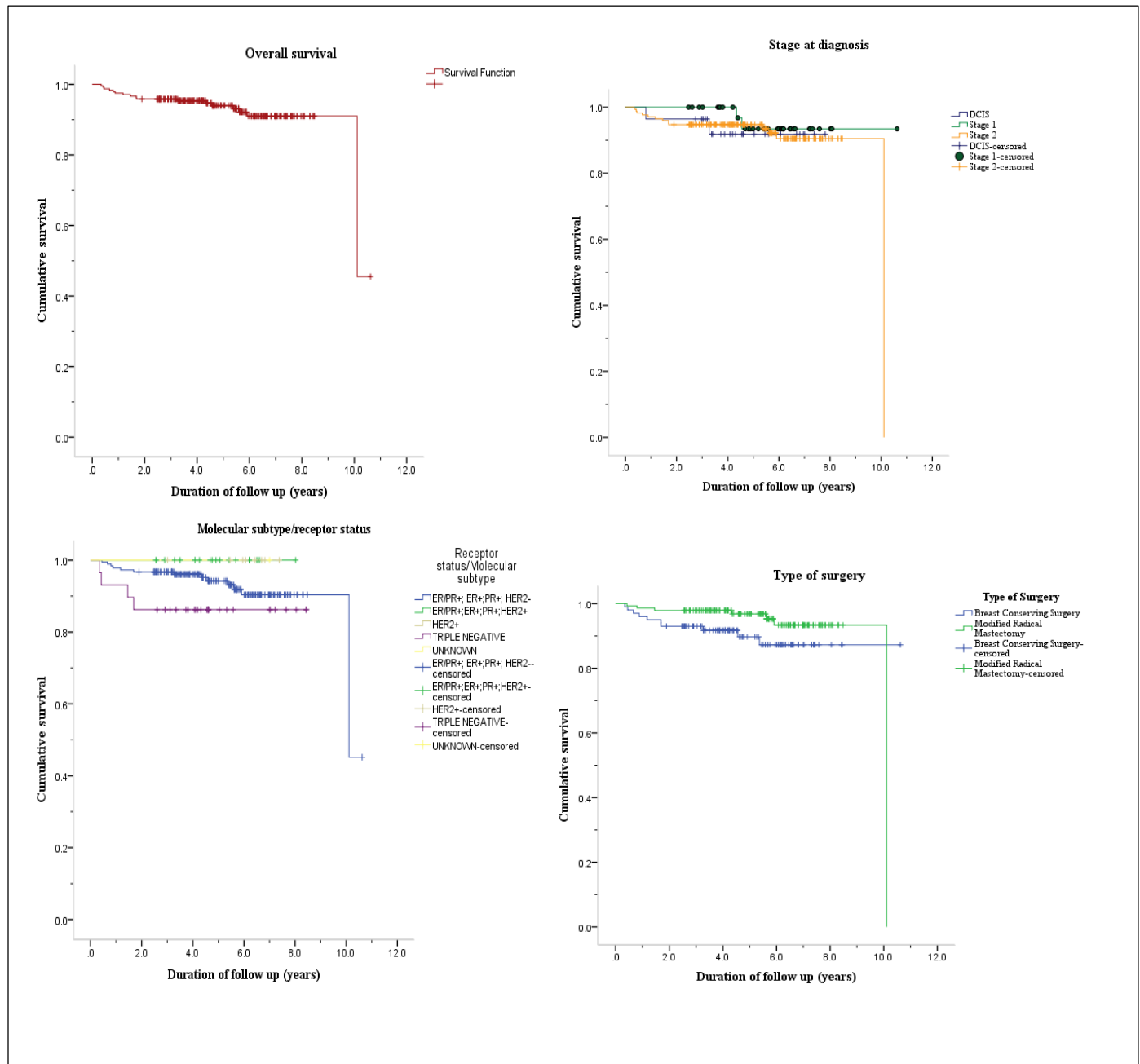


Figure 2. Kaplan–Meier curves for (a) overall survival; (b) survival based on molecular subtype; (c) survival based on stage; and (d) overall survival based on type of surgery.

