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Global Health and Cancer

Neoadjuvant Chemotherapy Use for Nonmetastatic Breast Cancer at Five Public South African Hospitals and Impact on Time to Initial Cancer Therapy

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast cancer • Neoadjuvant chemotherapy • Practice patterns • South Africa

Abstract

Background. In the U.S., neoadjuvant chemotherapy (NAC) for nonmetastatic breast cancer (BC) is used with extensive disease and aggressive molecular subtypes. Little is known about the influence of demographic characteristics, clinical factors, and resource constraints on NAC use in Africa.

Materials and Methods. We studied NAC use in a cohort of women with stage I–III BC enrolled in the South African Breast Cancer and HIV Outcomes study at five hospitals. We analyzed associations between NAC receipt and sociodemographic and clinical factors, and we developed Cox regression models for predictors of time to first treatment with NAC versus surgery.

Results. Of 810 patients, 505 (62.3%) received NAC. Multivariate analysis found associations between NAC use and black race (odds ratio [OR] 0.49; 95% confidence limit [CI], 0.25–0.96), younger age (OR 0.95; 95% CI, 0.92–0.97 for each year), T-stage (T4 versus T1: OR 136.29; 95% CI, 41.80–444.44), N-stage (N2 versus N0: OR 35.64; 95% CI, 16.56–76.73), and subtype (triple-negative versus luminal A: OR 5.16; 95% CI, 1.88–14.12). Sites differed in NAC use (Site D versus Site A: OR 5.73; 95% CI, 2.72–12.08; Site B versus Site A: OR 0.37; 95% CI, 0.16–0.86) and time to first treatment: Site A, 50 days to NAC versus 30 days to primary surgery (hazard ratio [HR] 1.84; 95% CI, 1.25–2.71); Site D, 101 days to NAC versus 126 days to primary surgery (HR 0.49; 95% CI, 0.27–0.89).

Conclusion. NAC use for BC at these South African hospitals was associated with both tumor characteristics and heterogenous resource constraints. ***The Oncologist*** 2019;24:933–944

Implications for Practice: Using data from a large breast cancer cohort treated in South Africa's public healthcare system, the authors looked at determinants of neoadjuvant chemotherapy use and time to initiate treatment. It was found that neoadjuvant chemotherapy was associated with increasing tumor burden and aggressive molecular subtypes, demonstrating clinically appropriate care in a lower resource setting. Results of this study also showed that time to treatment differences between chemotherapy and surgery varied by hospital, suggesting that differences in resource limitations were influencing clinical decision making. Practice guidelines and care quality metrics designed for low- and middle-income countries should accommodate heterogeneity of available resources.

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Introduction

For patients with early or locally advanced breast cancer, multiple randomized trials have shown that the choice of neoadjuvant versus adjuvant delivery of chemotherapy does not impact survival [1]. The decision to use neoadjuvant chemotherapy (NAC) is, therefore, based on practical considerations. It is indicated in patients with inoperable tumors, with the goal of reducing tumor volume to allow surgery, or for women with large resectable tumors who desire breast conserving surgery [2, 3]. NAC use also offers prognostic information; complete pathologic tumor response is a strong predictor of improved overall survival, especially in patients with estrogen and progesterone receptor negative subtypes [4].

Breast cancer incidence has been steadily increasing in low- and middle-income countries (LMICs) since the 1990s [5]. Although age-standardized incidence rates are lower in sub-Saharan Africa (SSA) than in high-income countries (HICs), age-standardized mortality is actually greater (17.2 vs. 14.9 deaths per 100,000 population) [6]. In South Africa, the 5-year overall survival of women diagnosed with breast cancer was estimated at 40%, as compared with over 85% in HICs [7]. The difference is partially explained by the different proportions of women who have advanced disease at diagnosis [8]. For instance, 48% of women diagnosed with nonmetastatic breast cancer at a large public hospital in Soweto, Johannesburg, South Africa from 2006 to 2012 had stage III disease [9]. Given the frequency of locally advanced disease, many patients in SSA are appropriate candidates for NAC [10]. In a cohort of Johannesburg patients with nonmetastatic disease, 35.2% received NAC [11].

In North America, use of NAC is strongly associated with tumor characteristics. Retrospective studies from the U.S. and Canada have consistently shown greater use with increasing T- and N-stage, aggressive molecular subtypes, and younger patients [12–14]. Those studies also found wide variation in NAC use across different institutions and regions [12, 14]. For patients in the National Cancer Database treated in 2010 and 2011, NAC use was also more common in non-Hispanic black and Hispanic patients than in white patients, even after adjusting for tumor stage and biology [15].

In SSA, clinical decisions may be affected by resource constraints (e.g., prolonged wait times or limited supply of standard therapies, doctors, and nurses). Detailed descriptions of treatment patterns are lacking. We analyzed clinical and sociodemographic factors potentially associated with receiving NAC among patients from a previously existing cohort: women enrolled in the South African Breast Cancer and HIV Outcomes (SABCHO) study [16]. In addition, we analyzed time to first therapy for NAC versus primary surgery and factors associated with early treatment.

Materials and Methods

Context and Setting

South Africa is an upper middle-income country with SSA's third highest per capita gross domestic product [17]. However, income inequality, as measured by the Gini index, is the second highest globally. Average household income for whites is six times that of blacks [17, 18]. Despite its relative wealth, South Africa faces significant health challenges. It has the fourth highest adult prevalence of HIV infection in the world (18.9%), and its life expectancy at birth (63.8 years) is ranked 190 of 224 countries [17]. Its private and public healthcare systems are inequitably resourced. In 2005, per capita annual expenditure for the 15% of the population exclusively served by the private system was $1,170, whereas that for the 64% who rely entirely on the public system was just $160 per capita [19]. The private system employs 79% of South African doctors [19].

The design and methods of the SABCHO study have been described previously [16]. A range of demographic, socioeconomic, and clinical data are being prospectively collected for 3,000 women recruited at diagnosis of breast cancer in five public hospitals in the South African provinces of Gauteng and KwaZulu-Natal. That study's primary aim is to assess the effects of HIV infection on breast cancer presentation, tumor biology, treatment responses, and survival. As detailed information on a breast cancer cohort of this size is rare in SSA, we used this existing cohort for our analysis.

