

Survival Outcomes of Breast Cancer in Sudanese Women: A Hospital-Based Study

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PURPOSE Breast cancer (BC) is the leading malignancy among Sudanese women. Yet, data on survival are limited. This study aimed to determine 5-year overall survival (OS) of BC in Sudanese women, and identify prognostic demographic and clinicopathologic factors.

PATIENTS AND METHODS A hospital-based retrospective study was conducted by reviewing data of women with BC diagnosed and treated at the National Cancer Institute—University of Gezira during 2012, and followed up to end of August 2018. Data were retrieved from medical records and analyzed, OS was determined, and the prognostic factors were explored.

RESULTS A total of 225 cases were recruited. The median age at presentation was 45 years (range, 22–85 years). Clinical stage I, II, III, and IV represented 3.1%, 31.6%, 48%, and 17.3%, respectively. Most women (81.3%) were treated with curative intent. Of those, 25.1% received neoadjuvant chemotherapy. Mastectomy was the commonest (61.7%) type of surgery. The median follow-up period was 59.8 months with mean OS time of 55.7 months. The 5-year cumulative survival rate was 58%. The 5-year OS rates for stages I, II, III, and IV were 71.5%, 82.4%, 56.5%, and 8.4%, respectively. For lymph node (LN)-positive cases, 5-year OS rate was 63% and for LN-negative was 83.5%. Presenting with advanced-stage disease and positive LN status associated with short OS times ($P < .005$).

CONCLUSION OS of women with BC in Central Sudan is worse than in the developed world, but similar to African countries. Our findings indicate that advanced stage at diagnosis and lymph nodal involvement are strong predictors of short survival times. Raising awareness and introducing early detection programs are critical for better survival of these patients.

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INTRODUCTION

Breast cancer (BC) has the highest incidence and mortality rates of all malignancies in women worldwide. The global BC burden is estimated to have risen to 2.1 million new cases and 627 thousand deaths in the year 2018, representing one in four of all new cancer cases and 15% of cancer deaths among women.¹

In Africa, BC incidence continues to increase in all parts of the continent reaching nearly 169 thousand in 2018, and it has been estimated by GLOBOCAN that by the year 2040, the number of incident cases might almost double from present estimates.² The rise of BC incidence in Africa could be attributed to many reasons, including population growth and aging, socio-economic changes, along with adoption of Western lifestyle imparting reproductive, hormonal, and dietary risk factors.^{1,3} BC mortality rate is much greater among

sub-Saharan African women in comparison to women in Western countries, despite that the incidence is much higher in Western women.^{4,5}

In Sudan, there is no national population-based cancer registry, so cancer estimates are generally based on hospital case series. Data from the Cancer Registry for Khartoum State for the period 2009–2010 reported BC to be the most common cancer among Sudanese women.⁶ Statistics from the National Cancer Institute—University of Gezira (NCI–UG) showed that incidence of BC accounts for 34% of cancer among female patients in 2017.⁷ Studies on clinicopathologic features of BC in Sudan revealed that Sudanese women, as elsewhere in sub-Saharan African countries, are diagnosed at younger age, advanced stage, with higher tumor grade, and extensive lymph node (LN) involvement compared with women in developed countries.^{8–10}

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CONTEXT

Key Objective

Data on outcomes of breast cancer (BC) in Sudan are limited. We analyzed survival of Sudanese women with BC, defined prognostic factors, and described treatment patterns.

Knowledge Generated

This study reveals that overall survival rate in Sudanese women with BC—similar to those of African countries—is poor compared with the developed world. Our data highlight that advanced stage at diagnosis is a strong predictor of short overall survival times, and suggest the possibility that these results may be affected by delayed presentation.

Relevance

In-depth research to uncover the factors contributing to our findings is necessary. Increasing public enlightenment of BC and emphasizing early detection are needed to improve survival of women with BC in Sudan.

BC survival rates in developing countries tend to be much lower than in developed countries.^{11–14} Survival rates of BC have increased notably all over the world in the past decades.^{11,12,14} The improvement in survival in developed countries was mainly attributed to advances in treatment modalities, as well as earlier detection as a result of raised awareness and widespread use of mammography screening programs.^{15,16} The clinical outcomes and survival of patients with BC is determined by several elements including demographic characteristics,^{17–20} socioeconomic characteristics^{21–24} of the patient, clinicopathologic features of the tumor,^{25,26} and factors relating to treatment.^{27–29}

Many studies on BC in Sudan were centered on describing the clinicopathologic characteristics of the disease.^{8–10} However, published data on survival of Sudanese women with BC are scarce.³⁰ Therefore, the current study was conducted to assess the 5-year survival of Sudanese women with BC treated at the NCI–UG, Sudan.

