Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.202073111-118

Clinicopathologic Features and Survival Analysis of Non-metastatic Breast Cancer Patients in Guatemala

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ARTICLE INFO

Received:
03 June 2020
Revised:
12 August 2020
Accepted:
18 August 2020

Key words:
Brest cancer;
Guatemala;
survival

ABSTRACT

Background: Breast cancer (BC) is a leading cause of cancer related death worldwide. Unfortunately, data concerning clinicopathologic features of this malignancy in non-developed countries is scarce. This study aims to characterize a cohort of Guatemalan female patients with non-metastatic BC and to determine risk factors for overall survival (OS).

Methods: We retrieved data on consecutive patients from the Instituto Guatemalteco de Seguridad Social that were treated from 2008 to 2014. Clinical features and long-term outcomes were retrieved from medical records. Univariate and multivariate Cox regression analyses were conducted to identify variables associated with OS.

Results: 954 BC patients were identified during the time frame. A total of 436 women (46%) were younger than 50 years old. BC molecular subtypes categorized 537 patients (56.3%) with luminal A disease, 186 (19.5%) patients with triple negative tumors, 153 cases (16.1%) with HER-2 enriched tumors, and 78 patients (8.2%) with luminal B tumors. Clinical stage at presentation was stage I: 4.7% (n=45); stage II: 48.1% (n=459), and stage III: 47.2% (n=450). The overall 5-year survival rate was 75.2% (95% Confidence Interval: 72.0–78.3). In the multivariate analysis clinical stage, triple negative tumors and HER2 enriched tumors were independently associated with poor survival.

Conclusion: The majority of patients with non-metastatic BC are diagnosed with advanced disease and many of them are younger than 50 years old. OS in this cohort of Guatemalan patients is lower than that reported in developed countries.

Introduction

Breast cancer (BC) is the most common malignancy and the major cause of cancer-related death among women worldwide.[1] In developing countries, the burden of this disease is reflected in the low incidence-to-mortality ratio, which it is often related to delays in diagnosis and to the unavailability of surgical or medical treatment.[2]

Clinical characteristics and outcomes of BC patients vary depending on the study population. Previous studies have acknowledged that Hispanic patients feature different tumor subtypes and share poor long-term outcomes in comparison to non-Hispanic populations.[3,4]

Guatemala is a low-middle income country (LMIC) with 17 million habitants, mainly composed by mestizos (60.1%) and indigenous (39.3%) people.[5] Like some other countries in Central America,

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Guatemala has undergone an epidemiological and demographic transition, and the incidence and mortality of BC is increasing, with few data reported on the clinical characteristics and determinants of overall survival (OS) and disease-free survival.[6]

Given the expected increase of BC incidence and mortality in the coming years, and the relevance of these unknown data to Health care providers, we decided to conduct this study in order to describe clinical characteristics of non-metastatic BC patients from Guatemala and to identify clinical determinants of OS.

Methods

We retrospectively reviewed the clinical records of all patients diagnosed with non-metastatic BC at the Instituto Guatemalteco de Seguridad Social (IGSS) between January 2008 and December 2014. The IGSS is a referral center that provides health services to about 17% of the Guatemalan employed population.[7] All cases were histologically confirmed by excisional or core needle biopsy before treatment. All patients were classified according to the American Joint Committee on Cancer Staging Manuel (TNM), Seventh Edition.[8] For eligible patients we collected clinical data from medical records.

The BC pathologist in charge assessed histological subtype, nuclear grade, and interpreted the immunohistochemical (IHC) analysis of all cases in formalin-fixed paraffin-embedded tissues from incisional biopsies taken for diagnosis. Estrogen receptor (ER), progesterone receptor (PR), Ki-67 index, and expression and/or HER2 gene amplification were conducted following current recommendations.[9, 10] HER2 was deemed positive based on American Society of Clinical Oncology (ASCO) guideline.[11] Breast cancer intrinsic subtypes were specified based on St Gallen 2015 Consensus.[12] Tumor size and lymph node involvement were reported in the pathological specimen after surgery.