The participating hospitals differ in their setting. Both Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital are urban quaternary care centers located in Johannesburg and affiliated with the University of Witwatersrand. CHBAH primarily serves the predominantly black population of the greater Soweto township area. Inkosi Albert Luthuli Central Hospital (IALCH) and Ngwelezana Hospital (NH) are both located in the province of KwaZulu-Natal: IALCH in Durban and NH near Empangeni. Although in different cities, they are both affiliated with the University of KwaZulu-Natal, share oncology clinicians and facilities, and were treated as one site for this analysis. Grey's Hospital is in Pietermaritzburg, a third city of KwaZulu-Natal, has its own oncology services, and serves the large surrounding rural area. Hospitals were anonymized for analysis.

Women with a new breast cancer diagnosis first see a surgeon. If their surgeon believes NAC is necessary, they are referred to a clinical oncologist, who is trained to administer medical and radiation therapies. The most commonly used chemotherapy regimens at our studies sites were combination doxorubicin/cyclophosphamide or 5-fluorouracil/epirubicin/cyclophosphamide, each with or without a taxane. Endocrine therapy is also available in the forms of tamoxifen and anastrozole. Trastuzumab is not routinely used at public hospitals. Patients receiving chemotherapy are typically prescribed ondansetron as needed for nausea and loperamide or diphenoxylate/atropine as needed for diarrhea. Granulocyte colony stimulating factor use is uncommon. Sliding scale fees based on an individuals' income are used at public facilities; many patients receive free care.

Study Design and Participants

We analyzed the prospectively collected data from participants enrolled in the SABCHO study; specifically, patients

diagnosed with breast cancer and enrolled between July 1, 2015 and July 1, 2017. Data were collected until April 1, 2018. Eligible patients were female, younger than 70 years, and diagnosed with American Joint Committee on Cancer, 7th edition, stage I, II, or III disease [20]. Eligible patients were also required to have disease appropriate for chemotherapy according to the European Society for Medical Oncology's practice guidelines for nonmetastatic breast cancer: either any stage of luminal B, HER2-enriched, or triple-negative breast cancer; or luminal A subtype presenting with T-stage ≥3, N-stage ≥2, or grade 3 histology [10].

Luminal A subtype was defined as estrogen receptor (ER) or progesterone receptor (PR) positive disease without human epidermal growth factor receptor 2 (HER2) overexpression and Ki-67 staining ≤15%. Patients with the luminal B subtype were ER or PR positive but did not meet criteria for luminal A disease or, in cases of missing Ki-67 staining, had grade 3 histology. HER2 enriched were ER/PR negative and HER2 overexpressing. Patients with triple-negative breast cancer (TNBC) were ER/PR negative and did not overexpress HER2. These subtype definitions are used by the clinicians at our study sites and were chosen for this study so as to best reflect the clinical information being used for decision making. Immunohistochemistry was performed by National Health and Laboratory Service of South Africa or by Lancet Laboratories, both of which are accredited by the South African National Accreditation System. The measures taken to ensure accurate immunohistochemical results have been previously described [21].

We excluded patients with unknown date of first treatment and, to reduce selection bias, patients who had received neither surgery nor chemotherapy by the time of analysis. Patients who had received breast surgery prior to presenting to a study site were excluded because decisions regarding their primary therapy had not been made at our study sites.

Variables

The dates of all biopsies, chemotherapy cycles, and surgeries were extracted to determine dates of diagnosis and order of chemotherapy and surgery receipt. Other extracted covariates included age at diagnosis, self-identified race, primary language, employment status, marital status, address, treating hospital, clinical TNM stage, histologic grade, estrogen and progesterone receptor status, HER2 expression status, HIV infection, and other noncommunicable comorbidities.

A survey of household wealth, including questions on water source, toilet facilities, and ownership of various amenities, was conducted with each participant at enrollment. Survey responses for all eligible patients underwent principal component analysis; patients were then ranked using the derived first principal component and separated into quintiles. This technique for creating a single measure to describe participants' wealth was adapted from the Demographic and Health Surveys Program's wealth index [22]. The longitude and latitude of each patient's address were determined using iTouchMap.com, and distance from the treating hospital was calculated using the Vincenty formula [23–25].

Time to first treatment (TTFT) was defined as the number of days from performance of the first biopsy confirming breast cancer to either the first dose of chemotherapy or the first definitive surgery.

All data were stored in an encrypted, web-based database specifically adapted for the SABCHO study from the existing electronic medical record system at participating sites.

Statistical Analysis

Eligible participants were categorized by whether they received chemotherapy prior to any definitive surgery, into a NAC group or a no NAC/primary surgery group. We calculated unadjusted odds ratios and 95% confidence limits to assess the statistical significance of simple associations between NAC receipt and the sociodemographic and clinical variables. To control for confounding relationships, we constructed logistic regression models for the entire cohort and for each hospital subgroup and computed adjusted odds ratios (OR) with 95% confidence limits (CI). Covariates in all models included NAC receipt and all other variables with a p value < .1 on unadjusted analysis of the full cohort or within any hospital subgroup.

The Kaplan-Meier technique and log-rank testing were used to measure differences in TTFT between the NAC and the surgery groups with each hospital subgroup [26]. Cox regression models for TTFT at each site were constructed including any available variable with a p value < .1 on bivariate log-rank testing.

All statistical analyses were conducted using SAS Studio, version 3.6 (SAS Institute Inc., Cary, NC), and time to event curves were produced using the R statistical package (Vienna, Austria).

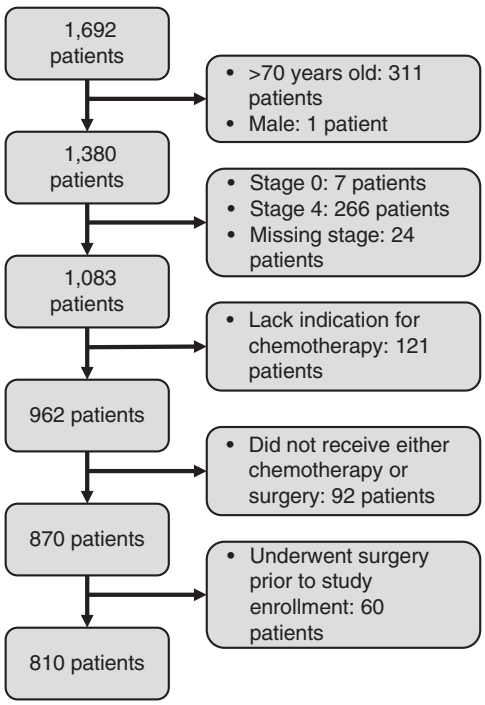

Figure 1. Patients eligible for analysis from those enrolled in the South African Breast Cancer and HIV Outcomes study between July 1, 2015, and July 1, 2017.