PATIENTS AND METHODS

Setting

This study was conducted at NCI–UG, located in Wad Medani, Gezira state in Central Sudan, at a distance of about 200 km southeast of Khartoum, the capital of the country. The Department of Oncology at NCI–UG is one of the two national referral cancer centers in Sudan to which patients with cancer are referred for assessment and further management. It serves about five million inhabitants of Gezira state, in addition to receiving referral patients from all over the country, but mainly from neighboring states within the central region. The cancer treatment modalities available at NCI–UG include radiotherapy (two cobalt-60 machines), chemotherapy, hormonal therapy, and palliative care. All patients with BC are reviewed at our weekly BC multidisciplinary team meeting at the NCI–UG in collaboration with surgery department, Wad Medani Teaching Hospital, and a clear road map of treatment is made for each patient. Adjuvant therapy depends on the stage, as per our local guidelines.³¹

Study Design

We performed a hospital-based retrospective study to assess the 5-year survival of Sudanese women with BC treated at NCI–UG, Sudan, between January and December 2012. Cases were required to have histologically confirmed BC, and have received at least one treatment modality at NCI–UG for inclusion in the study; cases with a second primary or with incomplete clinicopathologic data were excluded. Demographic, clinical, and pathologic data were retrieved by reviewing medical files of patients. For survival data, the follow-up of patients was completed by the end of August 2018.

Data Collection and Follow-Up

All patients with BC who had been treated at the NCI–UG during the study period were identified. A structured form was used to collect data from patients' medical files. These data included patient characteristics (eg, age at diagnosis, marital status, parity, menopausal status, and family history of malignancy); clinical data (presenting complaints, stage at diagnosis according to the American Joint Committee on Cancer (AJCC) 2009 system, involved breast, and background medical history); pathologic features (histopathologic subtype and grade); molecular biomarkers (expression of estrogen receptor [ER] and progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2] status); types of treatment; and survival data (date of diagnosis, date of last follow-up, or date of death). Survival data for patients who missed their scheduled appointment were obtained by telephone. Women were classified as postmenopausal if they were of age 60 years or older, or age < 60 years and being amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, or ovarian suppression.

Statistical Analysis

All analyses were performed with the Statistical Package for Social Sciences software, version 25 (SPSS Inc., Chicago, IL). Demographic, clinicopathologic, and received treatment modalities data were described using descriptive

statistics; continuous variables were summarized using median and range, whereas data were summarized as frequency and percentage for categorical variables. The overall survival (OS) was calculated in months from date of diagnosis to the date of death or censoring at last date that the patient was known to be alive. For all cases, the date of issuing the histopathologic or cytologic report was considered as the date of diagnosis. Kaplan-Meier method was used to estimate the 5-year survival rate. We used the logrank test to compare differences in survival curves. Two-tailed *P* value of $< .05$ was considered statistically significant in all analyses.

Ethical Considerations

Ethical approval was obtained from the Ethics Committee, Faculty of Medicine, University of Gezira.

RESULTS

Out of 1,407 patients with cancer diagnosed between January and December 2012 and received treatment at the NCI-UG, 240 (17%) were women with BC. Two hundred twenty-five women with BC met the criteria for inclusion in this study and 15 cases were excluded. The reasons for exclusion were not received any treatment modality at

NCI-UG ($n = 11$), having a second malignancy ($n = 1$), and missing diagnosis date ($n = 3$).

Characteristics of Patients

The median age at diagnosis was 45 years (range, 22-85 years). The largest number of cases (77, 34.2%) was 41-50 years of age. The median age at menarche was 14 years (range, 9-20 years). The majority of women were married, multiparous, housewives (171, 76%), and residents of rural areas. Moreover, approximately one third of cases were illiterate. Nearly half of the patients were premenopausal. The descriptive characteristics of patients are shown in [Table 1](#).