Patients were evaluated to receive neoadjuvant therapy in a multidisciplinary session. Patients with clinical response to neoadjuvant treatment were evaluated before each chemotherapy cycle, those with stable disease considered to be inoperable underwent radiotherapy followed by surgery. Pathological complete response (pCR) was considered to be the absence of any tumor cells both in the tumor and lymph nodes (ypTis or ypT0 and ypN0).[13]

The adjuvant/neoadjuvant treatment regimens were decided by the medical oncologist in charge, and consisted of one of the following regimens: a) four cycles of adriamycin 60 mg/m2 and cyclophosphamide 600 mg/m2 (AC) every 21-days followed by paclitaxel 80 mg/m2 weekly for 12 weeks or for 4 cycles of docetaxel 75 mg/m2 every 21-days; b) 4 cycles of neoadjuvant AC followed by surgery and 4 cycles of adjuvant docetaxel (recommended for high risk patients based on the presence of at least one of the following characteristics: four or more positive axillary nodes, grossly evident extracapsular nodal extension, large primary tumors, and very close (< 1mm) or positive deep margins of resection of the primary tumor); c) dose-dense chemotherapy (recommended for women suffering from advanced or inflammatory breast cancer); d) platinum-based regimen (recommended for patients with TNT); e) six cycles of cyclophosphamide 600 mg/m2, methotrexate 40 mg/m2 and 5-fluorouracil 600 mg/m2 (CMF regimen); f) 4 cycles of AC adjuvant (recommended in low risk patients); g) endocrine therapy (tamoxifen, anastrozol or letrozol). Patients with HER2 positive tumors received trastuzumab for 52 weeks in the adjuvant setting.

Routine follow-up of these patients comprised clinical examination every three months during the first three years and yearly thereafter. An annual mammography was performed on all included patients.

Statistical analysis

Continuous variables are presented as means and standard deviations (SD). Categorical variables are presented as frequencies. The comparisons between continuous variables were made by the ANOVA test. The Chi-square test was run to evaluate the statistical association between categorical variables. The Kaplan-Meier method was used to determine the probability of OS and DFS. Follow-up was determined from the date of diagnosis to the date of last follow-up or death from any cause. Recurrence was defined by the clinical or histopathological evidence of metastatic disease as measured by the RECIST 1.1 criteria. The survival curves were compared by the log-rank test. Univariate and multivariate Cox's regression analyses were performed to determine the hazard ratio (HR) with 95% confidence interval (95%CI) for OS. The multivariate model included only those variables with p values less than 0.10 in the univariate analysis. A p value less than 0.05 was assumed to be statistically significant. The statistical analysis was performed using SPSS version 22 for Mac (SPSS, Inc., Chicago, IL, USA).

Results

General characteristics

A total of 954 patients were identified during the time frame. Table 1 summarizes the clinical characteristics of the population and categorized based on breast cancer intrinsic subtype, as assessed by IHC. In total, 436 women (46%) were younger than 50 years old, and only 72 patients (7.5%) were older than 70 years. The majority of patients (n=725, 76%) were diagnosed with advanced disease (stages IIB to IIIC).

Table 1. Demographic characteristics of patients included in the study with breast cancer