Table 1. Demographic and clinical characteristics of nonmetastatic patients age 70 years or younger and enrolled in the SABCHO study between July 1, 2015, and July 1, 2017, who received chemotherapy, breast surgery, or both

Characteristics	Site A *n* = 329 *n* (%)	Site B *n* = 105 *n* (%)	Site C *n* = 198 *n* (%)	Site D *n* = 178 *n* (%)	All patients *n* = 810 *n* (%)	*p* value[a]
Demographic						
Mean age (SD), yr	49.8 (10.6)	52.4 (11.5)	48.9 (10.5)	51.8 (10.7)	50.4 (10.8)	.009
Mean distance from hospital (SD), km	22.2 (35.2)	103.4 (83.2)	20.4 (14.2)	44.3 (60.6)	37.1 (54.6)	<.0001
Ethnicity						
Black	301 (91.5)	76 (72.4)	157 (79.3)	106 (59.6)	640 (79.0)	<.0001
Asian	1 (0.3)	17 (16.2)	3 (1.5)	56 (31.5)	77 (9.5)	
White	3 (0.9)	3 (2.9)	30 (15.2)	12 (6.7)	48 (5.9)	
Colored (mixed race)	24 (7.3)	9 (8.6)	8 (4.0)	4 (2.3)	45 (5.6)	
Household language						
Zulu	110 (33.4)	69 (65.7)	49 (24.8)	101 (56.7)	329 (40.6)	<.0001
English	9 (2.7)	26 (24.8)	22 (11.1)	69 (38.8)	126 (15.6)	
Sotho	91 (27.7)	3 (2.9)	27 (13.6)	0 (0.0)	121 (14.9)	
Tswana	40 (12.2)	1 (1.0)	18 (9.1)	0 (0.0)	59 (7.3)	
Afrikaans	18 (5.5)	3 (2.9)	23 (11.6)	4 (2.3)	48 (5.9)	
Xhosa	24 (7.3)	1 (1.0)	18 (9.1)	3 (1.7)	46 (5.7)	
Pedi	24 (7.3)	0 (0.0)	18 (9.1)	0 (0.0)	29 (3.6)	
Other	26 (7.9)	2 (1.9)	23 (11.6)	1 (0.6)	52 (6.4)	
Relationship status						
Married	108 (32.8)	40 (38.1)	79 (40.1)	64 (36.0)	291 (36.0)	.06
Never married	103 (31.3)	34 (32.4)	45 (22.8)	52 (29.2)	234 (28.9)	
Widowed	60 (18.2)	20 (19.1)	24 (12.2)	32 (18.0)	136 (16.8)	
Divorced	27 (8.2)	9 (8.6)	24 (12.2)	17 (9.6)	77 (9.5)	
In relationship (not married)	31 (9.4)	2 (1.9)	25 (12.7)	13 (7.3)	71 (8.8)	
Missing	0	0	1	0	1	
Employment						
Unemployed	166 (50.5)	62 (59.1)	75 (38.1)	112 (62.9)	415 (51.3)	<.0001
Employed (part or full time)	118 (35.9)	21 (20.0)	95 (48.2)	53 (29.8)	287 (35.5)	
Retired	45 (13.7)	22 (21.0)	26 (13.2)	12 (6.7)	105 (13.0)	
Student	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.3)	
Missing	0	0	1	0	1	
Household wealth percentile[b]						
≤20th	48 (14.6)	42 (40.0)	29 (14.7)	43 (24.2)	162 (20.0)	<.0001
21st–40th	78 (23.7)	19 (18.1)	31 (15.7)	34 (19.1)	162 (20.0)	
41st–60th	66 (20.1)	11 (10.5)	44 (22.3)	36 (20.2)	157 (19.4)	
61st–80th	59 (17.9)	16 (15.2)	32 (16.2)	33 (18.5)	140 (17.3)	
>80th	78 (23.7)	17 (16.2)	61 (31.0)	32 (18.0)	188 (23.2)	
Clinical						
Stage at diagnosis						
I	15 (4.6)	4 (3.8)	5 (2.5)	5 (2.8)	29 (3.6)	.07
II	129 (39.2)	28 (26.7)	57 (28.8)	45 (25.3)	259 (32.0)	
III	185 (56.2)	73 (69.5)	136 (68.7)	128 (71.9)	522 (64.4)	

(continued)

Table 1. (continued)