## Discussion

The primary objective of the study was to determine the recurrence rates and the pattern of recurrence for early breast cancer in a single institution. The key features noted in this cohort demographics, which was

predominantly of African race, was on average an earlier age of breast cancer diagnosis (average age of 51 years, *SD* 13) compared with what is found in the Western literature (64–75 years) (12), and yet conforming to previous studies done within the region (17).



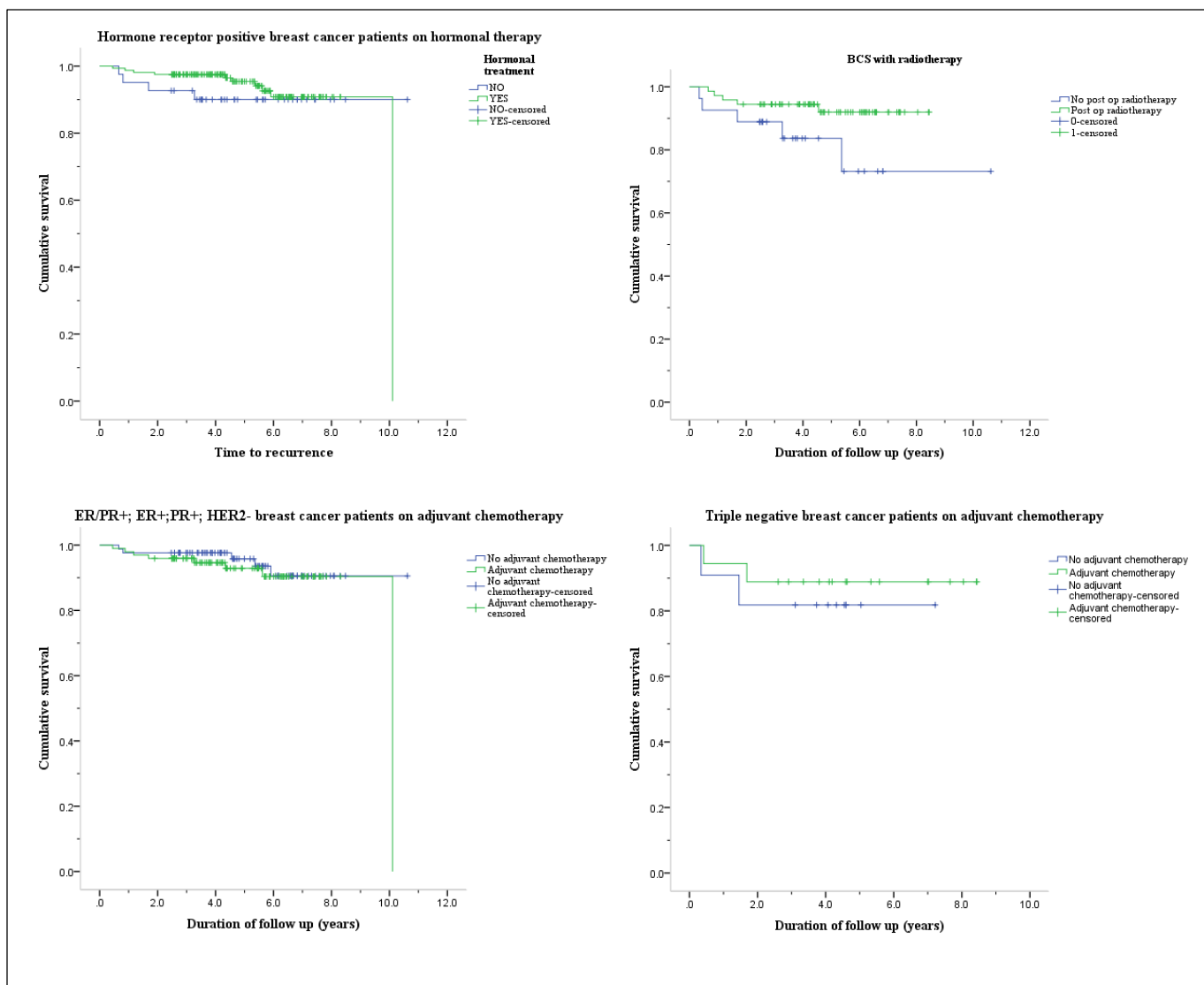


Figure 3. Kalan–Meier curves for (a) hormonal therapy for patients with ER/PR+ breast cancer; (b) radiotherapy post breast conserving surgery; (c) adjuvant chemotherapy for hormone receptor positive breast cancer; and (d) adjuvant chemotherapy for triple negative breast cancer.

In this cohort, we note that 98% of the women presented with symptoms of a palpable breast mass, a presentation that differs from that of Western populations, where up to 30% of breast cancers are detected on screening (13), and indeed reflects scenarios in the absence of national screening programs or a lack of patient awareness (14).

The distribution of morphological subtypes among women of African descent has been presumed to be hormone receptor poor, with a higher prevalence of triple-negative and HER2 overexpressing breast cancer

(15). Contrary to this, hormone receptor-positive breast cancer prevalence in this study was at 76%, while triple-negative cancer was at 12.1%, and HER2+ cancer at 2.9% (16). This morphological distribution was similar to what was found by a study done by Sayeed et al. in the same setting, where hormone receptor breast cancer was found to represent 72% (217/301) of all breast cancers (17).

The 5-year OS for all patients was 94% with a cumulative incidence of 6% for ER/PR+/HER2– breast cancer and 14% for triple-negative breast cancer.