	Characteristic	All (n=954)	Luminal A (n=537; 56.3%)	Luminal B (n=78; 8.2%)	HER2 (n=153; 16.1%)	Triple Negative (n=186; 19.5%)	P Value
Age (Years, SD)	Age	52.4 ± 12.5	54.0 ± 12.2	52.08 ± 12.9	51.05 ± 12.9	49.37 ± 11.9	< 0.001
Clinical stage (%)	IA	5 (0.5)	5 (0.9)	0 (0)	0 (0)	0 (0)	0.016
	IB	40 (4.2)	25 (4.7)	2 (2.6)	9 (5.9)	4 (2.2)	
	IIA	184 (19.3)	117 (21.8)	13 (16.6)	24 (15.7)	30 (16.0)	
	IIB	275 (28.8)	158 (29.4)	26 (33.3)	35 (22.9)	56 (30.1)	
	IIIA	318 (33.3)	174 (32.4)	27 (34.8)	49 (32.0)	68 (36.6)	
	IIIB	119 (12.5)	54 (10.1)	9 (11.4)	30 (19.6)	26 (14.0)	
	IIIC	13 (1.4)	4 (0.7)	1 (1.3)	6 (3.9)	2 (1.1)	
Histological Type (%)	Ductal	893 (93.6)	490 (91.2)	74 (94.9)	150(98.0)	179 (96.2)	
	Lobular	59 (6.2)	47 (8.8)	4 (5.1)	1 (0.7)	7 (3.8)	< 0.001
	Unknown	2 (0.2)	0 (0)	0 (0)	2 (1.3)	0 (0)	
Nuclear grade (%)	Low	122 (12.8)	91 (16.9)	6 (7.7)	10 (6.5)	15 (8.1)	
	Intermediate	403 (42.2)	258 (48.2)	38 (48.7)	48 (31.4)	59 (31.7)	
	High	310 (32.5)	109 (20.2)	23 (29.5)	85 (55.5)	93 (50.0)	< 0.001
	Unknown	119 (12.5)	79 (14.7)	11 (14.1)	10 (6.5)	19 (10.2)	
Body Mass Index (%)	Obese	232 (24.3)	132 (24.6)	21 (26.9)	30 (19.6)	49 (26.3)	
	Overweight	362 (37.9)	208 (38.7)	26 (33.3)	58 (37.9)	70 (37.7)	
	Normal	336 (35.2)	183 (34.1)	26 (33.3)	64 (41.8)	63 (33.9)	
	Underweight	12 (1.3)	7 (1.3)	1 (1.3)	1 (0.7)	3 (1.6)	0.158
	Unknown	12 (1.3)	7 (1.3)	4 (5.2)	0 (0)	1 (0.5)	
Treatment (%)	Adjuvant chemotherapy	549 (57.5)	329 (61.3)	43 (55.1)	85 (55.6)	92 (49.5)	< 0.001
	Neoadjuvant chemotherapy	184 (19.3)	85 (15.8)	12 (15.4)	30 (19.6)	57 (30.6)	
	Chemotherapy + Radiotherapy	36 (3.8)	20 (3.7)	1 (1.3)	5 (3.3)	10 (5.4)	
	Surgery alone	8 (0.8)	2 (0.4)	0 (0.0)	3 (2.0)	3 (1.6)	
	Surgery + endocrine therapy	82 (8.6)	72 (13.4)	8 (10.3)	1 (0.7)	1 (0.5)	
	Neoadjuvant and adjuvant chemotherapy	93 (9.7)	28 (5.2)	13 (16.7)	29 (19.0)	23 (12.4)	
	Unknown	2 (0.3)	1 (0.2)	1 (1.3)	0 (0.0)	0 (0.0)	

Medical therapy and response to neoadjuvant chemotherapy

A total of 678 (71.0%) patients were treated with adjuvant chemotherapy, and 277 patients (29%) underwent neoadjuvant therapy. Among patients receiving preoperative chemotherapy, we identified 72 patients (26%) with pCR, and 183 patients (66%) with partial response. A total of 8 cases (3%) had progressive disease during neoadjuvant chemotherapy.

Pathological complete response was achieved by 27% and 33% of patients with HER2 positive tumors and TNT, respectively. The OS analysis showed that patients achieving pCR had better OS than their counterparts (Hazard ratio: 0.56; 95%CI: 0.36-0.88; p=0.001).