Clinicopathologic Features

The median duration between recognition of symptoms and presentation was 6 months (range, 1-72 months). Most of the women (96.9%) presented with breast lump, whereas the remaining (3.1%) presented with metastatic disease-related complaints. Of the whole group, 26.7% women presented with abnormal overlying skin, and 7.1% women presented with fungating breast. Axillary LNs were palpable in 42.2% of patients. The median tumor size at presentation was 6 cm (range, 1-12 cm). Right breast was involved in 49.8%, whereas 48.4% presented with left breast and 1.8% women had bilateral BC.

The majority of patients (65.3%) were diagnosed with late-stage disease (stage III and IV), mainly (48%) with stage III ([Table 2](#)). Among 39 patients with stage IV disease, 25 patients had single-site metastases and 14 had multiple-site metastases. The most common sites of distant metastases were bone ($n = 20$), closely followed by liver ($n = 18$) and lung ($n = 15$).

The majority (94%) of tumors were invasive ductal carcinoma and most of the tumors were moderately differentiated (53.9%). Among 189 women (84%) for whom immunohistochemistry (IHC) were available, 94 (49.7%) patients had positive hormone receptor (ER- and/or PR-positive), whereas 95 (50.3%) had negative hormone receptor tumors (ER- and PR-negative), as shown in [Table 2](#). Only a small number of patients (20.4%) were tested for HER2 status.

Treatment Modalities

Among 183 women who underwent breast surgery, modified radical mastectomy and breast-conserving surgery were performed in 61.7% and 38.3%, respectively. Forty-six (25.1%) cases underwent surgery after receiving neoadjuvant chemotherapy. Adjuvant therapy depends on the disease stage. Patients for whom an operation was not possible because of advanced metastatic disease received palliative treatment (42 patients; 18.7%). Among all women, 70.7% received radiotherapy, and hormonal therapy (tamoxifen or aromatase inhibitors) was prescribed to 41.8% of patients. [Figure 1](#) displays a chart summarizing

TABLE 1. Descriptive Characteristics of Patients (N = 225)

Characteristic	Number	%
Age at diagnosis, years		
< 40	53	23.6
≥ 40	172	76.4
Education (n = 221)		
Illiterate	70	31.7
Primary	65	29.4
Secondary	57	25.8
University	29	13.1
Residence		
Urban	97	43.1
Rural	128	56.9
Marital status		
Single	29	12.9
Married	144	64.0
Divorced	18	8.0
Widow	34	15.1
Parity (n = 218)		
Nulliparous	57	26.1
Primiparous	18	8.3
Multiparous	143	65.6
Menopausal status (n = 215)		
Premenopausal	101	47.0
Postmenopausal	114	53.0

NOTE. Total number of patients = 225.

TABLE 2. Clinicopathologic Features of Breast Cancer (N = 225)

Characteristic	Number	%
Clinical disease stage		
Stage I	7	3.1
Stage II	71	31.6
Stage III	108	48.0
Stage IV	39	17.3
Tumor status (n = 223)		
T1	21	9.4
T2	76	34.1
T3	41	18.4
T4	85	38.1
Nodal status (n = 168)		
N0	58	34.5
N1	59	35.1
N2	27	16.1
N3	24	14.3
Metastasis status		
M0	186	82.7
M1	39	17.3
Histopathologic type		
Ductal carcinoma in situ	2	0.9
IDC	196	87.1
ILC	7	3.1
Others	20	8.9
Tumor grade (n = 206)		
G1 (well differentiated)	10	4.9
G2 (moderately differentiated)	111	53.9
G3 (poorly differentiated)	85	41.2
Hormone receptor expression (n = 189)		
ER+/PR+	79	41.8
ER+/PR-	13	6.9
ER-/PR+	2	1.0
ER-/PR-	95	50.3

NOTE. Total number of patients = 225.

Abbreviations: ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; N, lymph node; PR, progesterone receptor; T, tumor size.

the treatment modalities used in management of patients with BC.

Survival Analysis

With a median follow-up period of 59.8 months, there were 107 (47.6%) women alive, 92 (40.9%) women died, and 26 (11.6%) were lost to follow-up. For those who were alive at last follow-up, there were 87.9% (94/107) women free of disease and 12.1% (13/107) women with disease progression.