# PATTERN OF RECURRENCE IN EARLY BREAST CANCER

Studies have demonstrated this recurrence pattern with predominant hormone receptor-positive breast cancer recurring within the first 5 years of follow-up (18, 19). HER2+ breast cancer is associated with poor survival and distant metastasis, in contrast to the findings in this study, which could be attributed to the small number of patients with HER2+ breast cancer, the short duration of follow-up, and the high loss to follow-up in the study (20).

Adjuvant treatment (hormonal therapy and trastuzumab) in sub-Saharan Africa is mostly inaccessible to most breast cancer patients. Socioeconomic factors and

education have been cited as the most common causes of non-adherence, and failure to complete treatment (21). In this series, only 81% of women eligible for hormonal therapy had documented therapy provided with a 6.1% non-adherence, and a 19% loss to follow-up, while only 63% of women with HER2+ breast cancer received Herceptin.

The 5-year cumulative incidence of recurrence in patients with ER/PR+ breast cancer was higher in those who did not receive adjuvant hormonal treatment however, with continued follow-up the incidence between the two groups was similar.

Table 3. 5- and 10-year survival rates based on tumor characteristics and treatment modalities

	N	NUMBER OF EVENTS	5-YEAR SURVIVAL	10-YEAR SURVIVAL	LOG RANK TEST	<i>p</i> - VALUE
<i>Overall survival</i>			94%	91%	$\chi^2 = 0.841$	0.657
Ductal carcinoma in situ			91%	-		
Stage I			93%	93%		
Stage II			94%	45%		
<i>Receptor status</i>						
ER/PR+/HER2-			94%	45%		
ER/PR+/HER2+			100%	100%		
HER2+			100%	100%		
Triple-negative			86%	—		
<i>Type of surgery</i>						
Breast conserving surgery	100	10	89%	87%	2.68	0.102
Modified radical mastectomy	141	7	97%	91%		
<i>Hormonal treatment (ER/PR+)</i>						
Tamoxifen/aromatase inhibitor	161	10	95%	90%	2.89	0.59
No hormonal treatment	41	4	90%	90%		
<i>Radiotherapy (breast conserving surgery)</i>						
Radiotherapy	27	5	94%	92%	3.4	0.06
No radiotherapy	72	5	86%	73%		
<i>Adjuvant chemotherapy</i>						
ER/PR+/HER2- (no adjuvant chemotherapy)	85	5	95%	90%	0.54	0.46
ER/PR+/HER2- (adjuvant chemotherapy)	98	8	93%	90%		
Triple-negative (no adjuvant chemotherapy)	11	2	81%	—	0.32	0.57
Triple-negative (adjuvant chemotherapy)	8	2	89%	—		

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.



