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Real-world breast cancer treatment patterns and guideline-concordant treatment completion among Malawian women

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Abstract

Purpose In Sub-Saharan Africa (SSA), resource-stratified guidelines for breast cancer treatment are increasingly recommended, but treatment receipt and outcomes according to these guidelines are underreported. Here, we describe breast cancer treatment patterns by stage and curative-intent guideline-concordant treatment (GCT) receipt among Malawian women.

Methods A prospective cohort of breast cancer patients were enrolled from December 2016 to October 2018 at Kamuzu Central Hospital with an assessment of demographics, stage, and treatment received, including neoadjuvant (NAC), adjuvant (AdC) and palliative chemotherapy and breast surgery. Curative-intent GCT was defined as having completed breast surgery and at least 4 cycles of chemotherapy. Overall survival (OS) was calculated using Kaplan Meier methods and odds ratios using logistic regression.

Results 91 patients were included, of whom 13 (14%) presented as stage II, 54 (59%) as stage III, and 24 (26%) as stage IV. Curative treatment was recommended for 65 of 91 (71%) patients, of whom 47 (72%) were initiated on NAC, 14 (22%) on upfront breast surgery, and 4 (6%) received no treatment. Only 63% (41/65) of patients received curative-intent GCT as recommended with non-GCT associated with stage III (vs. stage II) disease (OR 0.10 CI (0.01–0.89)), HIV positivity ((OR 0.25 CI (0.06–0.99)) and hormone receptor (HR) negative/HER2 positive subtype ((OR 0.07 CI (0.01–0.49)). Curative-intent GCT was associated with improved OS (44.1 vs. 23.2 months; $p=0.00$) compared to non-GCT.

Conclusion While curative-intent GCT was associated with improved survival in this Malawian cohort, treatment completion rates were suboptimal. Resource-stratified guidelines must be paired with locally relevant, multilevel implementation strategies to target barriers to treatment completion.

Keywords Breast cancer, Treatment, Malawi

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Introduction

Women in sub-Saharan Africa (SSA) are disproportionately affected by breast cancer and experience a 3-year overall survival (OS) of only 36–59% compared to nearly 90% 5-year OS among women in high-income countries (HIC) [1–3]. Improvements in early diagnosis and access to essential treatments in SSA could result in a combined 18–22% absolute survival gain and a one-third reduction in breast cancer deaths [2]. Numerous international efforts including a collaboration between the African Cancer Coalition (ACC) and the National Comprehensive Cancer Network (NCCN) which released the NCCN Harmonized Guidelines™ for sub-Saharan Africa in 2017, have created clinical care guidelines that aim to increase access and awareness of proven treatments tailored to resource availability [4–6]. While completion of guideline-concordant treatment (GCT) has been associated with improved outcomes in cancer patients in HIC, only a few studies have evaluated the application of region-specific guidelines [7–11]. The African Breast Cancer-Disparities in Outcomes Cohort (ABC-DO) which evaluated women diagnosed with breast cancer from Namibia, Nigeria, Uganda, South Africa and Zambia found that only 36% of patients with non-metastatic disease initiated surgery and systemic therapy with or without radiotherapy [11]. Treatment abandonment was also common and occurred in up to 38% of patients in Nigeria specifically [11]. GCT of breast cancer has not yet been studied in Malawi, a low-income country in southeastern Africa.

There were 1543 new breast cancer patients and 842 breast cancer-related deaths in Malawi in 2022 [12]. To provide a robust description of patient characteristics and clinical outcomes, the first prospective breast cancer cohort in Malawi was initiated in 2016 at Kamuzu Central Hospital (KCH) as part of the longstanding clinical research collaboration between the University of North Carolina (UNC) and the Malawi Ministry of Health [13]. Through this collaboration, access to timely diagnostic pathology, chemotherapy, surgery, and endocrine therapy (ET) in concordance with NCCN harmonized guidelines for SSA were available and recommended [5]. An analysis of the first 100 patients in this cohort showed a high prevalence of stage III/IV disease (75%) and median overall survival of 20.2 months [13]. While survival can be partially attributed to the advanced stage at presentation, treatment receipt and associated outcomes were not well-characterized. In this study, we aim to describe the application of NCCN harmonized guidelines for SSA by determining: (1) common treatment patterns by stage and (2) completion of curative-intent GCT and related outcomes in this prospective Malawian cohort of women with breast cancer.

Methods

Study design and patients

KCH is a referral hospital for Malawi's central and northern regions, with a catchment area of about half the country's 19 million population. The breast cancer cohort eligibility and enrollment details are included elsewhere [13]. Patients 18 years and older consecutively enrolled in this prospective cohort from December 2016 to October 2018 were included. Patients were excluded from the current analysis if complete clinical or pathologic staging at diagnosis was unavailable. All patients were followed until death, loss to follow-up (LTFU), or the last censorship date of July 26, 2023. Patients were considered LTFU if they had missed their previous appointment, had not been in contact with clinic staff for at least three months and were unreachable. This study was approved by the Institutional Review Board at UNC and the Malawi National Health Science Research Committee in compliance with the Declaration of Helsinki. All patients provided written informed consent at the time of enrollment.

