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Geriatric Oncology

Real-World Outcomes Among Older Mexican Women with Breast Cancer Treated with Neoadjuvant Chemotherapy

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

Key Words. Breast neoplasms • Neoadjuvant therapy • Older adults • Mexico • Developing countries

Abstract

Background. Older patients with breast cancer treated in high-income countries often present with early-stage disease, leading to a lack of information on the use of neoadjuvant chemotherapy in this population. We analyzed the real-world outcomes of older women with breast cancer treated with neoadjuvant chemotherapy at a single institution in Mexico.

Materials and Methods. The study included 2,216 patients treated with neoadjuvant chemotherapy. Regarding achievement of pathologic complete response (defined as no invasive residual tumor in the breast and lymph nodes), 243 patients aged ≥65 years were compared with 1,973 patients aged <65 years. Disease-free survival and overall survival were compared between groups according to pathologic complete response and subtype, defined by hormone receptor and human epidermal growth receptor 2 (HER2) status.

Results. Older women were less likely to have a pathologic complete response than their younger counterparts (26.3 vs. 35.3%, $p < .001$). When response rates by subtype were analyzed, this difference was significant only for women with triple-negative tumors. Achieving less than a pathologic complete response was associated with a greater chance of recurrence, but age was not an independent factor for recurrence for any subtype. Reaching a pathologic complete response was significantly associated with improved survival among older women with breast cancer, with the exception of those with hormone receptor–positive, HER2– disease.

Conclusion. Although older women have fewer pathological complete responses, their outcomes after neoadjuvant chemotherapy are comparable to those of younger patients. This is particularly relevant for the treatment of older adults with breast cancer in developing countries, who present in advanced stages and more often need neoadjuvant therapy.

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Implications for Practice: The majority of older patients with breast cancer in high-income countries present with early-stage disease, leading to a lack of information regarding the use of neoadjuvant chemotherapy in real-world settings. This article reports the outcomes of older Mexican women with breast cancer who received neoadjuvant chemotherapy compared with their younger counterparts. Although older women (particularly those with triple-negative tumors) were less likely to have a pathologic complete response after neoadjuvant treatment, age was not an independent factor for recurrence. Achieving a pathologic complete response was associated with improved survival, regardless of age.

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Introduction

Neoadjuvant chemotherapy (NACT) is the standard of care for the treatment of patients with locally advanced breast cancer (BC) and for specific BC subtypes, in which the achievement of a pathologic complete response (pCR) has been found to correlate with a better prognosis [1, 2]. In addition, the use of NACT can help identify patients with insufficient response who might benefit from the use of additional chemotherapy or targeted therapy. The achievement of a pCR is dependent on several factors, including hormone receptor (HR) status, human epidermal growth receptor 2 (HER2) expression, and the type of treatment used [3].

One of the factors strongly associated with achieving a pCR after NACT is young age, which may be related to the fact that both the HER2+ and triple-negative breast cancer (TNBC) subtypes are more common among younger women [4]. However, BC is a disease of aging, and its worldwide incidence rates are high among older adults. Currently, 450,000 new BC cases occur in women aged ≥70 years every year, representing about 25% of the global incidence [5, 6]. However, by the year 2040 the incidence of BC in women aged ≥70 years will double, and 900,000 older adults will be diagnosed with BC every year [6]. This represents a challenge to health systems worldwide, which are ill-prepared to shoulder this increase in the burden of BC, and to treating oncologists, who may be unable to make evidence-based decisions because of a lack of older adult–specific data.

Unfortunately, most randomized controlled trials (RCTs) evaluating novel treatments for BC have included a population composed of younger and fitter individuals, and patients aged ≥65 years remain largely underrepresented [7, 8]. This underrepresentation of older adults is also found in trials of NACT strategies. As an example, a recent pooled analysis of eight RCTs of NACT conducted by the German Breast Group found that only 6.3% of included patients (566 of 8,949) were aged ≥65 years [9]. This lack of information regarding the outcomes of older adults with BC treated with NACT represents an important gap in knowledge, particularly for patients presenting with large tumors and for those with TNBC or HER2+ disease, who could obtain the most benefits from neoadjuvant strategies [10].