The 5-year OS was 58% (Fig 2A). In univariate analysis, demographic, clinical, and pathologic factors were

included (Table 3). Only the clinical disease stage and LN involvement were significantly associated with OS, where 5-year OS rates for stage I, II, III and IV were 71.5%, 82.4%, 56.5%, and 8.4%, respectively (Fig 2B). Concerning the lymph nodal status, 5-year OS rates for patients with node-negative cancers and node-positive cancers were 83.5% and 63%, respectively (Fig 2C).

DISCUSSION

Little is known about the survival outcomes of BC in Sudan.³⁰ A previous study was limited by a small sample size and short follow-up time, thus we designed our present study to assess OS and related prognostic factors of BC in a case series of 225 Sudanese women diagnosed during the year 2012.

In this study, we demonstrated 5-year OS rate of 58%, a little higher than that reported in Uganda (51.8%), Ghana (47.9%), Indonesia (51.1%), and Malaysia (49%),³²⁻³⁵ and less than that reported from Eastern Mediterranean region (69.2%), India (78%), Vietnam (80.6%), and Brazil (87%).³⁶⁻³⁹ Yet, this rate was much lower than survival rates in more developed countries such as the United States (91%), Canada (88%), Australia (88.3%), Japan (85.5%), and Western European countries—which generally exceed the limit of 85%.^{14,16,40} The low OS rate observed in African women could be because of late presentation and aggressive nature of BC, together with lack of screening programs and limited access to healthcare services.^{4,41}

Our findings showed that approximately two thirds of patients presented with advanced disease (stage III and IV), most commonly with stage III (48%). This is similar to previously reported findings from Sudan,⁸⁻¹⁰ Africa,⁴²⁻⁴⁷ and Arab countries^{48,49}; however, this is different from Western countries, where most of the women present with early stage.^{8,42,50} Late presentation of patients with advanced clinical disease stage—when the prognosis is poor—could be attributed to several factors including cultural issues, low socioeconomic status, little breast health awareness, and delay in seeking medical advice, besides lack of screening and early detection programs.^{4,41} We revealed that the 5-year OS rate was associated with the disease stage at diagnosis in a general trend of an inverse relationship. The negative association between the clinical stage and survival rates was largely documented by many authors.^{34,39,44,47,49,51} Our findings regarding 5-year OS rates per stage were to some extent comparable to data from developing countries,^{34,49} but poorer than that from developed countries.^{13,14,16} Interestingly, in our study, women with stage I had poorer survival compared to those with stage II, taking into account the small number—only seven patients—of cases diagnosed with stage I in the current study. The worse survival recorded for stage I can be explained by the fact that in this subgroup of patients, two deaths occurred; of them, one woman was an elderly