Study procedures

Enrolled patients underwent breast cancer diagnostic, sociodemographic and clinical evaluation as described previously [13]. Enrolled patients completed staging based on the 7th American Joint Committee on Cancer (AJCC) TNM staging system, which was performed using clinical examination, chest radiography, and abdominal ultrasonography or CT chest and abdomen [14]. For a minority of patients, clinical staging information was incomplete at diagnosis; however, pathologic staging at the time of upfront breast surgery (without receiving systemic therapy) in accordance with the AJCC 7th edition TNM staging system was available and replaced clinical staging [14]. Otherwise, any patient with missing pathologic or clinical TNM staging was excluded. KCH institutional treatment guidelines for breast cancer were modeled after NCCN Harmonized Guidelines for SSA and recommended as follows: Patients with non-metastatic breast cancer were recommended to initiate one of the following curative-intent treatment pathways: (1) neoadjuvant chemotherapy (NAC) followed by breast surgery or (2) breast surgery followed by adjuvant chemotherapy (AdC) [5]. First-line recommended NAC and AdC was Doxorubicin 60mg/m^2 and Cyclophosphamide 600mg/m^2 (AC) every 21 days for 4–6 cycles followed by Paclitaxel (T) 175mg/m^2 every 21 days for 3–4 cycles. Women who underwent breast surgery received a modified radical mastectomy with axillary lymph node dissection. Patients with metastatic breast cancer were recommended to initiate palliative chemotherapy with Paclitaxel 175 mg/ m^2 every 21 days until disease progression as reported by clinician documentation and ascertained using either clinical examination or

follow-up imaging. Alternative chemotherapy regimens were recommended based on availability. Endocrine therapy (ET) with tamoxifen or anastrozole was recommended for hormone receptor (HR) positive patients for five years for non-metastatic patients and at provider discretion for metastatic patients. Radiation and human epidermal growth factor receptor 2 (HER2)-directed therapy were not available.

Study definitions

Treatment intent (curative or palliative) was recorded by providers alongside each recommended treatment. Patients with non-metastatic breast cancer who were treated with curative intent were evaluated for GCT. Curative-intent GCT was defined as completion of breast surgery and at least 4 cycles of chemotherapy (NAC, AdC, or both). Among chemotherapy regimens recommended in the NCCN Harmonized Guidelines for SSA, four cycles of chemotherapy were the minimum required to complete a NAC or AdC regimen. Thus, 4 cycles was deemed the threshold for completion in this study [5].

Statistical methods

Differences in patient characteristics based on the initial stage were computed using chi-squared tests for categorical variables and one-way ANOVA for continuous variables. Subsequent trend analysis was conducted using Pearson's correlation coefficient for $p < 0.05$. Crude odds ratios for completion of curative-intent GCT for patients without metastatic breast cancer were calculated for clinical and demographic variables with 95% confidence intervals. A logistic regression model was created using variables with crude odds ratios with a p-value of < 0.1. A p-value of < 0.05 was deemed to be statistically significant. The number of cycles of chemotherapy was compared between HIV-negative and positive patients using the Wilcoxon rank sum test. OS was measured from diagnosis to last follow-up, death, or documented LTFU. Kaplan-Meier methods and log-rank test were used to estimate OS and calculate differences between groups. All analyses were conducted using Stata version 16.1 [15].

Results

Patient characteristics by presenting stage

Of 100 enrolled patients, 91 were included in this analytical cohort. Nine patients were excluded due to lack of clinical or pathologic staging data. Full demographic and clinical characteristics are seen in Table 1. Thirteen patients (14%) presented with Stage II, 54 (59%) with Stage III, and 24 (26%) with Stage IV disease. The median age at diagnosis was 50 years (IQR 42–58) and did not vary by presenting stage. Seventeen patients (19%) were HIV-positive; HIV status was not associated with presenting stage. Patients diagnosed at advanced stage were more likely to be part-time or not employed outside the home($p = 0.019$), live outside the capital city of Lilongwe ($p = 0.009$) and have ECOG performance status of 2 or greater ($p = 0.00$). Family history of cancer ($p = 0.134$) or breast cancer ($p = 0.070$), prior self or clinical breast exam were not associated with presenting stage. Palpable breast masses were common in 38%, 74% and 92% of patients with stage II, III and IV disease, respectively ($p = 0.001$). Patients with stage II disease had the highest rates of HR-positive disease (91%) compared to patients with stage III disease (36%) and patients with stage IV disease (56%). Patients with stage III disease had the highest rate of triple-negative disease (38%), notably more than patients with stage IV disease (13%). Individual tumor grades did not significantly vary by stage.

Curative-Intent treatment patterns

Treatment pathways are highlighted in Fig. 1. Patients with Stage II disease were most often initiated on NAC (54%) rather than upfront breast surgery (38%) or no treatment (8%). Similarly, patients with Stage III disease were most often started on NAC (74%) rather than upfront breast surgery (17%), no treatment (6%), or palliative chemotherapy (4%). For patients who received NAC, 86% of those with stage II disease went on to receive breast surgery compared to only 55% of patients with stage III disease. Median number of NAC cycles received was 6 for 1 patient with stage II disease and 3 (IQR 2–4) for 22 patients with Stage III disease. However, chemotherapy was often delivered as "sandwich chemotherapy," split between NAC and AdC, among both patients with stage II (6;50%) and stage III disease (18; 33%) as seen in Table 2. In this case, a median of 11 cycles (IQR 10–13) were given. A minority of patients underwent upfront breast surgery, including 38% and 17% of patients with stage II and III disease, respectively. For those who did undergo upfront breast surgery, most (100% of stage II and 78% of stage III) patients went on to receive adjuvant chemotherapy.