In Mexico, as in other low- and middle-income countries (LMICs), BC is the most common neoplasm among women, and rapid population aging has led to an increase in the number of older adults with BC [11, 12]. Regrettably, because of a lack of early detection programs and to the existence of barriers for timely access to high-quality cancer care, many older patients are diagnosed with locally advanced tumors, which might require the use of NACT [11, 13–15]. Therefore, understanding the outcomes of older women treated with neoadjuvant strategies in LMICs might provide guidance for treating a significant proportion of patients, for which current information from RCTs is lacking. Additionally, there are insufficient data to suggest that the achievement of a pCR after NACT is a marker of better outcomes among older women with BC [16].

In this retrospective study, we assessed the clinical and pathological outcomes of older Mexican patients with BC

Table 1. Patient characteristics by age group

Characteristic	<65 years (*n* = 1,973), *n* (%)	≥65 years (*n* = 243), *n* (%)	*p* value
T stage			
T1	52 (2.6)	4 (1.7)	**<.001**
T2	672 (34.0)	69 (28.4)	
T3	690 (35.0)	63 (25.9)	
T4	548 (27.8)	106 (43.6)	
NA	11 (0.6)	1 (0.4)	
N stage			
N0	191 (9.7)	16 (6.6)	**.017**
N1	915 (46.4)	97 (39.9)	
N2	729 (37.0)	112 (46.1)	
N3	137 (6.9)	17 (7.0)	
NA	1 (<0.1)	1 (0.4)	
Histological type			
Ductal	1,740 (88.2)	209 (86.0)	.076
Lobular	168 (8.5)	22 (9.0)	
Mixed	50 (2.5)	6 (2.5)	
Others	15 (0.8)	6 (2.5)	
Grade			
1	224 (11.3)	28 (11.5)	.958
2	533 (27.0)	69 (28.4)	
3	1,108 (56.2)	134 (55.2)	
NA	108 (5.5)	12 (4.9)	
ER			
Negative	755 (38.2)	76 (31.3)	**<.001**
Positive	1,218 (61.8)	167 (68.7)	
PR			
Negative	831 (42.1)	104 (42.8)	.158
Positive	1,142 (57.9)	139 (57.2)	
HER2			
Positive	619 (31.4)	70 (28.8)	.415
Negative	1,354 (68.6)	173 (71.2)	
Biological subtype			
HR+/HER2−	1,011 (51.2)	146 (60.0)	**.038**
TNBC	445 (22.6)	40 (16.5)	
HR−/HER2+	237 (12.0)	30 (12.4)	
HR+/HER2+	280 (14.2)	27 (11.1)	
Type of surgery			
BCS	198 (10.0)	10 (4.1)	**.002**
Mastectomy	1,630 (82.6)	206 (84.8)	
NA	145 (7.4)	27 (11.1)	
Adjuvant hormone therapy			
Yes	1,254 (63.6)	164 (67.5)	.228
No	719 (36.4)	79 (32.5)	
Radiotherapy			
Yes	1,633 (82.8)	202 (83.1)	.828
No	337 (17.2)	41 (16.9)	

Abbreviations: BCS, breast-conserving surgery; ER, estrogen receptor; HER2, human epidermal growth receptor 2; HR, hormone receptor; NA, not available; PR, progesterone receptor; TNBC, triple-negative breast cancer.