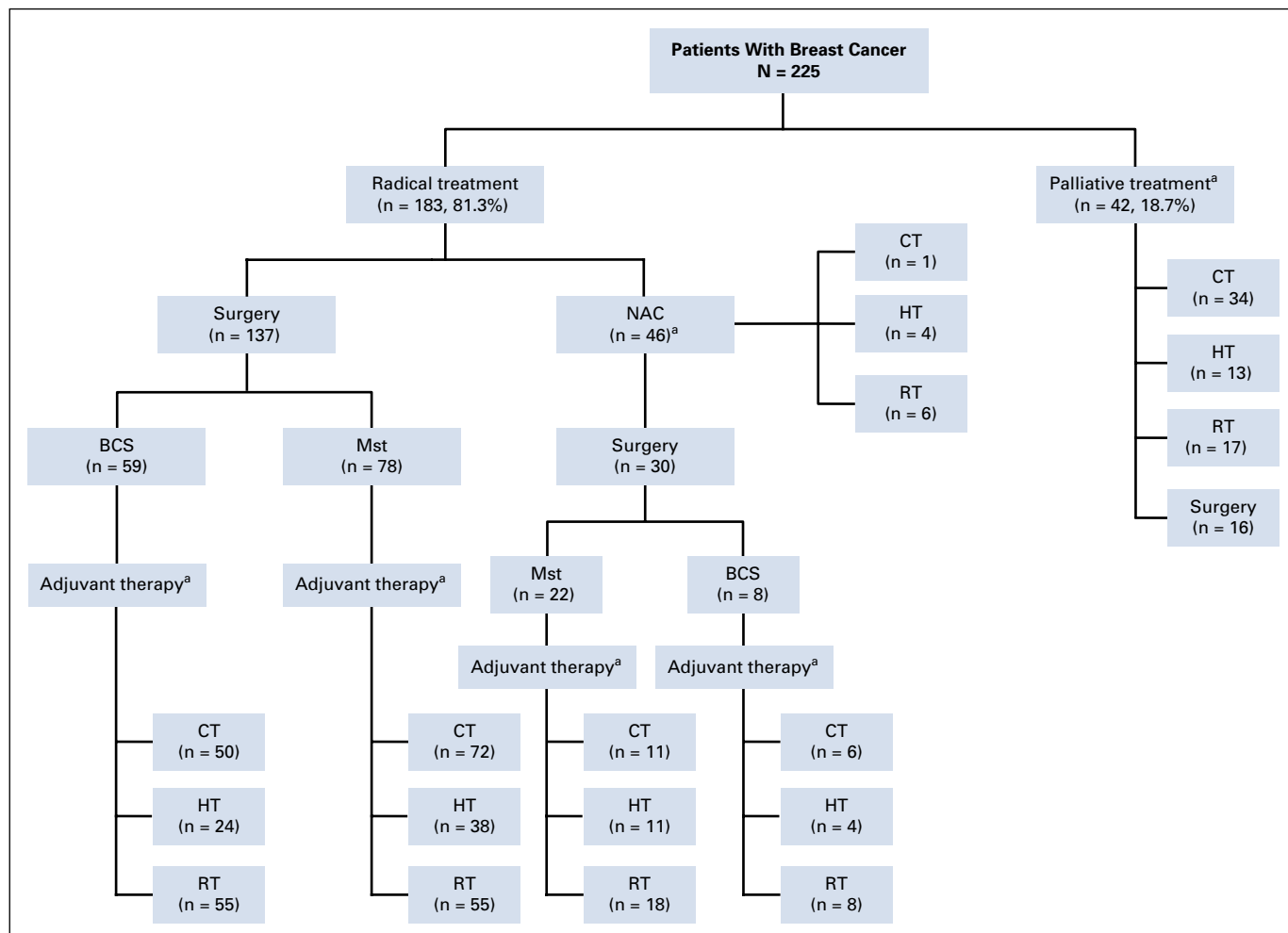


FIG 1. Treatment modalities used in the management of patients with breast cancer. BCS, breast conserving surgery; CT, chemotherapy; HT, hormonal therapy; Mst, mastectomy; n, number of patients; NAC, neoadjuvant chemotherapy; RT, radiotherapy. ^aPatients might have received more than one treatment modality.

with other comorbidities and the other patient was lost to follow-up and came after the disease had relapsed.

We found that about two thirds of patients had LN involvement at the time of diagnosis, and the higher proportion of LN positivity was frequently observed in African populations.^{34,42,44,52} Approximately one fifth of patients (39, 17.3%) presented with distant metastasis. The high representation of LN involvement and distant metastasis could be explained by the late presentation of most patients when the disease is already in advanced stages. We demonstrated that women with negative LN status had better OS than women with positive LN status. A statistically significant association was found between 5-year OS rate and LN involvement, similar to many studies.^{34,38,44,51,53}

The median age at presentation was 45 years, in agreement with researchers from other African countries^{5,34,42,44,47} and developing countries^{32,38,49} but considerably lower than that reported from Western countries,^{4,54} where the median age was being in the sixth decade. This variation could be attributed in part to ethnicity and genetic background.⁵⁵ It is

noteworthy that younger population age distribution in the developing countries compared with the developed ones contributes largely to the younger age at presentation of patients with BC. A link has been demonstrated between OS and age at presentation in several studies.^{32,35,44,51} However, data on the association of patient age with BC outcome are controversial on whether age is independent of biologic and clinicopathologic factors.

We showed that premenopausal women comprised nearly half of the patients; this agrees with some studies,^{53,56} although many authors showed predominance of premenopausal status among African women.^{42-44,47} Postmenopausal patients were shown to have better survival than premenopausal patients⁴⁷; by contrast, our data indicate that premenopausal women had better survival compared with postmenopausal ones.