Characteristics	Site A *n* = 329 *n* (%)	Site B *n* = 105 *n* (%)	Site C *n* = 198 *n* (%)	Site D *n* = 178 *n* (%)	All patients *n* = 810 *n* (%)	*p* value[a]
T-stage						
0	3 (0.9)	1 (1.0)	3 (1.5)	2 (1.1)	9 (1.1)	<.0001
1	27 (8.2)	13 (12.8)	20 (10.1)	5 (2.8)	65 (8.1)	
2	153 (46.5)	38 (37.3)	82 (41.4)	49 (27.5)	322 (39.9)	
3	66 (20.1)	21 (20.6)	32 (16.2)	42 (23.6)	161 (20.0)	
4	80 (24.3)	29 (28.4)	61 (30.8)	80 (44.9)	322 (39.9)	
Missing	0	3	0	0	3	
N-stage						
0	104 (31.6)	17 (16.2)	60 (30.3)	33 (18.5)	214 (26.4)	<.0001
1	166 (50.5)	37 (35.2)	43 (21.7)	112 (62.9)	358 (44.2)	
2	48 (14.6)	37 (35.2)	81 (40.9)	22 (12.4)	188 (23.2)	
3	11 (3.3)	14 (13.3)	14 (7.1)	11 (6.2)	50 (6.2)	
Grade						
1	10 (3.1)	5 (5.2)	4 (2.1)	2 (1.4)	21 (2.8)	<.0001
2	142 (43.6)	41 (42.7)	59 (30.3)	85 (61.2)	327 (43.3)	
3	174 (53.4)	50 (52.1)	132 (67.7)	52 (37.4)	408 (54.0)	
Missing	3	9	3	39	54	
Receptor status						
ER and/or PR positive	256 (77.8)	76 (72.4)	152 (76.8)	127 (71.4)	611 (75.4)	.34
HER2 over expression	108 (32.8)	25 (23.8)	63 (31.8)	54 (30.3)	250 (30.9)	.36
Molecular subtype						
Luminal A	17 (5.2)	13 (12.4)	21 (10.6)	40 (21.7)	91 (11.2)	<.0001
Luminal B	239 (72.6)	63 (60.0)	131 (66.2)	93 (50.5)	526 (64.5)	
HER2 enriched	13 (4.0)	5 (4.8)	21 (10.6)	14 (7.9)	53 (6.5)	
TNBC	60 (18.2)	24 (22.9)	25 (12.6)	37 (20.8)	146 (18.0)	
Comorbidities[c]						
HIV positive	83 (25.2)	26 (24.8)	44 (22.2)	42 (23.6)	195 (24.1)	.98
Hypertension	105 (31.9)	44 (41.9)	52 (26.4)	60 (33.7)	261 (32.3)	.049
CAD/CHF	4 (1.2)	7 (6.7)	3 (1.5)	7 (3.9)	21 (2.6)	.003
Diabetes mellitus	27 (8.2)	16 (15.2)	8 (4.1)	30 (16.9)	81 (10.0)	<.0001
Stroke	6 (1.8)	1 (0.95)	1 (0.5)	2 (1.1)	10 (1.2)	.94
Asthma/COPD	12 (3.7)	8 (7.6)	12 (6.1)	13 (7.3)	45 (5.6)	.24

[a]Wilcoxon rank-sum test for continuous characteristics. Pearson's chi-squared test for categorical characteristics.
[b]Derived from the first principle from principal component analysis of a household wealth survey, as described in *Materials and Methods.*
[c]HIV screening performed in all reporting negative status. Other comorbidities self-reported.
Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SABCHO, South African Breast Cancer and HIV Outcomes; TNBC, triple-negative breast cancer.

Ethics

All participants provided informed consent for data collection and analysis. The SABCHO study and this project are overseen by the human research ethics committees of the University of Witwatersrand and the University of KwaZulu-Natal, both of South Africa, and the institutional review board of Columbia University of New York City.

Results

Between July 2015 and July 2017, 1,692 patients were enrolled in the SABCHO study. Of those, 810 were eligible for analysis: 329 (40.6%) from Site A, 105 (13.0%) from Site B, 198 (24.4%) from Site C, and 178 (22.0%) from Site D (Fig. 1). Their overall mean age was 50.4 years (range, 21.6–70.0; Table 1). Sites varied with respect to their mean distance from patients' homes: Site C patients were closest to the center (20.4 km, SD 14.2), whereas Site B patients were furthest (103.4 km, SD 83.2). Notable differences in the distribution of sociodemographic factors were also seen across sites (Table 1; Fig. 2). Clinical characteristics also varied across study sites. Site D reported 44.9% of tumors as T4 at presentation, compared with 24.3%, 28.4%, and 30.8% at Sites A, B, and C, respectively. Both

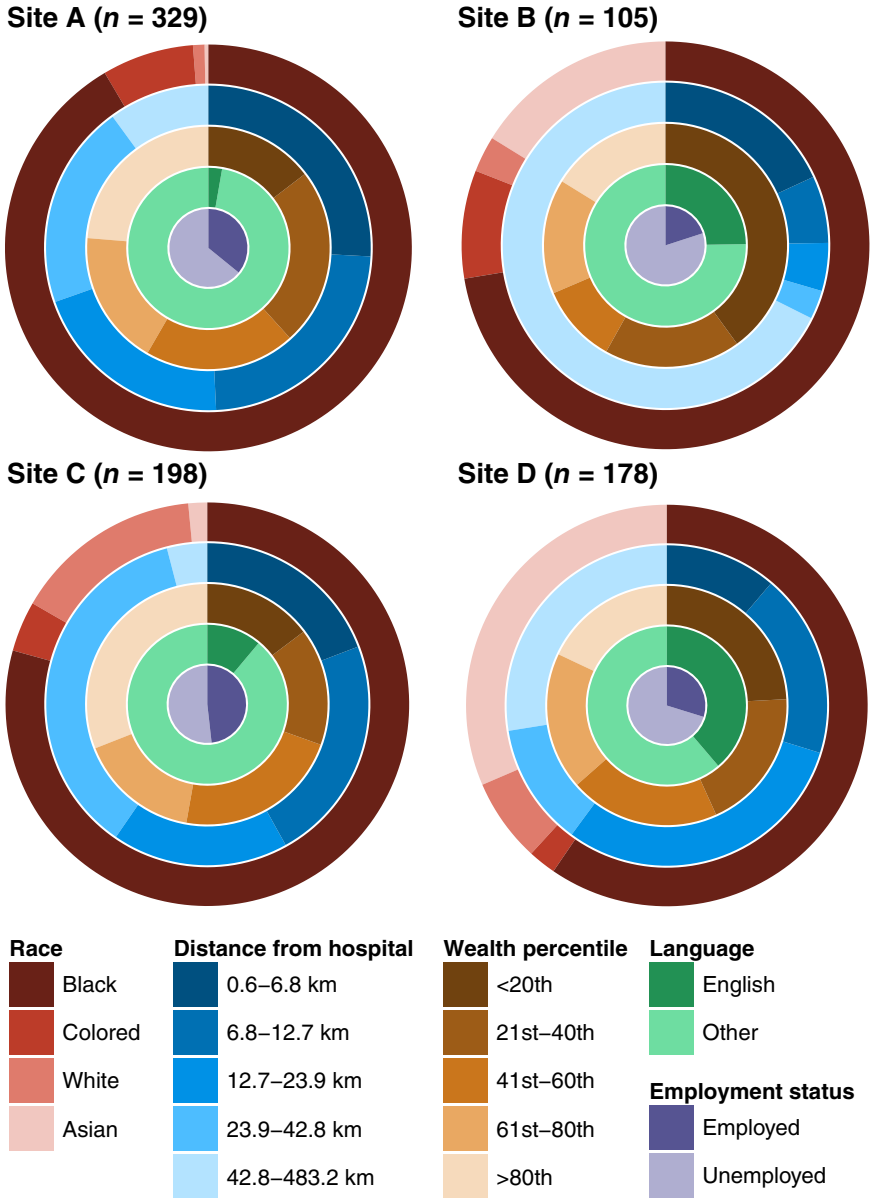

Figure 2. Distribution of self-reported race, distance from hospital quintiles, household wealth quintiles, primary language, and employment status at each study site. Patient assignment to quintiles for distance from the hospital and household wealth are based on the entire cohort of eligible study patients.