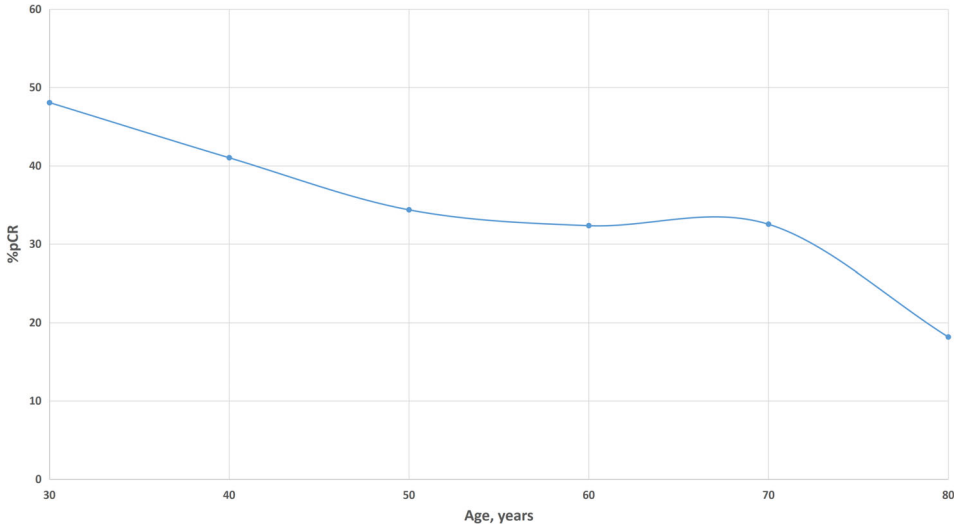

Figure 1. Pathologic complete response according to age.
Abbreviation: pCR, pathologic complete response.

Table 2. Pathologic complete response according to age and subtype

Subtype	Age	pCR, %	*n*	OR (95% CI)	*p* value
All subtypes	<65	35.33	697	0.66 (0.48–0.91)	**.010**
	≥65	26.33	64		
HR+/HER2−	<65	21.86	221	0.62 (80.67–1.04)	.070
	≥65	14.38	21		
Luminal A	<65	23.82	161	0.78(0.41–1.47)	.450
	≥65	20.25	16		
Luminal B	<65	17.91	60	0.44 (0.16–1.18)	.105
	≥65	7.46	5		
TNBC	<65	45.39	202	0.34 (0.15–0.77)	**.010**
	≥65	22.50	9		
HR−/HER2+	<65	56.54	134	1.17 (0.50–2.71)	.717
	≥65	63.33	19		
HR+/HER2+	<65	50.00	140	0.95 (0.40–2.24)	.906
	≥65	55.49	15		

Logistic model including age, T stage, N stage, nuclear grade. Values in bold are statistically significant.
Abbreviations: CI, confidence interval; HER2, human epidermal growth receptor 2; HR, hormone receptor; OR, odds ratio; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

treated with NACT at a single institution in Mexico City and compared them with their younger counterparts.

Materials and Methods

We conducted an observational retrospective cohort study including all consecutive patients with a diagnosis of BC treated with NACT at Instituto Nacional de Cancerología (INCan), a cancer center in Mexico City, between 2007 and 2015. Patients who received at least one cycle of chemotherapy before undergoing surgery were included. Approval for the study was obtained from the Ethics and Research Committees at INCan. Patient characteristics, including stage at diagnosis, treatment type, histopathology (including immunophenotype), disease-free survival (DFS), and overall survival (OS), were recorded. Patients were divided in two groups according to age at diagnosis: ≥65 years old and <65 years old. Those aged ≥65 years were considered to be older patients with BC.

Breast pathologists performed the histologic assessments. Estrogen receptor and progesterone receptor were analyzed using immunohistochemistry (IHC) [17, 18]. For HR+ cases the semiquantitative "H-score" was used to define receptor expression intensity. This method provides an overall score (0–300) based on the sum of ordinal weighted percentiles of cells stained weak, moderate, and strong [19]. The H-score was used to classify HR+ tumors as either luminal A or luminal B subtypes according to previously published methodology [19]. Because of a lack of Ki67 assessments in a significant proportion of cases, the H-score