Regimens containing an anthracycline or taxane (listed in Table 2) were given as first-line chemotherapy in 100% and 69% of patients with stage II and III disease, respectively. However, receipt of both an anthracycline and taxane as NAC was low (14% and 13% for patients with stage II and III disease; Table 2). Additionally, receipt of ET was low among patients with HR-positive disease and initiated in 30% of patients with stage II and 40% with stage III disease.

Palliative-Intent treatment patterns

Among patients receiving palliative chemotherapy as initial treatment, 24 (92%) had stage IV, and 2 (4%) had unresectable stage III disease (Fig. 1). Patients with stage IV disease received a median of 3 cycles (IQR 1–9) of

Table 1 Treatment patterns among a prospective cohort of Malawian women with breast cancer, December 2016-October 2018, by stage at presentation

	Stage II	**Stage III**	**Stage IV**
	n = 13	***n = 54***	***n = 24***
Overall Treatment Combinations:			
No Treatment	1 (4)	3 (5)	1 (4)
Surgery alone	0 (0)	2 (4)	0 (0)
Chemotherapy Alone	1 (4)	20 (36)	23 (96)
Surgery and chemotherapy	11 (92)	29 (54)	0 (0)
Underwent Surgery as Modified Radical Mastectomy	11 (92)	31 (57)	0 (0)
Type of chemotherapy:	*n = 12*[#]	*n = 49*[#]	*n = 23*[#]
Neoadjuvant alone, n (%)	1 (8)	22 (45)	--
Median number of cycles n (IQR)	6 (-)	3 (2–4)	
Adjuvant alone, n (%)	5 (42)	7 (13)	--
Median number of cycles n (IQR)	6 (5–9)	6 (4–6)	
Neoadjuvant and Adjuvant, n (%)	6 (50)	18 (33)	--
Median number of cycles n (IQR)	8 (7–9)	11 (10–13)	
Palliative, n (%)	0 (0)	2 (7)	23 (100)
Median number of cycles n (IQR)	0 (0)	11 (9–12)	3 (1–9)
First chemotherapy regimen n (%)	*n = 12*[#]	*n = 49*[#]	*n = 23*[#]
	AC 9 (75)	T 13 (27)	Doc/Plat 8 (35)
	T 2 (17)	AC 11 (22)	T 7 (30)
	CAF 1 (8)	TAC 4 (8)	CAF 2 (9)
		CAF 4 (8)	CMF 2 (9)
		CMF 4 (8)	Other 4 (17)
		TC 2 (4)	
		Other 11 (22)	
Type of Neoadjuvant Chemotherapy Received:	*n = 7*	*n = 40*	
Anthracycline	5 (71)	22 (55)	
Taxane	1 (14)	12 (30)	
Anthracycline + Taxane	1 (14)	5 (13)	
Other	0 (0)	1 (2)	
Initiated endocrine therapy (ever) if Hormone Receptor Positive n (%)	*n = 10*[^]	*n = 18*[^]	*n = 13*[^]
	3 (30)	8 (44)	4 (31)[%]

[#]n is based on the number of patients who received chemotherapy (the sum of patients who received chemotherapy alone or surgery and chemotherapy)

[^]n for endocrine therapy is based on number of patients with hormone receptor positive disease (see Table 2)

[%]Endocrine therapy may not be indicated for all patients with Stage IV hormone receptor positive disease

AC = Doxorubicin, Cyclophosphamide

TAC = Docetaxel, Cyclophosphamide, Doxorubicin

T = Paclitaxel

TC = Docetaxel, Cyclophosphamide

Doc/Plat = Docetaxel, Carboplatin or Cisplatin

CAF = Cyclophosphamide, Doxorubicin, Fluorouracil

CMF = Cyclophosphamide, Methotrexate, Fluorouracil

chemotherapy. A minority received single-agent paclitaxel (30%) as initial chemotherapy with various other regimens given as seen in Table 2.

Guideline-Concordant, Curative-Intent treatment completion

Of 67 patients with Stage II and Stage III disease, 65 patients were recommended to initiate curative-intent treatment whereas 2 patients with very locally advanced Stage III disease were recommended to receive palliative treatment only. Forty-one (63%) of these 65 patients completed curative-intent GCT as recommended. Individual factors associated with non-GCT included HIV-positive status, Stage III disease (vs. Stage II), and HR-negative/ HER2-positive subtype on univariate analysis, with HR-negative/ HER2-positive receptor subtype persisting on multivariate analysis (Table 3).