Site A and Site C had approximately 30% of women as N0, whereas Site B and Site D reported 16.2% and 18.5% as N0, respectively. Only 37.4% of tumors were considered grade 3 at Site D, compared with 58.7%, 52.1%, and 67.7% at Sites A, B, and C, respectively. Although hormone receptor positivity and HER2 overexpression were distributed similarly at all sites, more Site D patients had luminal A subtype and fewer had luminal B subtype (21.7% and 50.5%, respectively) than did Site A (5.2% and 72.6%), Site B (12.4% and 60.0%), or Site C (10.6% and 66.2%). HIV prevalence was 24% for the whole cohort and similar across sites.

Of the 810 patients, 505 (62.3%) received neoadjuvant chemotherapy. On bivariate analysis, the sociodemographic characteristics positively associated with NAC receipt were younger age (OR 0.97; 95% CI, 0.96–0.99) and low household wealth percentile (>80th percentile compared with ≤20th percentile; OR 0.54; 95% CI, 0.35–0.84; Table 2).

Clinical factors associated with NAC use on bivariate analysis included higher T-stage (T4 compared with T1: OR 126.46; 95% CI, 48.61–329.01), higher N-stage (N2 compared with N0: OR 17.99; 95% CI, 10.62–30.50), molecular subtype (luminal B compared with luminal A: OR 0.59; 95% CI, 0.37–0.95), HIV infection (OR 1.92; 95% CI, 1.35–2.74), and hypertension (OR 0.71; 95% CI, 0.54–0.95). Study site was also strongly correlated with NAC use. At our reference site, Site A, 51.4% received NAC, but at Site D, 83.7% of patients did (OR 4.86; 95% CI, 3.09–7.65), at Site C, 66.2% of patients did (OR 1.85; 95% CI, 1.28–2.67), and at Site B, 53.3% of patients did (OR 1.08; 95% CI, 0.70–1.68; Table 2).

On multivariate analysis of the entire cohort, the only demographic factors that remained associated with NAC use were younger age (OR 0.95; 95% CI, 0.92–0.97 for each

Table 2. Unadjusted odds ratios for neoadjuvant chemotherapy use by demographic and clinical factors

Characteristics	Neoadjuvant chemotherapy (*n* = 505), *n* (%)	No neoadjuvant chemotherapy (*n* = 305), *n* (%)	Odds ratio (95% CI)
Demographics			
Mean age (SD), yr	49.2 (10.7)	52.4 (10.7)	0.97 (0.96–0.99)[a]
Mean distance from hospital (SD), km	37.8 (56.0)	36.0 (52.2)	1.00 (0.998–1.003)
Ethnicity			
Black	403 (63.0)	237 (37.0)	1.13 (0.80–1.60)
Other	102 (60.0)	68 (40.0)	
Primary language			
English	83 (65.9)	43 (34.1)	1.12 (0.80–1.79)
Other	422 (61.7)	262 (38.3)	
Relationship status			
Partnered	219 (60.5)	142 (39.5)	0.87 (0.65–1.16)
Not partnered	285 (63.8)	162 (36.2)	
Employment status			
Employed	185 (64.0)	104 (36.0)	1.12 (0.83–1.51)
Unemployed	319 (61.4)	201 (38.7)	
Household wealth percentile			
≤20th	113 (69.8)	49 (30.2)	1 (Ref)
21st–40th	105 (64.8)	57 (35.2)	0.80 (0.50–1.27)
41st–60th	106 (67.5)	51 (32.5)	0.90 (0.56–1.45)
61th–80th	76 (54.3)	64 (45.7)	0.51 (0.32–0.83)[a]
>80th	104 (55.3)	84 (44.7)	0.54 (0.35–0.84)[a]
Clinical			
T-stage			
0	2 (22.2)	7 (77.8)	0.96 (0.18–5.15)
1	14 (21.5)	51 (78.5)	1 (Ref)
2	99 (30.8)	223 (69.3)	1.62 (0.86–3.06)
3	144 (89.4)	17 (10.6)	30.86 (14.20–67.05)[a]
4	243 (97.2)	7 (2.8)	126.46 (48.61–329.01)[a]
N-stage			
0	61 (28.5)	153 (71.5)	1 (Ref)
1	229 (64.0)	129 (36.0)	4.45 (3.09–6.43)[a]
2	165 (87.8)	23 (12.2)	17.99 (10.62–30.50)[a]
3	50 (100.0)	0 (0.0)	NC
Grade			
1	11 (52.4)	10 (47.6)	1 (Ref)
2	190 (58.1)	137 (41.9)	1.26 (0.52–3.05)
3	253 (62.0)	155 (38.0)	1.48 (0.62–3.58)
Molecular subtype			
Luminal A	62 (68.1)	29 (31.9)	1 (Ref)
Luminal B	294 (55.9)	232 (44.1)	0.59 (0.37–0.95)
HER2 enriched	41 (77.4)	12 (22.6)	1.60 (0.73–3.49)
TNBC	109 (74.7)	37 (25.3)	1.38 (0.77–2.45)
HIV status			
Positive	143 (73.3)	52 (26.7)	1.92 (1.35–2.74)[a]
Negative	362 (58.9)	253 (41.1)	

(continued)

Table 2. (continued)