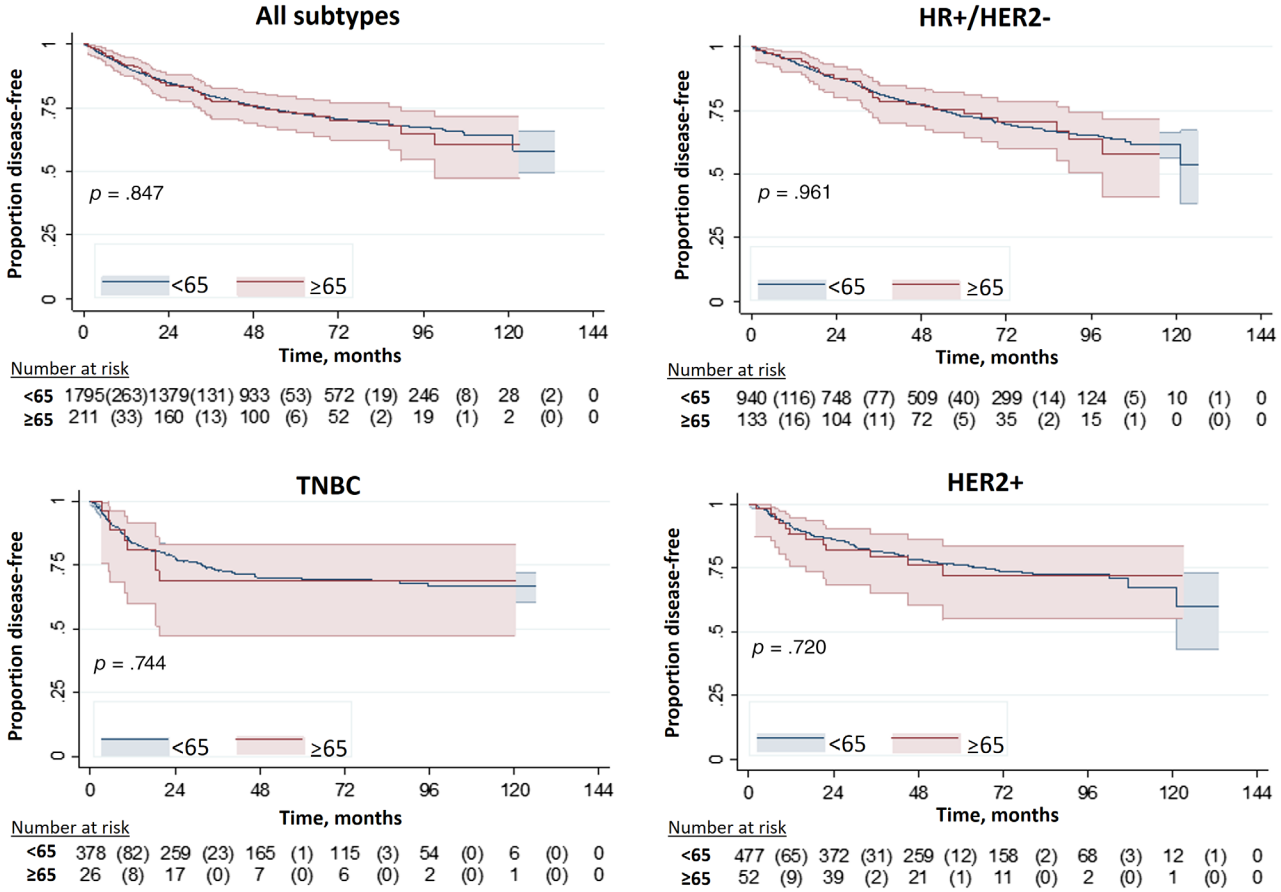

Figure 2. Disease-free survival by subtype and age.
Abbreviations: HER2, human epidermal growth receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer.

was used to further categorize HR+ tumors: those with an H-score ≥200 were labeled as luminal A, whereas those with an H-score <200 were labeled as luminal B [20]. HER2 was determined by IHC and deemed negative in cases of 0 (no membrane staining) or 1+ (weak and incomplete membrane staining) scores. Tumors were considered as HER2+ in cases of 3+ IHC staining or amplified fluorescence in situ hybridization (FISH) and HER2− in cases with 0 or 1+ IHC or 2+ IHC plus negative FISH [21]. Cases with negative estrogen receptor, progesterone receptor, and HER2 were labeled as TNBC.

Clinical and radiographic staging procedures were used for all patients. The tumors' T stage was defined using clinical or ultrasound measurements, whereas clinical N stage was defined by the presence of axillary lymph nodes on palpation or ultrasound examination. Metastatic disease was evaluated using various imaging methods. Clinical data were obtained from the electronic medical record and transferred to the dedicated database by coders.

Pathological complete response was defined according to the U.S. Federal Drug Administration criteria as no residual invasive tumor on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled lymph nodes (noninvasive breast residuals [ypT0/is, ypN0] were considered as pCR) [22]. The existence of invasive residuals in the breast and/or axilla was considered as residual invasive disease. After completing treatment, patients began surveillance following current recommendations and guidelines, with hormonal therapy prescribed to patients with HR+ disease. Patients with HER2+ disease completed 1 year of anti-HER2 therapy regardless of the amount of residual disease. DFS was calculated from the time of diagnosis to the date of first documentation of recurrent disease or last relapse-free visit, whereas OS was calculated from the date of diagnosis to the date of last visit or death.