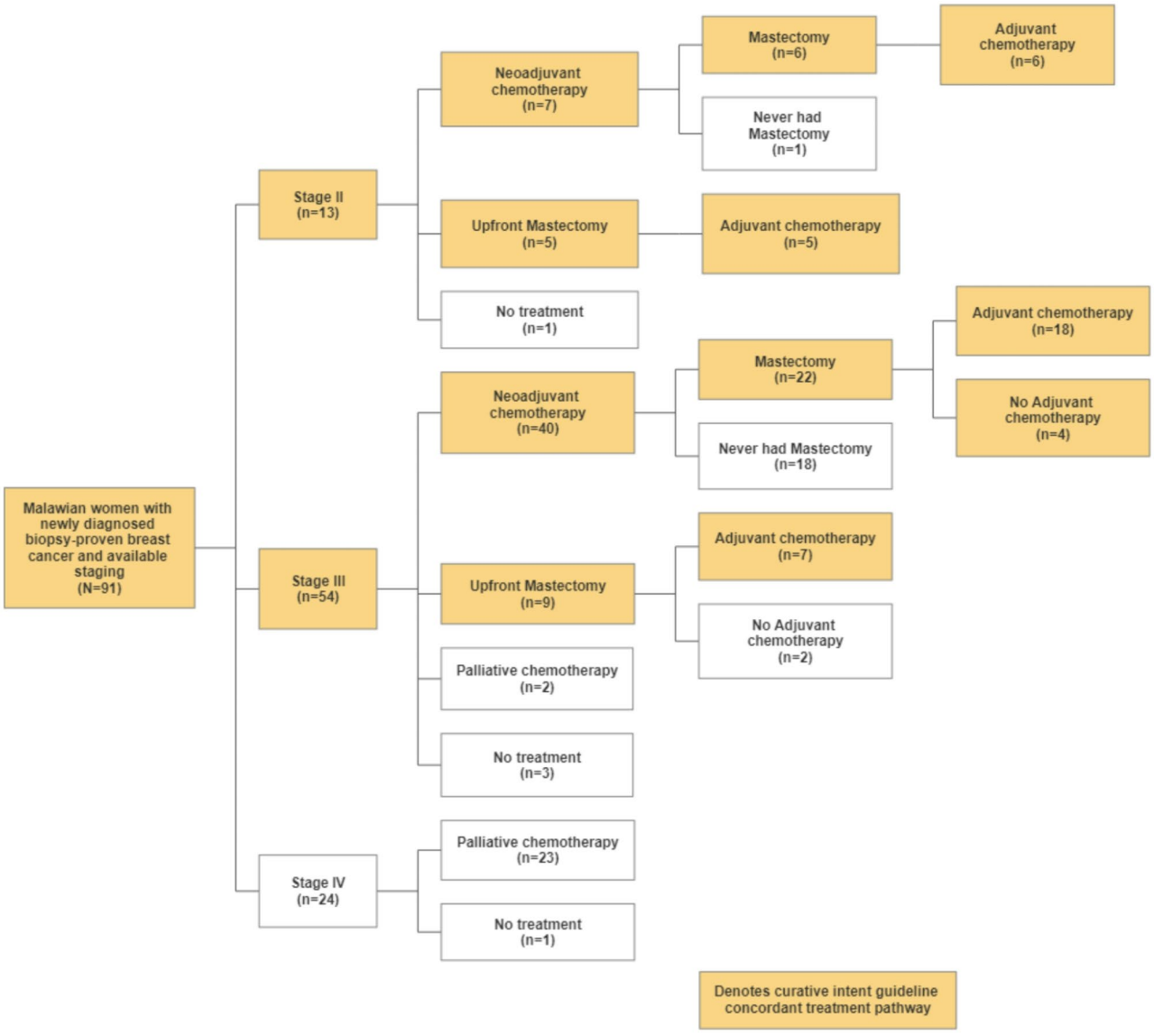


Fig. 1 Guideline-concordant treatment pathways among a prospective cohort of Malawian women with breast cancer, December 2016-October 2018, by stage at presentation

Patients with HIV

In an exploratory analysis, patients with HIV received fewer total cycles of chemotherapy than patients without HIV (3 vs. 8 cycles; $p = 0.03$) and a trend toward less chemotherapy for NAC (2.5 vs. 4 cycles; $p = 0.07$) and palliative chemotherapy (2 vs. 6 cycles; $p = 0.1$) though this did not reach statistical significance.

Survival

Median follow-up for the entire cohort was 19.6 months (IQR 6.2–42.3 months) with a maximum of 66.8 months. OS for the cohort was 23.2 months (95% Confidence Interval (CI) 17.1–35.7) and varied by stage at presentation. Median OS for patients with stage II disease was not reached (NR; CI 24.5-NR) compared to 34.0 months (19.6–42.3) and 8.2 months (1.5–16.4; $p = 0.00$) for patients with stage III and IV disease. Additionally, OS varied by initial chemotherapy received in which OS of patients receiving AdC was NR (95% CI 24.7-NR) compared to 36.6 months (CI 23.2–43.9),10.2 months (CI 3.6–16.4), and 3.0 months (CI 0.07–21.4; $p = 0.00$) for those receiving NAC, palliative chemotherapy and no chemotherapy, respectively (Fig. 2a). Importantly, patients who received curative-intent GCT had a significantly longer median OS compared to those who received non-GCT (44.1 months (CI 35.7-NR) vs. 23.2 months (13.5–37.2; $p = 0.00$; Fig. 2b).