Characteristics	Neoadjuvant chemotherapy (*n* = 505), *n* (%)	No neoadjuvant chemotherapy (*n* = 305), *n* (%)	Odds ratio (95% CI)
Other comorbidities			
Hypertension	150 (52.5)	136 (47.6)	0.71 (0.54–0.95)[a]
CAD/CHF	10 (40.0)	15 (60.0)	0.47 (0.21–1.06)
Diabetes mellitus	50 (54.4)	42 (45.7)	0.85 (0.55–1.31)
Stroke	8 (72.7)	3 (27.3)	1.94 (0.51–7.39)
Asthma/COPD	28 (59.6)	19 (40.4)	1.07 (0.59–1.95)
Hospital			
Site A	169 (51.4)	160 (48.6)	1 (Ref)
Site B	56 (53.3)	49 (46.7)	1.08 (0.70–1.68)
Site C	131 (66.2)	67 (33.8)	1.85 (1.28–2.67)[a]
Site D	149 (83.7)	29 (16.3)	4.86 (3.09–7.65)[a]

[a]Significant at $p < 0.05$

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence limit; COPD, chronic obstructive pulmonary disease; HER2, human epidermal growth factor receptor 2; NC, not calculable; TNBC, triple-negative breast cancer.

year) and black race (OR 0.49; 95% CI, 0.25–0.96; Table 3). Also associated with NAC use were T-stage (T4 versus T1: OR 136.29; 95% CI, 41.80–444.44), N-stage (N2 compared with N0: OR 35.64; 95% CI, 16.56–76.73), and molecular subtype (TNBC compared with luminal A: OR 5.16; 95% CI, 1.88–14.12). The difference in NAC use between Site D and Site A remained (OR 5.73; 95% CI, 2.72–12.08); a difference between Site B and Site A emerged (OR 0.37; 95% CI, 0.16–0.86). No significant difference remained between Site C and Site A (Table 3).

Multivariate analysis within each hospital subgroup found significant associations with younger age, T-stage, and N-stage at Site A; T-stage and subtype at Site B; T-stage, N-stage, and molecular subtype at Site C; and younger age, T-stage, and subtype at Site D (Table 3).

Time from biopsy and diagnosis to first treatment varied by both treatment and study site. At Site A, the median time to initiation of NAC was 50 days and that to receive primary surgery was 30 days (hazard ratio [HR] 1.84; 95% CI, 1.25–2.71; Fig. 3A). At Site B, the median times were 62 days for NAC and 83.5 days for surgery (HR 0.58; 95% CI, 0.25–1.35; Fig. 3B). At Site C, median times were 49 days for NAC and 43 days for surgery (HR 1.22; 95% CI, 0.77–1.95), and at Site D, median times were 101 days for NAC and 126 days for surgery (HR 0.49; 95% CI, 0.27–0.89; Fig. 3C, 3D). Because many patients treated at Site B or Site D had previously had a biopsy and diagnosis at a local clinic, we also assessed time from first clinic presentation to first treatment for these two sites as sensitivity analyses. The pattern of findings was unchanged.

Discussion

The purpose of our analysis was to explore primary treatment decision making for patients with breast cancer within South Africa's public healthcare system. In our cohort, clinical aspects, including increasing T-stage, increasing N-stage, and more aggressive molecular subtypes (i.e., HER2 enriched and TNBC), were strong predictors of NAC receipt. Patients with breast cancer in SSA have much later stage disease at presentation than women in the U.S. [27]. Given that a primary benefit of NAC is allowing patients with large breast tumors to receive less extensive surgery, the frequency of NAC for women with high volume or aggressive disease is appropriate and similar to the pattern of use seen in the U.S., although a smaller proportion of U.S. women receive NAC (15%–20%) [3, 14]. Also, as in the U.S., and likely reflecting appropriate consideration of performance status, older patients were less likely to receive NAC than younger patients.

Unlike in the U.S., our black patients were slightly less likely than others to receive NAC. Among women in the U.S. National Cancer Data Base, NAC use is reported to be slightly more common among Hispanic and non-Hispanic black women than among white women, even after adjusting for clinical, socioeconomic, and facility factors [15]. Our findings may reflect unmeasured barriers to repeated hospital visits or differences in each site's practices.

We observed striking variations in NAC use among the four sites. For example, 83.7% of patients at Site D received NAC, compared with 51.4% at Site A, an adjusted OR of 7.03. In the U.S., regional variations in NAC use for breast cancer and in other cancer treatments are well documented [14, 28]. A study of the Breast Cancer Surgical Outcomes database has also identified variations in NAC use by institution [12]. Our findings prompted our clinicians to discuss decision-making approaches at each site. All of them described tumor size, nodal status, and molecular subtype as important considerations. Our findings are consistent with their reports.

The resource constraints of LMICs could also influence NAC use in a variety of ways. For example, NAC enables some patients to receive breast conserving surgery. Such patients must then receive whole breast radiotherapy in order to achieve outcomes equivalent to mastectomy, but radiotherapy is in severely short supply in SSA [29, 30]. Another consideration is that excellent response to NAC could decrease the precision of subsequent breast surgery by obscuring the original

Table 3. Adjusted odds ratios for neoadjuvant chemotherapy use by demographic and clinical characteristics, including analysis of all eligible patients and subgroup analysis of patients from each study site