Median OS among patients with pCR was 100 months (95% CI: 46.9-153.0), while patients without pCR had a median OS time of 73 months (95%CI: 59.7 – 86.3 months). (Figure 1)

Long-term outcomes

After a median follow up of 52 months, a total of 242 patients died (25.4%) and 255 (26.8%) had a recurrent event. Only 28.4% of these recurrent events were confirmed by biopsy. The majority of patients with recurrent events (n=167; 65.5%) were treated with chemotherapy, followed by best supportive care in 34 patients (13.3%), and hormonal therapy in 27 patients (10.6%). Only 15.6% of patients with hormone-receptor positive disease at recurrence were treated with hormonal therapy.

Most common distant sites at recurrence included lung (n=114; 44.7%), bone (75; 29.4%), central nervous system (n=47; 18.4%), and liver (n=38; 14.9%). Local recurrent disease was presented in 35 (13.7%) cases.

Overall median survival time after breast cancer diagnosis was 112 months (95%CI: 95.3 – 128.8), and the overall 5-year survival rate was 75.2% (95% CI: 72.0 – 78.3).

Median OS and DFS according to clinical stage, breast cancer subtype, and tumor grade are provided in Table 2. The results of the univariate and multivariate analyses for OS are depicted in Table 3. Figure 2 depicts the rate of OS according to breast cancer intrinsic subtype. 5-year OS according to clinical stage was 88.1% (95%CI: 78 – 97%) for stage I, 87.4% (95%CI: 84 – 90%) for stage II, and 60% (55 – 64%) for stage III. (Figure 3)

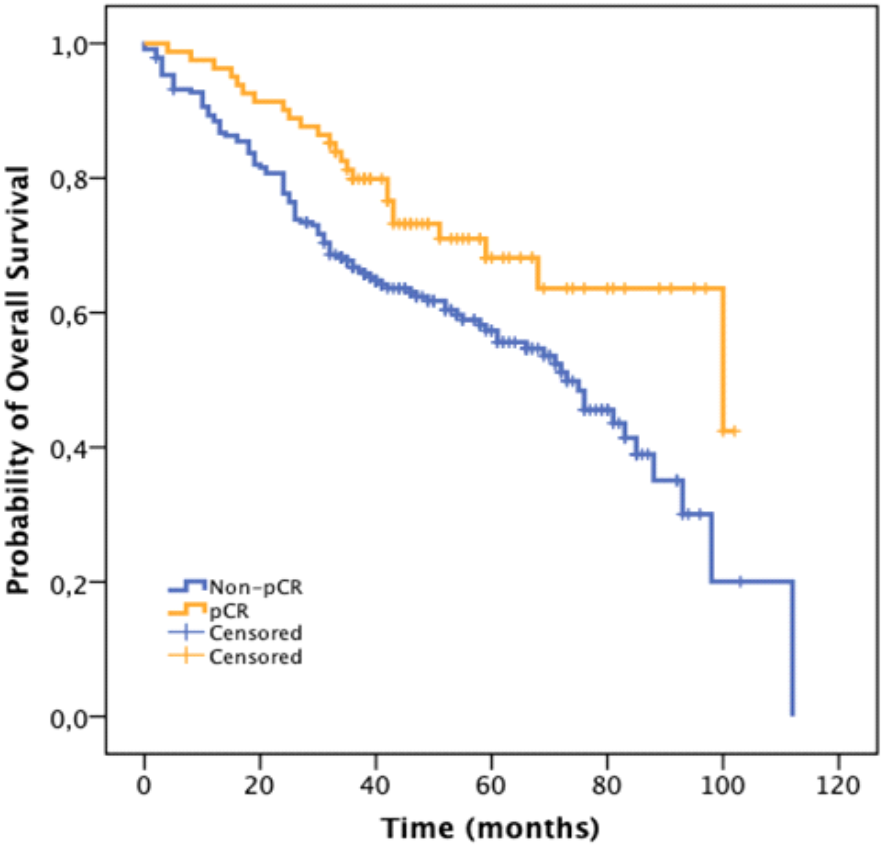

Figure 1.