Our results revealed that most of the tumors had high histologic grade (G2 and G3), similar to findings reported from other African countries.^{34,42,44,52} Many authors have documented the relation of OS and histologic grade of

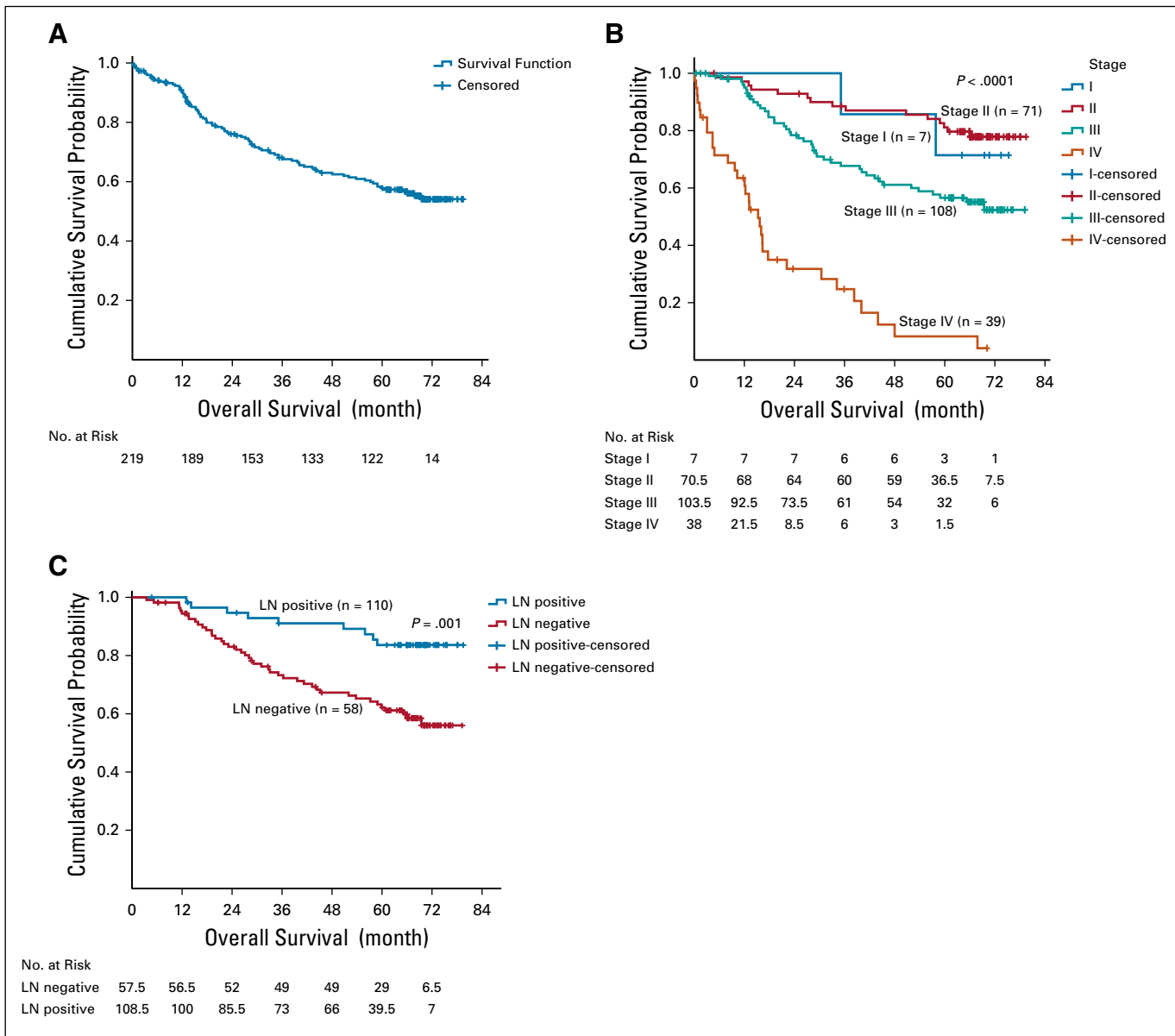


FIG 2. Overall survival (OS) of patients with breast cancer (N = 225). (A) Cumulative survival curve. (B) OS according to clinical stage (N = 225). (C) OS according to lymph node involvement (n = 186).

tumor.^{39,44,51,56} In this study, there was an obvious trend toward better survival for patients with well-differentiated tumors.