	Odds ratios (95% CI)				
Characteristics	**Site A (*n* = 329)**	**Site B (*n* = 105)**	**Site C (*n* = 198)**	**Site D (*n* = 178)**	**All patients (*n* = 810)**
Age, yr	0.92 (0.87–0.98)[a]	0.91 (0.81–1.03)	0.94 (0.86–1.02)	0.91 (0.85–0.99)[a]	0.95 (0.92–0.97)[a]
Black race	0.38 (0.09–1.61)	0.67 (0.07–6.62)	0.39 (0.06–2.53)	0.96 (0.17–5.41)	0.49 (0.25–0.96)
Household wealth percentile					
≤20th	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1(Ref)
21st–40th	2.20 (0.47–10.36)	2.38 (0.21–26.86)	1.04 (0.06–16.78)	0.85 (0.07–10.36)	1.06 (0.46–2.45)
41st–60th	2.61 (0.49–13.90)	3.76 (0.11–128.77)	2.27 (0.17–31.34)	1.86 (0.17–19.77)	1.37 (0.57–3.28)
61th–80th	2.00 (0.41–9.68)	0.96 (0.06–15.37)	7.95 (0.55–115.29)	1.69 (0.18–16.35)	1.29 (0.55–2.99)
>80th	3.57 (0.76–16.87)	0.13 (0.004–4.33)	3.74 (0.37–37.41)	3.50 (0.25–48.07)	1.40 (0.62–3.17)
T-stage					
0	NC	NC	0.81 (0.001–530.90)	NC	0.44 (0.05–3.77)
1	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
2	1.59 (0.20–12.61)	0.15 (0.01–2.29)	2.47 (0.25–24.52)	1.30 (0.13–13.50)	1.18 (0.52–2.71)
3	385.27 (334.36 to >999)[a]	14.67 (1.56–138.47)[a]	45.56 (3.09–671.46)[a]	83.81 (3.93 to >999)[a]	41.33 (15.24–111.17)[a]
4	689.33 (53.51 to >999)[a]	20.11 (1.36–298.25)[a]	NC	124.14 (5.46 to >999)[a]	136.29 (41.80–444.44)[a]
N-stage					
0	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
1	7.63 (2.19–26.56)[a]	3.58 (0.37–34.40)	4.40 (0.89–21.79)	0.24 (0.05–1.10)	2.33 (1.32–4.13)[a]
2	437.26 (67.14 to >999)[a]	1.26 (0.12–13.16)	829.34 (65.48 to >999)[a]	NC	35.64 (16.56–76.73)[a]
3	NC	NC	NC	NC	NC
Molecular subtype					
Luminal A	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Luminal B	2.57 (0.33–20.28)	1.84 (0.22–15.63)	8.04 (0.74–87.75)	3.37 (0.50–22.61)	1.86 (0.81–4.25)
HER2 enriched	2.45 (0.13–47.77)	NC	33.57 (1.53–738.58)[a]	28.35 (1.18–683.48)[a]	8.00 (2.33–27.50)[a]
TNBC	4.63 (0.45–47.25)	53.28 (1.52 to >999)[a]	16.15 (0.66–392.54)	39.46 (1.72–903.95)[a]	5.16 (1.88–14.12)[a]
Comorbidities					
HIV Infection	1.81 (0.58–5.69)	1.07 (0.15–7.85)	1.95 (0.25–15.52)	3.21 (0.40–25.58)	1.58 (0.83–3.01)
Hypertension	2.45 (0.70–8.61)	2.77 (0.26–29.59)	0.43 (0.05–3.69)	1.81 (0.43–7.76)	1.24 (0.69–2.23)
CAD/CHF	2.69 (0.08–94.53)	6.13 (0.19–197.17)	0.002 (<0.001 to >999)	0.12 (0.01–1.53)	0.43 (0.10–1.87)
Diabetes mellitus	1.82 (0.29–11.33)	1.87 (0.12–28.16)	0.003 (<0.001 to >999)	0.24 (0.04–1.29)	0.79 (0.34–1.86)
Hospital[b]					
Site A					1 (Ref)
Site B					0.37 (0.16–0.86)[a]
Site C					1.36 (0.71–2.63)
Site D					5.73 (2.72–12.08)[a]

[a]Significant at $p < .05$
[b]Treating study site was included as a covariate in the regression model of the entire study cohort and excluded from the individual models for each hospital subgroup.
Abbreviations: CAD, coronary artery disease; CI, confidence limit; CHF, congestive heart failure; HER2, human epidermal growth factor receptor 2; NC, not calculable; TNBC, triple-negative breast cancer.

tumor's margins. Many LMICs have limited ability to place radiopaque tumor site markers prior to chemotherapy or to access advanced imaging for defining the boundaries of nonpalpable disease; incomplete tumor bed resection may increase need for repeat surgeries or risk of local recurrence [31]. Providers at our sites confirmed regular use of tumor site markers, but this is not necessarily the case in lower resourced areas.

In many SSA patient populations, loss to follow-up during cancer treatment is >40% [32–34]. For patients at high risk for loss to follow-up, clinicians may favor initial resection of detectable disease when possible over delaying surgery to target micrometastatic disease with NAC. Although distance from the hospital was not predictive of NAC receipt, it is notable that NAC use was significantly less common at Site B, where patients travelled the furthest mean distance.

In LMICs, the availability of surgery and of chemotherapy is also heterogenous on both the international and intranational levels [35]. These sorts of differences may have contributed to the choice of first treatment at our sites, an effect we explore by describing the variations in time from diagnosis to treatment initiation with either primary surgery or NAC. At Site A, median time to start NAC was 20 days longer than for surgery (HR, 1.84) whereas at