Table 2 Demographic, clinical and pathologic characteristics of women with newly diagnosed breast cancer in a prospective Malawian cohort enrolled December 2016-October 2018

	Stage II	Stage III	Stage IV	
	(n = 13)^	***(n = 54)^***	***(n = 24)^***	***p* value**
Demographics				
Mean Age (years)	45	51	49	p = 0.231[a]
Education status: n (%)				
Did not complete primary school	4 (31)	34 (63)	13 (54)	p = 0.108[b]
Completed at least primary school	9 (69)	20 (37)	11(46)	
Socioeconomic Status				
Occupation: n (%)				
Employed full time	6 (46)	14 (26)	2 (8)	p = 0.026[b]*; p = 0.019[c]
Employed part time	2 (15)	2 (4)	1 (4)	
Housewife	3 (23)	17 (31)	9 (38)	
Unemployed	1 (8)	7 (13)	9 (38)	
Other	1 (8)	14 (26)	3 (12)	
House Flooring				
Dirt/Dung/Sand[#]	10 (77)	27 (50)	11 (46)	p = 0.215[b]
Cement/tiles[$]	3 (23)	27 (50)	13 (54)	
Residence: n (%)				
Lilongwe	6 (46)	8 (15)	2 (8)	p = 0.011[b]*; p = 0.009
Outside of Lilongwe	7 (54)	46 (85)	22 (92)	
		n = 53		
Family history of cancer n (%)	5 (38)	9 (17)	3 (13)	p = 0.134[b]
Family history of breast cancer n (%)	3 (23)	2 (4)	2 (8)	p = 0.070[b]
Performed self-breast exam in the past				p = 0.742[b]
Yes	7 (54)	21 (39)	16 (67)	
No	6 (46)	33 (61)	8 (33)	
Underwent clinical breast exam in the past		*n = 53*		p = 0.773[b]
Yes	12 (92)	45 (85)	21 (88)	
No	1 (8)	8 (15)	3 (12)	
			n = 23	
HIV positive n (%)	1 (8)	11 (20)	5 (22)	p = 0.532[b]
Clinical Findings n (%)				
Palpable breast mass > 5cm	5 (38)	40 (74)	22 (92)	p = 0.002[b];p = 0.001[c]
Breast ulceration present	0 (0)	14 (26)	12 (50)	p = 0.005[b];p = 0.001[c]
ECOG				
0–1	13 (100)	52 (96)	15 (63)	p = 0.000[b]*;p = 0.000[c]
≥2	0 (0)	2 (4)	9 (37)	
Tumor characteristics n (%)				
Histology	*n = 11*	*n = 44*	n = 20	p = 0.795[b]
Invasive Ductal Carcinoma	10 (91)	38 (86)	20 (100)	
Invasive Lobular Carcinoma	0 (0)	1 (2)	0 (0)	
Other	1 (9)	5 (11)	0 (0)	
Grade	*n = 11*	*n = 50*	*n = 23*	p = 0.515[b];p = 0.39[c]
1	4 (36)	15 (30)	4 (17)	
2	3 (27)	16 (32)	9 (39)	
3	4 (36)	15 (30)	10 (43)	
Unable to grade	0 (0)	4 (8)	0 (0)	
Hormone Receptor Status	*n = 11*	*n = 50*	*n = 23*	p = 0.0028[b]*;p = 0.40[c]
ER/PR+/HER2-	9 (82)	16 (32)	9 (39)	
ER/PR+/HER2+	1 (9)	2 (4)	4 (17)	
ER/PR-/HER2+	0 (0)	9 (18)	5 (22)	
ER/PR-/HER2-	1 (9)	19 (38)	3 (13)	
Undetermined^		4 (8)	2 (9)	

Table 2 (continued)

	Stage II	Stage III	Stage IV	
	(n = 13)^	***(n = 54)***^	***(n = 24)***^	***p* value**
T2	8 (62)	2 (4)	0 (0)	p = 0.00[b];p = 0.00[c]
T3	5 (38)	14 (26)	1 (4)	
T4	0 (0)	35 (65)	22 (92)	
Unable to Assess	0 (0)	2 (4)	0 (0)	
Missing	0 (0)	1 (2)	1 (4)	
N0	7 (54)	6 (11)	1 (4)	p = 0.00[b],p = 0.00[c]
N1	6 (46)	32 (59)	6 (25)	
N2	0 (0)	9 (17)	9 (38)	
N3	0 (0)	3 (6)	6 (25)	
Unable to Assess	0 (0)	4 (7)	1 (4)	
Missing	0 (0)	0 (0)	1 (4)	