It has been described that African women with BC have hormone receptor–negative tumors.⁵⁷ Remarkably, a considerable proportion of hormone receptor–positive tumors were reported in our current study, with almost half of the patients having hormone receptor status data available. Our findings are in line with a study from India,³⁸ although greater than the rates demonstrated by other authors in African women.^{34,46} Assessment of hormone receptor (HR) status reflects on the prognosis and choice of therapy and hormonal manipulation of BC. Our data showed a better

survival in women with HR-positive tumors, although a statistical significance was not reached. Associations between 5-year OS rate and expression of hormone receptors were reported previously.^{39,51}

In the present study, HER2 status was not tested in the majority (80%) of patients. Despite the fact that HER2 is a well-known predictor of response to HER2-targeted therapy and prognostic marker of outcome in patients with BC,⁵⁸ we were not able to explore such associations because of the limitation of poor IHC reporting and the small number of patients tested for HER2 status. During the study period, HER2 testing by IHC was only available in few private laboratories in Khartoum, the capital of Sudan, with high

TABLE 3. Univariate Analysis of Prognostic Factors of 5-Year OS

Variable	Total No. of Cases	No. of Events	5-Year OS	Logrank
Age at diagnosis, years				<i>P</i> = .314
< 40	53	19	65.0%	
≥ 40	172	73	56.5%	
Marital status				<i>P</i> = .921
Single	29	12	63.0%	
Married	144	56	59.0%	
Divorced	18	8	53.0%	
Widow	34	16	51.5%	
Residence				<i>P</i> = .188
Urban	97	35	62.5%	
Rural	128	57	54.0%	
Parity (n = 218)				<i>P</i> = .541
Nulliparous	57	20	65.0%	
Primiparous	18	6	64.0%	
Multiparous	143	62	54.8%	
Menopausal status (n = 215)				<i>P</i> = .344
Premenopausal	101	39	62.0%	
Postmenopausal	114	50	53.0%	
Clinical disease stage				<i>P</i> < .0001
Stage I	7	2	71.5%	
Stage II	71	15	82.4%	
Stage III	108	43	56.5%	
Stage IV	39	32	8.4%	
LN involvement (n = 168)				<i>P</i> = .001
Negative	58	9	83.5%	
Positive	110	43	63.0%	
Tumor grade (n = 206)				<i>P</i> = .230
G1	10	1	89.0%	
G2	111	47	57.0%	
G3	85	31	62.8%	
Hormone receptor expression (n = 189)				<i>P</i> = .604
Positive	94	34	65.0%	
Negative	95	35	61.0%	

NOTE. Total number of patients = 225.

Abbreviations: LN, lymph node; OS, overall survival.

cost. Moreover, HER2-targeted therapy (trastuzumab) was prohibitive and not accessible to the majority of Sudanese women with BC. In this case series, HER2-positive (3 + score) patients with BC did not receive HER2-targeted therapy. To date, HER2 investigation by fluorescence in situ hybridization—for testing the amplification of *HER2* gene—is not available in Sudan. Therefore, all HER2 equivocal by IHC (2 + score) is considered negative and goes untreated.

Treatment based on multimodality approach is practiced in our institution depending on the patient's age and general health status, clinical disease stage, and

pathologic and biologic characteristics of the tumor, in addition to factors such as the preference of the patient. Concerning surgical management, which was part of the treatment modalities in a total of 183 women of the whole cohort, the majority of patients underwent mastectomy. This is comparable to findings from Oman,⁴⁹ but greatly different from that described in Tanzania where mastectomy was the only type of surgery provided.⁴⁴ Advanced stages at presentation might explain the predominance of mastectomy as the most practiced form of surgical management.

The limitations of this study were the retrospective nature and thus the reliance on existing data in the medical files, emphasizing a need to empower a good system of data documentation in hospital records. In addition to that, survival of patients with BC estimated from institutional case series indicates experiences in specific settings that cannot be generalized to the total population. However, since NCI–UG is one of only two referral centers in Sudan, our findings could give an insight into BC outcomes in the whole country.

In conclusion, Sudanese female patients with BC presented at a young age, with advanced disease. The 5-year OS rate of Sudanese women with BC was worse than in their counterparts in the developed world, but relatively similar to findings from developing countries in the neighboring regions. Clinical disease stage and lymph nodal involvement were significant predictors of OS. Our findings necessitate serious strategies to promote BC awareness and encourage breast self-examination among Sudanese women, as well as to introduce early detection programs of the disease that can enable early interventions.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No potential conflicts of interest were reported.

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