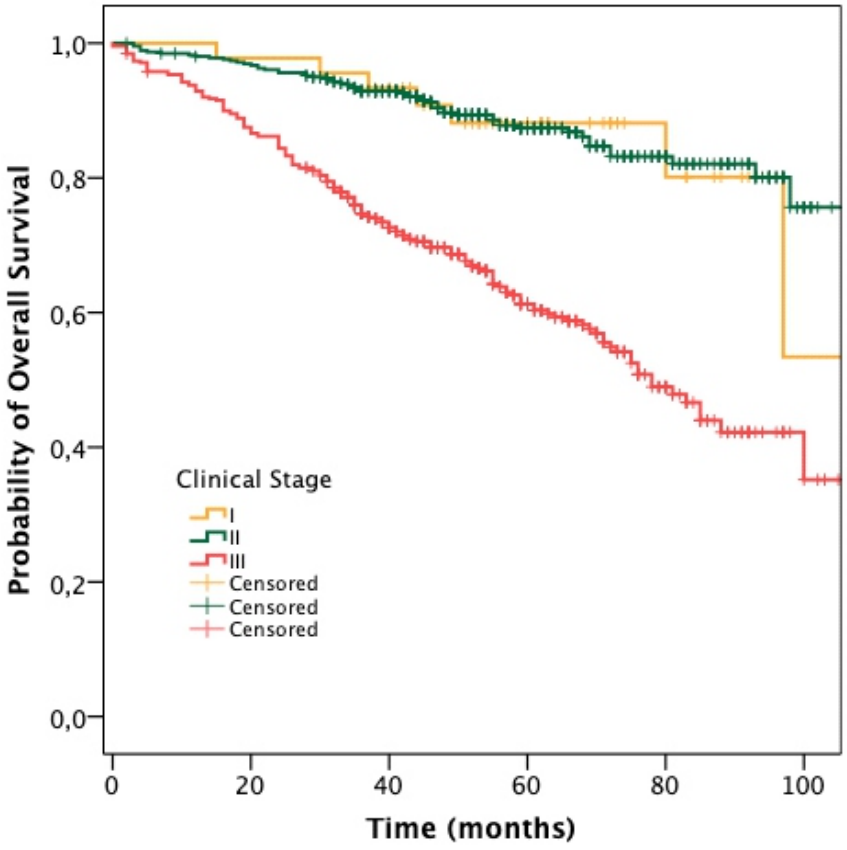

Figure 2.

Table 2. Overall survival and disease-free survival according to clinical stages, intrinsic breast cancer subtypes, and tumor grade.

	Variable	Median Disease-Free Survival (months) (95% CI)	P Value	Median Overall Survival (months) (95% CI)	5 years Overall Survival rate (95% CI)	P Value
Clinical stage	IA	33 (27.9 – 38.1)	< 0.001	97 (72.9 – 121.1)	80 (47 – 100)	< 0.001
	IB	35 (17.3 – 52.7)		Not reached*	89 (79 – 98)	
Intrinsic	IIA	30 (26.6 – 33.4)		Not reached*	88 (82 – 93)	
breast cancer	IIB	24 (19.9 – 28.1)		85 (72.7 – 127.6)	86 (81 – 90)	
subtype	IIIA	21 (16.7 – 25.3)		51 (34.0 – 67.9)	71 (65 – 76)	
	IIIB	16 (10.0 – 22.0)		35 (28.3 – 41.6)	39 (29 – 48)	
	IIIC				44 (16 – 71)	
	Luminal A	31 (25.9 -36.0)	< 0.001	112 (non calculable**)	83 (79 – 86)	< 0.001
	Luminal B	35 (24.8 – 45.2)		78 (non calculable**)	68 (56 – 79)	
	HER2 positive	19 (13.3 – 24.6)		Not reached*	69 (61 – 77)	
	Triple negative	16 (21.2 – 26.9)		72 (57.5 – 86.5)	59 (51 – 66)	
	Histological grade		< 0.001			
	I or II	30 (26.4 – 33.6)		112 (95.2 – 128.8)	83 (79 - 87)	< 0.001
	III	19 (15.4 – 22.6)		85 (73.6 – 96.4)	60 (53 - 66	

*Not reached: Longer follow-up is needed in order to achieve the median overall survival in this subgroup.
**Non-calculable: The formula for the estimation of the 95% confidence interval was not applicable due to large sample variation.