Data are presented as medians, means, or proportions. Descriptive statistics, univariate, bivariate, and multivariate analyses, and regressions were carried out using STATA (version 14). Student's *t* test and Mann-Whitney *U* tests were used to compare variables between groups. Chi-square tests were used to compare baseline characteristics between age groups (≥65 years vs. <65 years). Logistic regression models including age, subtype, and other relevant clinical factors were used to assess which patient and tumor characteristics were associated with achieving a pCR. The Kaplan-Meier method was used to calculate survival outcomes. Cox proportional hazards regression models were used to estimate relapse and survival risk between subgroups. Cox regression models were adjusted for relevant variables such as age, T stage, N stage, and nuclear grade. Values of $p < .05$ were considered as statistically significant, and all presented *p* values are two-sided.

Table 3. Multivariate analyses for disease-free and overall survival

		Disease-free survival		Overall survival	
Subtype	**Characteristic**	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**	***p* value**
All subtypes	Age group				
	<65	1.0	—	1.0	—
	≥65	0.8 (0.58–1.03)	.079	0.8 (0.56–1.14)	.216
	Response				
	pCR	1.0	—	1.0	—
	<pCR	0.4 (0.34–0.51)	**<.001**	0.3 (0.21–0.39)	**<.001**
HR+/HER2−	Age group				
	<65	1.0	—	1.0	—
	≥65	0.8 (0.53–1.10)	.151	0.7 (0.42–1.14)	.148
	Response				
	pCR	1.0	—	1.0	—
	<pCR	0.5 (0.37–0.73)	**<.001**	0.3 (0.17–0.53)	**<.001**
TNBC	Age group				
	<65	1.0	—	1.0	—
	≥65	0.6 (0.29–1.40)	.263	0.9 (0.46–1.72)	.728
	Response				
	pCR	1.0	—	1.0	—
	<pCR	0.3 (0.14–0.41)	**<.001**	0.2 (0.11–0.35)	**<.001**
HER2+	Age group				
	<65	1.0	—	1.0	—
	≥65	1.1 (0.51–2.38)	.802	1.1 (0.51–2.50)	.765
	Response				
	pCR	1.0	—	1.0	—
	<pCR	0.4 (0.24–0.67)	**<.001**	0.3 (0.20–0.57)	**<.001**

Multivariate Cox model including age, T stage, N stage, nuclear grade. Values in bold are statistically significant.
Abbreviations: CI, confidence interval; HER2, human epidermal growth receptor 2; HR, hormone receptor; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

Results

During the studied period, 2,216 women with BC received NACT at INCan. Of these, 1,973 patients (89%) were aged <65 years, and 243 (11%) were aged ≥65 years. Median follow-up was 60.7 months. The most common BC subtype was HR+, HER2− (52.2%, *n* = 1,157), followed by HER2+ (25.9%, *n* = 574) and TNBC (21.9%, *n* = 485). The proportion of HR+, HER2− tumors was significantly higher in older women (60.1% vs. 51.2%), whereas the proportion of TNBC was lower (16.5% vs. 22.6%; *p* = .04). Older patients were more likely to have more advanced disease, with a larger proportion of T4 primary tumors and N2 axillary involvement. Patient characteristics are shown in Table 1.

Among older women with BC treated with NACT, 64 (26.3%) achieved a pCR, compared with 667 patients (35.3%) in the <65 group (*p* < .01). pCR was found to be associated with age, with an odds ratio for pCR of 0.66 (95% confidence interval [CI], 0.48–0.91) among older women (Fig. 1). This was driven mainly by the higher proportion of HR+, HER2− tumors among older women and by decreased pCR rates among older women with TNBC (22.5 vs. 45.4%, *p* = .01). Differences in pCR according to each subtype between both age groups are shown in Table 2.