[a]one way ANOVA

[b]Chi square test

[c]Trend analysis by Pearson's correlation coefficient

^n unless otherwise noted

*p values < 0.05

[#] surrogate for low socioeconomic status

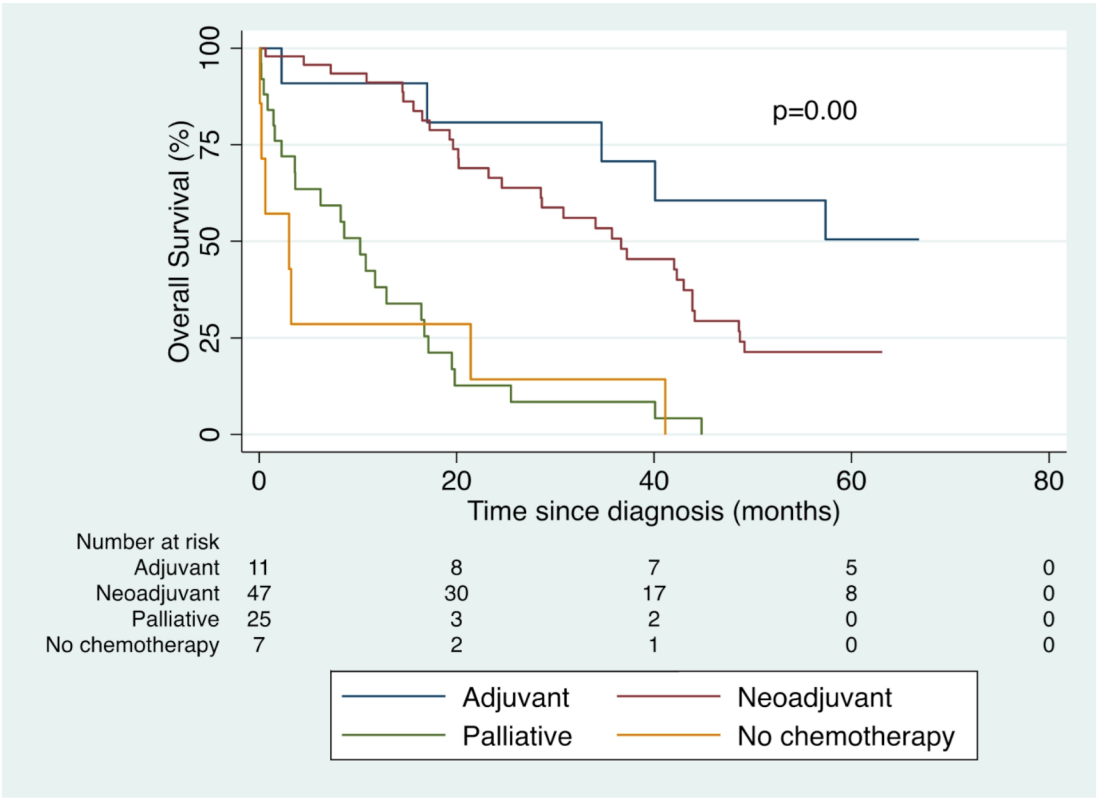
[$] surrogate for higher socioeconomic status

Table 3 Odds ratio for completion of curative-intent guideline-concordant treatment (GCT) among a prospective cohort of Malawian women with breast cancer, December 2016-October 2018

Total (*n = 65*)	**Unadjusted OR (95% CI)**	***p* value**	**Adjusted OR (95% CI)[a]**	***p* value**
Age	0.99 (0.95–1.02)	0.53		
Residence				
Lilongwe	1 (Ref)			
Outside Lilongwe	0.85 (0.22–3.18)	0.8		
Occupation				
Employed full time	1 (Ref)			
Employed part time	0.66 (0.92–4.81)	0.68		
Housewife	0.45 (0.11–1.78)	0.26		
Unemployed	0.33 (0.05–1.85)	0.21		
Other	0.53 (0.11–2.41)	0.41		
HIV Status				
Negative	1 (Ref)			
Positive	0.25 (0.06–0.99)	0.049*	0.17 (0.03–1.02)	0.053**
Stage				
II	1 (Ref)		1 (Ref)	
III	0.10 (0.01–0.89)*	0.040*	0.26 (0.02–2.76)	0.26
Tumor > 5cm				
Yes	0.73 (0.25-2.0)	0.56		
No	1 (Ref)			
ER/PR+/HER2-	1 (Ref)		1 (Ref)	
ER/PR+/HER2+	0.45 (0.03–6.05)	0.5	0.36 (0.02–5.65)	0.46
ER/PR-/HER2+	0.07 (0.01–0.49)*	0.007*	0.12 (0.01–0.97)*	0.047*
ER/PR-/HER2-	0.49 (0.12–1.93)	0.31	0.60 (0.12–2.90)	0.53
Unable to assess	0.11 (0.01–1.51)**	0.10**	0.37 (0.02–6.87)	0.51