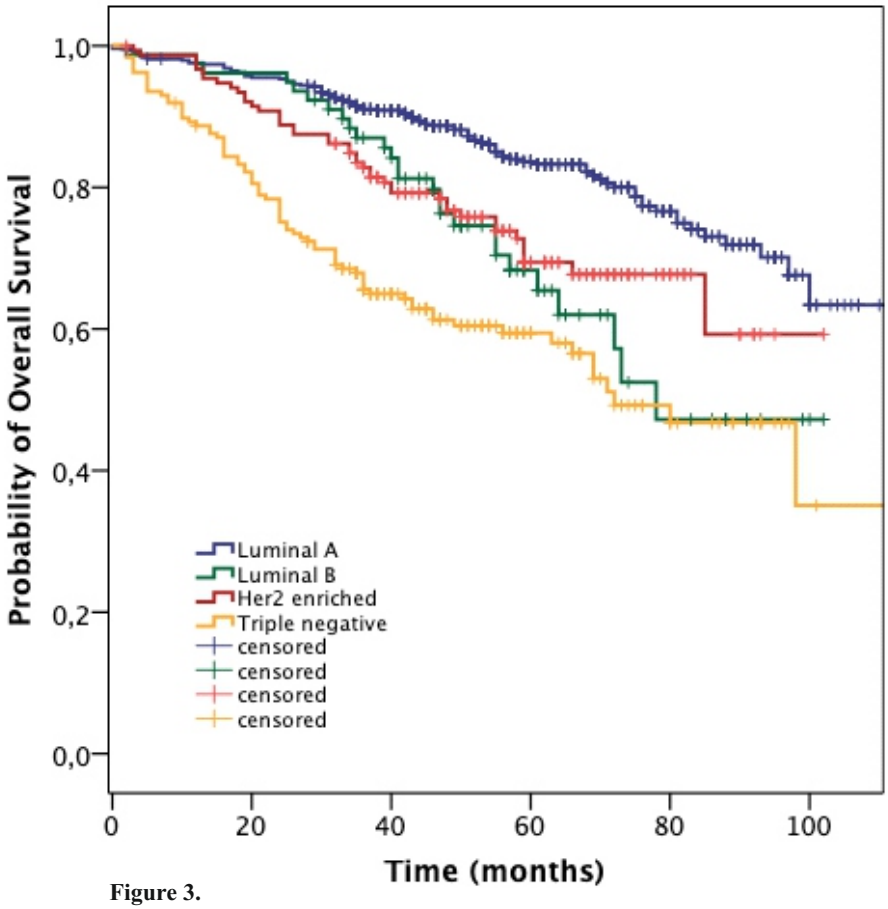

Figure 3.

Table 3. Univariate and multivariate analysis of overall survival for the entire population

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P Value	Hazard ratio (95% CI)	P Value
Age (years)	1.00 (0.99-1.01)	0.98		
Clinical stage		< 0.001		<0.001
I	Reference		Reference	
II	3.56 (1.66-7.57)		2.72 (1.83 – 4.05)	
III	3.79 (2.81-5.10)		5.44 (3.66 – 8.10)	
ER positive	0.45 (0.35-0.58)	< 0.001	1.11 (0.68 – 1.81)	0.67
HER2 positive	1.28 (0.97-1.70)	0.081	1.87 (1.21 – 2.89)	0.005
Triple negative	2.55 (1.94-3.34)	< 0.001	3.32 (1.88 – 5.89)	<0.001