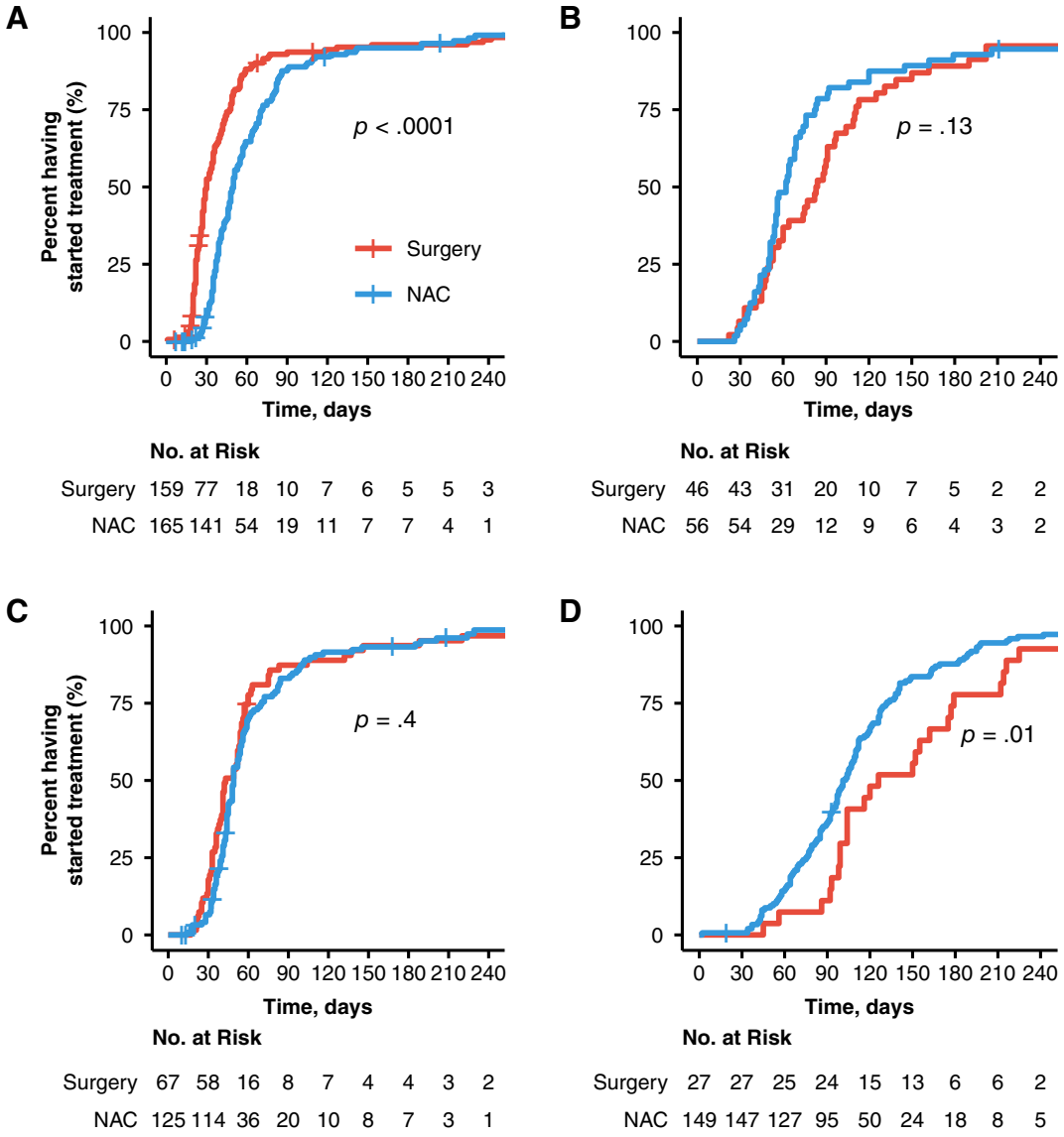

Figure 3. Time to first therapy at each treating study site by initial treatment modality. **(A):** Site A. **(B):** Site B. **(C):** Site C. **(D):** Site D. The *p* values were calculated via log-rank testing.
Abbreviation: NAC, neoadjuvant chemotherapy.

Site D, NAC was started 25 days earlier than surgery (HR, 0.49). At Sites B and C, time to initiation was not significantly different by modality.

Providers acknowledged those differences in access to chemotherapy and surgery across sites. Site A had adequate availability of surgeons and operating rooms but intermittent delays to start chemotherapy; Site C had delays to chemotherapy and, recently, longer waits for surgery. Both Site B and Site D had delays in scheduling surgery, and Site D's medical oncology department lost staff through 2017. There were also differences in the extent to which providers reported taking treatment availability into consideration. Site B's providers did describe favoring NAC during times of surgical delay, whereas Site D clinicians reporting choosing between NAC or surgery entirely on the basis of tumor characteristics. In our cohort, for whom primary surgery and NAC are both clinically appropriate, the differences between each site's use of NAC is also attributable to a subtle mix of provider preference, site protocols, treatment availability, and other resource constraints.

Consideration of treatment availability is likely valid, as treatment delays may be clinically detrimental. Literature on the impact of time to initiate breast cancer therapy is inconsistent, but delays beyond 60–80 days seem associated with poorer survival, especially in later-stage patients [36–39]. In regions or individual centers where the wait for one modality is notably longer than that for another, and where NAC and primary surgery are otherwise equivalent, it may be entirely appropriate to choose the treatment with the shorter wait.

The clinical impact of NAC versus primary surgery in LMICs has not been specifically studied. Trials from HICs have found that breast cancer survival is not affected by use of neoadjuvant versus adjuvant chemotherapy, and patients of African and European descent do not appear to differ greatly

in biologic chemotherapy sensitivity [1]. However, clinical decision making based on resource constraints may still affect treatment outcomes. For instance, given the log-kill hypothesis of chemotherapy dosing, all planned cycles of preoperative chemotherapy should be delivered without interruption for surgery [40]. At a large hospital in Rwanda, 22% of patients with breast cancer had chemotherapy split into neoadjuvant and adjuvant portions, typically because surgical timing was often delayed and unpredictable [41]. The patients in our cohort did not receive such split chemotherapy, but the practice may be common in poorer areas of SSA.

These results should be considered within the limitations of our study design. The size and geographic scope of the SABCHO database is smaller than those used to study treatment patterns in the U.S., but our study sample is the largest prospective cohort of patients with breast cancer in SSA of which we know. These results may also not be generalizable to other hospital and cancer centers in SSA, given the wide variations in available resources, clinician training quality, and patient sociodemographics. Resources are distributed erratically in LMICs. The potential of that heterogeneity to affect treatment patterns, including NAC use, is consistent with our findings. Therefore, resource appropriate guidelines and quality metrics designed for low-resource settings require the flexibility to accommodate not just limited tests and treatments but also the local variations in those constraints.

The findings presented here call for future investigation. The higher levels of HER2 positivity and lower levels of hormone receptor negativity given the young mean age of our cohort may be the consequence of differences in germline and somatic variations, impact of known risk factors, or epidemiology of presentation in the absence of a screening programs. These findings are consistent with our earlier work but are not yet fully explained [21]. These types of differences in tumor biology could modify NAC effectiveness as compared with adjuvant chemotherapy. Information on pathologic response to NAC is available in the SABCHO dataset, and analysis is in progress. Ultimately, the survival of patients who receive NAC and those who receive postoperative chemotherapy should be compared. We will conduct such comparisons within our cohort, but populations from other LMICs should also be studied before we draw broad conclusions. Data on use of neoadjuvant endocrine therapy was not yet available, but we also plan to address its role, as it represents a potentially valuable tool for luminal subtype patients, especially if surgery is delayed.

Conclusion

We have found that use of NAC at these public South African hospitals is primarily associated with clinical considerations rather than with sociodemographic characteristics. The extent of NAC also varies significantly between institutions. We also have found that time to initiation of therapy can vary between NAC and surgery within a study site and that the pattern of that variation can differ across sites. We suspect that the differences in NAC use may be partially attributable to differences in each site's access to chemotherapy and surgery. Further work on the cause of these variations is needed.

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Disclosures

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