*$p < 0.05$

**$p \leq 0.1$



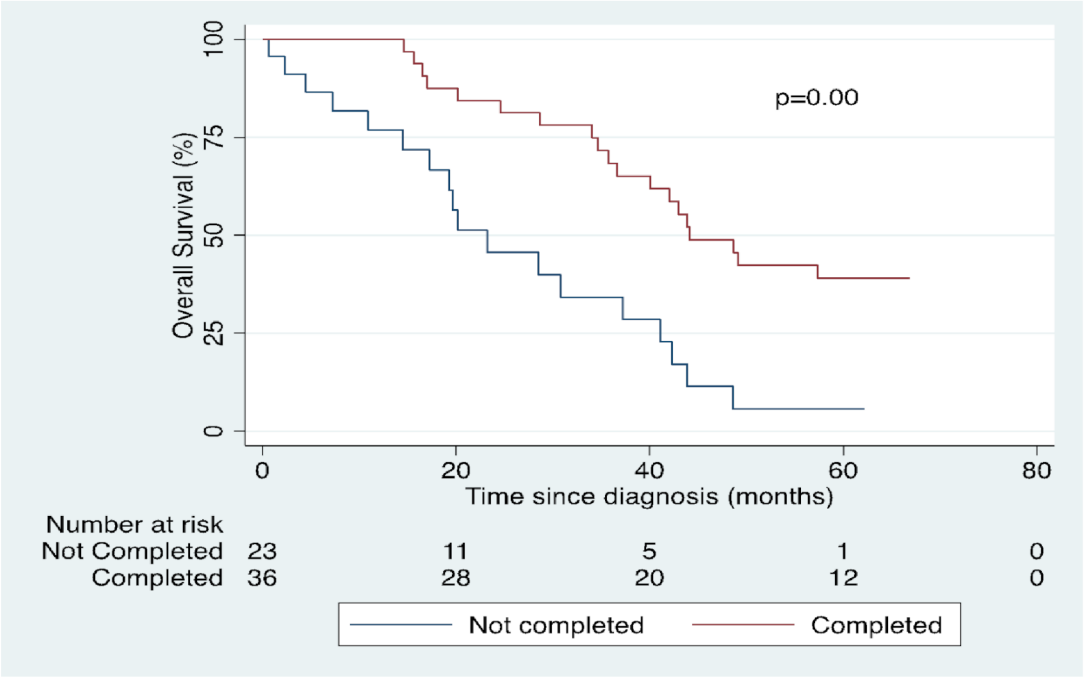


Fig. 2 **a**) Overall survival of women with newly diagnosed breast cancer in a prospective Malawian cohort enrolled December 2016-October 2018, by first chemotherapy received
b) Overall survival of women with newly diagnosed breast cancer in a prospective Malawian cohort enrolled December 2016-October 2018, by completion of guideline-concordant treatment

Discussion

This prospective cohort analysis highlights real-world breast cancer treatment patterns in a public referral hospital in Malawi where resource-adapted guidelines were adopted. While the African Breast Cancer-Disparities Outcomes (ABC-DO) cohort study has most recently evaluated treatment completion and guideline concordance among patients with breast cancer across SSA, this study provides a detailed examination of a single center experience of breast cancer patients in Malawi and the treatment pathways taken throughout their disease course [11]. Most patients in our cohort presented with non-metastatic breast cancer and received curative-intent treatment with suboptimal guideline-concordant treatment completion, demonstrating the challenges of delivering multimodality breast cancer care in a resource-limited setting even when guidelines are recognized and recommended.

All patients in this cohort presented with at least stage II disease, reflecting the absence of population-based screening or a widely available early detection pathway for breast cancer in Malawi [16, 17]. Advanced stage at presentation was associated with part-time or unemployment and living outside the urban center. Given that more than 85% of Malawians live in rural communities where healthcare is less accessible, delays in both health care-seeking behaviors and referrals within the health system likely contribute to more advanced presentations [18, 19]. Stage at presentation determined survival in our cohort with advanced stage associated with worse prognosis as has been seen across clinical settings including SSA [2, 20–23]. Further, late stage and poor survival are likely underestimated in our cohort given we excluded 9 patients for incomplete staging, all of whom were LTFU or died prior to staging. Additionally, aggressive pathologic characteristics such as triple negative, HER2 positive, and grade 3 disease were not associated with higher stage at presentation further suggesting that delayed presentations and poor access to timely evaluation likely play a critical role in the advanced presentation. Interventions that target early recognition of breast cancer symptoms and decentralized evaluation among trained health care providers in rural communities should be prioritized.

The majority (70%) of patients with non-metastatic disease received NAC, which is similar to published rates from Mozambique, Rwanda, and the ABC-DO study though higher than a registry-based population study from the African Cancer Registry Network (11%) where NAC rates were often missing [9, 11, 24, 25]. In HIC, NAC is often selected over AdC due to the opportunity for patients to undergo breast-conserving surgery, limited axillary surgery, or pathologic and clinical response assessment. Still, disease-free and OS among patients receiving NAC and AdC are equivalent in major clinical trials [26, 27]. Conversely in our cohort, NAC was often administered to render a patient with unresectable disease a surgical candidate rather than as an equivalent option to AdC. This channeling of NAC to the most difficult-to-treat patients is a likely explanation for their worse OS compared to those receiving AdC alone. Further, among those who received NAC, patients with stage III disease experienced poor treatment outcomes compared to those with stage II disease. They were less likely to undergo breast surgery, received less NAC and were more likely to receive an alternative chemotherapy regimen not recommended by local guidelines. Given few patients with stage II (14%) or stage III (13%) disease received both an anthracycline and taxane as NAC, these patterns can likely be attributed to inadequate treatment response, early recurrence or death due to occult metastatic disease and poor treatment tolerability related to very locally advanced disease. Additionally, in this study we did not evaluate specific reasons for not reaching breast surgery which requires further investigation. Rates of breast surgery have varied significantly across SSA ranging from 35 to 100% and are thought to reflect limited surgical capacity, clinical factors, and individual patient and provider attitudes toward breast surgery [28–33].