Table 4. Cox regression and hazard ratio models

	B(COEFFICIENT)	p VALUE	HAZARD RATIO	95% CI LOWER	UPPER
Age	-0.026	0.478	0.974	0.907	1.047
Menopausal status	0.684	0.429	1.982	0.364	10.801
Family history of breast cancer	13.314	0.987	605485.693	0.000	.
Tumor size	-0.003	0.892	0.997	0.955	1.041
Nodal involvement	-0.717	0.266	0.488	0.138	1.729
Lymphovascular invasion	-0.454	0.489	0.635	0.176	2.294
Nottingham Grade		0.030			
GRADE (1)	3.356	0.007	28.683	2.451	335.650
GRADE (2)	-13.693	0.982	0.000	0.000	.
GRADE (3)	-0.240	0.712	0.787	0.221	2.807
Type of surgery	0.666	0.320	1.946	0.524	7.224
Radiotherapy	0.451	0.528	1.570	0.387	6.375
Hormonal therapy	0.132	0.910	1.141	0.115	11.336
Duration of hormonal therapy	0.037	0.872	1.038	0.662	1.626
Adjuvant chemotherapy	0.274	0.691	1.315	0.341	5.074
Compliance to hormonal therapy	0.214	0.778	1.239	0.281	5.468

This reiterates the findings in larger trials that demonstrate a survival benefit of adjuvant hormonal treatment in patients with hormone receptor-positive breast cancer. The findings in this study could also be attributed to the duration of hormonal treatment, which was on average 3.9 years (*SD* 1.9 years). Randomized controlled trials have demonstrated the benefit of extended hormonal treatment with the incidence of recurrence being higher in patients who discontinued hormonal therapy (18); hence extended hormonal treatment should be considered in this subgroup of breast cancer patients.

Overall, the recurrence rate for early breast cancer in this study was found to be 7.1%, with a recurrence rate of 10% (10/98) and 5% (7/141) following breast conserving therapy (BCT) and modified radical mastectomy (MRM), respectively, a rate comparable to internationally documented recurrence rates (22, 23). Adjuvant radiotherapy appears to confer better survival, especially in patients who underwent BCS, reflecting the findings of a study done by Kunkler et al., whereby the 10-year cumulative incidence of recurrence in BCS with and without adjuvant radiotherapy was 0.9% and 9.5%, respectively (24).

A total of 11 out of 17 recurrences (64%) were initially identified by either a clinical breast examination or a

self-breast examination. Despite the fact that randomized clinical trials have not demonstrated a reduction in breast cancer mortality with clinical breast examination, in populations where the uptake for breast cancer screening is low and the majority of the women present with symptoms, clinical breast examination should be considered as an important adjunct to screening and creation of breast cancer awareness (25).

### Conclusion

From this study, we can conclude that early breast cancer in our setting has a good OS and low recurrence rates that are comparable to that found in Western countries.

### Study limitations

There was a significant number of eligible candidates who were omitted from analysis because of incomplete documentations. There was a 19% loss to follow-up/transfer of care of patients who had completed their treatment in this institution.

This study was conducted in a private tertiary facility; furthermore, it also had a small sample size, and the recurrence rate may not be representative of the general population.

## Recommendations

In this study, only 0.4% of women presented with asymptomatic breast cancer detected only after screening. This points to a major gap and the need to promote breast cancer screening in order to detect breast cancer at an early curable stage.

This was a retrospective study with the use of medical records that are not ideal for research. We recommend a long-term prospective study to determine the recurrence rates and survival for women managed for early breast cancer.

## Author contributions

CM and MM equally contributed to the writing, reviewing and editing the original draft.

All authors equally contributed to conceptualization, methodology and supervision.

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