Discussion

Our study reports, for the first time, a clinical depiction of a cohort of Guatemalan patients with non-metastatic BC. These findings show that the majority of cases presented with large tumors and lymph nodal metastases. It has been postulated that lack of access to health services and lack of screening policies are responsible for the high incidence of locally advanced tumors in this particular population.[14] Indeed, only one-third of patients were diagnosed at an early stage, suggesting a lack of BC awareness and little access to screening and health care services. Previous authors have reported that adherence to mammography guidelines is considerably low among Guatemalan females as a consequence of a lack of insurance coverage and low education.[15]

Our findings also showed that the percentage of patients with TN tumors (19.5%) is higher than that reported for Caucasian (10-12.5%)[16,17] and Asian populations (8%)[18], and similar to that reported in Mexico (23.1%)[19] and Costa Rica (17.1%)[20] Indeed, clinical characteristics of patients with TN tumors are very similar to Mestizo populations reported elsewhere[21], such as young age at diagnosis, and high grade histological differentiation. These differences in BC subtypes among ethnic groups can reflect variations in the prevalence of risk factors, as well as a consequence of intrinsic genetic variations.[22]

Our study also revealed a high proportion of patients younger than 50 years old. This percentage is higher than that reported for American populations according to the SEER Registry (46% vs. 19%)[16], but similar to the percentage previously reported in Mexican patients.[21] Similarly, Hispanic patients living in USA usually are younger than their White counterparts.[17] This finding is of paramount importance for screening purposes in our country.

Although BC mortality in Guatemala ranks among the lowest worldwide1, the 5-year OS is considerably lower than that reported in developed countries.[23] Similarly, the 5-year OS by subtype was lower than previously reported, particularly in TN and HER2 positive tumors.[23] These differences can be attributed to the unavailability of medical therapies or delays in referral and treatment initiation in our cohort, as previous authors have already noticed,[24] but also can be a reflection of the over-representativeness of young patients with high grade and TN tumors, since some authors have argued that young age at diagnosis is independently related to worse long-term prognosis.[25]

Our study also described the results of neoadjuvant chemotherapy in operable BC patients. Although the percentage of patients undergoing preoperative treatment was similar to that reported in other cohorts (19.3%)[26, 27], our data suggest that neoadjuvant therapy was underused, since the majority of patients in our cohort had locally advanced disease. In concordance with previous reports[28], our data showed an OS improvement in favor of those patients who achieved pCR, a finding that must be interpreted cautiously because of the small sample size undergoing neoadjuvant chemotherapy in our cohort.

The Guatemalan government´s expenditure on health care is among the lowest of Central American countries.[29] This, and other challenges such as the low health insurance coverage[30], and the low prevalence of screening, are among the main barriers this country faces in order to reduce the burden of BC. Other needs that must be fulfilled include the lack of national cancer centers and protocols, the lack of trained personnel, and poor access to primary care in rural areas.[14,30]

Our findings cannot accurately reflect the prognosis and clinical characteristics of all Guatemalan patients affected with BC due to its unicenter design. Besides, its retrospective design could bias the results due to some missing data from clinical records. For instance, we did not have access to other potential confounder variables associated with prognosis, such as smoking[31], alcohol consumption[32], or previous hormone use.[33] Despite these caveats, our study provides a first clinical picture that can contribute to improve health policies in Guatemala. Further national efforts must be carried out to better describe the epidemiology of cancer patients in our country.

In summary, our studied population is diagnosed at locally advanced stages, indicating the need to increase awareness about BC among Guatemalan women and to improve the screening program for earlier detection of the disease. Given the high percentage of BC patients under the age of 50, we recommend starting screening mammography prior this age.

Conflict of Interest

Hugo Castro has received honoraria from Roche, Novartis, Bayer, Pfizer, consulting for Roche and Bayer. Allan Ramos-Esquivel has received honoraria from Roche and Pfizer, consulting for Roche, Bayer, and Novartis; and travel and accommodations expenses from Bayer, Roche, Novartis, and Johnson & Jonhson.

Other authors declare no conflicts of interest.

Financial Support

This work was partly funded by Roche Servicios S.A.

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