Importantly, curative-intent GCT among patients in our study was associated with improved OS. Completion of curative-intent GCT occurred in 63% of our cohort which is similar to other studies from SSA (35–74%) which have varying definitions of GCT [9, 11, 24, 25]. Encouragingly, a study comparing patients with T4 breast cancer from the U.S. and Nigeria showed similar recurrence-free and OS when multimodality treatment was completed highlighting that equitable treatment access is a major determinant in outcomes and should be prioritized [34]. Barriers to completing GCT have been identified in recent studies from Botswana at both the provider level including lack of resources, staffing and clearly defined national cancer control policies as well as at the patient level including cancer stigma, social determinants of health and health systems barriers [7, 35]. In our study, a specific factor associated with non-GCT included HR-negative/HER2-positive disease. This aligns with the poor overall prognosis of HER2 driven disease when HER2-directed therapy is not available and highlights the need for access to HER2-directed therapy in this population to improve survival [36, 37]. HER2 therapies have remained cost prohibitive in Malawi especially when administered as per major clinical trials with IV formulations for a duration of one year [38]. Strategic implementation of HER2 biosimilars, subcutaneous formulations and alternative lengths of treatment are likely to be effective and cost-effective and should be studied in Malawi and SSA

and could help to inform HER2-directed treatment in the region [39, 40].

We also found that HIV-positive patients were less likely to complete GCT on univariate analysis. HIV-positive patients received fewer total cycles of chemotherapy and a trend toward less NAC despite a similar distribution of stage at presentation, suggesting that HIV positive patients may be prescribed chemotherapy less often or tolerate chemotherapy less, as has been hypothesized in studies from a variety of settings [41–44]. Patients living with both HIV and breast cancer have also reported intersectional stigma of breast cancer and HIV, parallel health systems and increased toxicity as barriers to breast cancer treatment [45]. Receiving both HIV and cancer care in joint appointments by trusted providers could potentially diminish this burden on our patients.

Rates of endocrine therapy initiation (30% in Stage II; 44% in Stage III) in our cohort were also low, similar to studies from SSA and HIC where 15–49% of women never initiate recommended ET [46, 47]. This represents a missed opportunity to decrease breast cancer recurrence risk and improve survival among HR-positive patients. Barriers to ET initiation and continuation have mostly been identified in studies outside of SSA and include uncomfortable menopausal symptoms, beliefs about medication efficacy, and provider-patient relationship issues [48, 49]. One study from Ethiopia reported financial hardship, transportation issues and health system factors as reasons for tamoxifen non-adherence [50]. While endocrine therapy including tamoxifen and letrozole are relatively inexpensive and recognized as World Health Organization (WHO) Complementary Essential Medicines, obtaining them requires frequent travel to centralized health centers in Malawi which places a significant burden on patients who have already gone through surgery and chemotherapy [51]. Additionally, patient-provider conversations around risks and benefits of endocrine therapy are complex worldwide and involve a detailed discussion of side effect burden, recurrence, and fertility for younger patients which may not be adequately conveyed or realized among providers and/or patients. Interventions which facilitate these conversations between patients and trusted individuals, including community health workers and providers paired with improved access to these drugs could potentially increase initiation rates. In Ethiopia, it was a nurse-led multipronged endocrine therapy intervention which improved endocrine therapy persistence at 1 year and could be modeled in similar settings [52].

In our cohort, patients who presented with metastatic disease had poor performance status, received little treatment and had poor survival. These patients most commonly received multi-agent rather than recommended single-agent palliative chemotherapy which likely contributed to increased toxicity and poor outcomes in this debilitated patient population [5]. This represents an opportunity to ensure guideline recommended treatment protocols are accessible to providers, reflect local standards and resources, and reviewed regularly as a treating group to improve patient outcomes.

Our study has certain limitations. Clinical response assessments and reasons for LTFU/death were not documented limiting our interpretation of clinical and treatment outcomes data. We are implementing an enhanced electronic data collection tool for improved real-time clinical, treatment, and pathologic response assessments in this prospective cohort that will allow for more robust data collection, improved interpretation of outcomes and patient tracking and navigation which can reduce LTFU. Further, we used a single definition of treatment completion based on the number of cycles of chemotherapy regardless of the chemotherapy regimen chosen which reflected the availability of treatment-related data and allowed for the switching of regimens in the setting of chemotherapy stock-outs. A more detailed definition of treatment completion based on individual chemotherapy regimens and paired with an evaluation of chemotherapy dose intensity in the future could significantly increase our knowledge of chemotherapy receipt in breast cancer patients.

Conclusion

Breast cancer survival in our Malawian cohort was poor and can partially be attributed to late-stage disease presentations. Strategies for de-centralized detection of breast cancer should be prioritized in Malawi and SSA to combat advanced presentations and improve breast cancer outcomes. Promisingly though, completion of GCT for breast cancer was associated with increased survival. These findings underscore the need to pair resource-adapted guidelines with locally relevant implementation strategies that can equip complex and often strained health systems to administer and patients to receive high quality, multimodality breast cancer care.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JM, SE, LS and TT. The first draft of the manuscript was written by JM and all authors reviewed and approved the manuscript.

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Data availability
The dataset generated during and analyzed during the current study are not publicly available to maintain patient confidentiality but deidentified data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board at UNC and the Malawi National Health Science Research Committee in compliance with the Declaration of Helsinki. All patients provided written informed consent at the time of enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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