Achieving a pCR was associated with improved DFS and OS regardless of age. Although older women achieved lower pCR rates, we found no differences in DFS between older and younger women when all subtypes were considered (5-year DFS 72.6% vs. 72.6%, *p* = .85; Fig. 2). Out of the entire population, 595 patients (27%) had a recurrence, out of which 397 (67%) were systemic and 168 (22%) were local. There was no difference in the proportion of systemic versus local responses between age groups (*p* = .24). Achieving less than a pCR was independently associated with a greater chance of recurrence when taking into account all tumor subtypes, although age was not. When the influence of both age and residual disease on DFS for each particular subtype was analyzed using multivariate analysis (Table 3), we found that being aged ≥65 years did not influence the risk of recurrence for any subtype (Fig. 2). Likewise, the achievement of a pCR remained as an independently significant protective factor for recurrence across all subtypes and all ages (Table 3). However, among older women with HR+, HER2− tumors, 5-year DFS was 78% (95% CI, 50%–91%) for those with a pCR and 73% (95% CI, 62%–81%) for those with less than pCR, and this difference was not significant (*p* = .86; Fig. 3). Age was not a predictor of

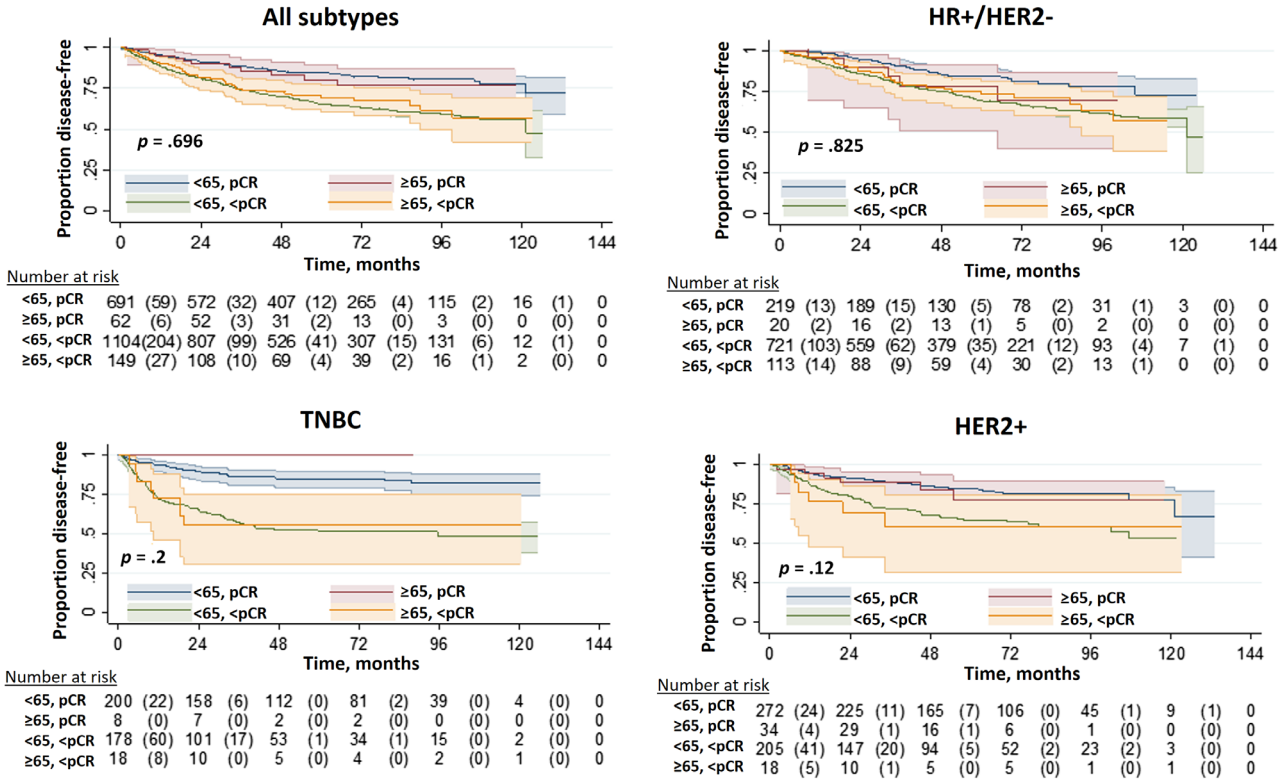

Figure 3. Disease-free survival by subtype according to age and achievement of a pathologic complete response.
Abbreviations: HER2, human epidermal growth receptor 2; HR, hormone receptor; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

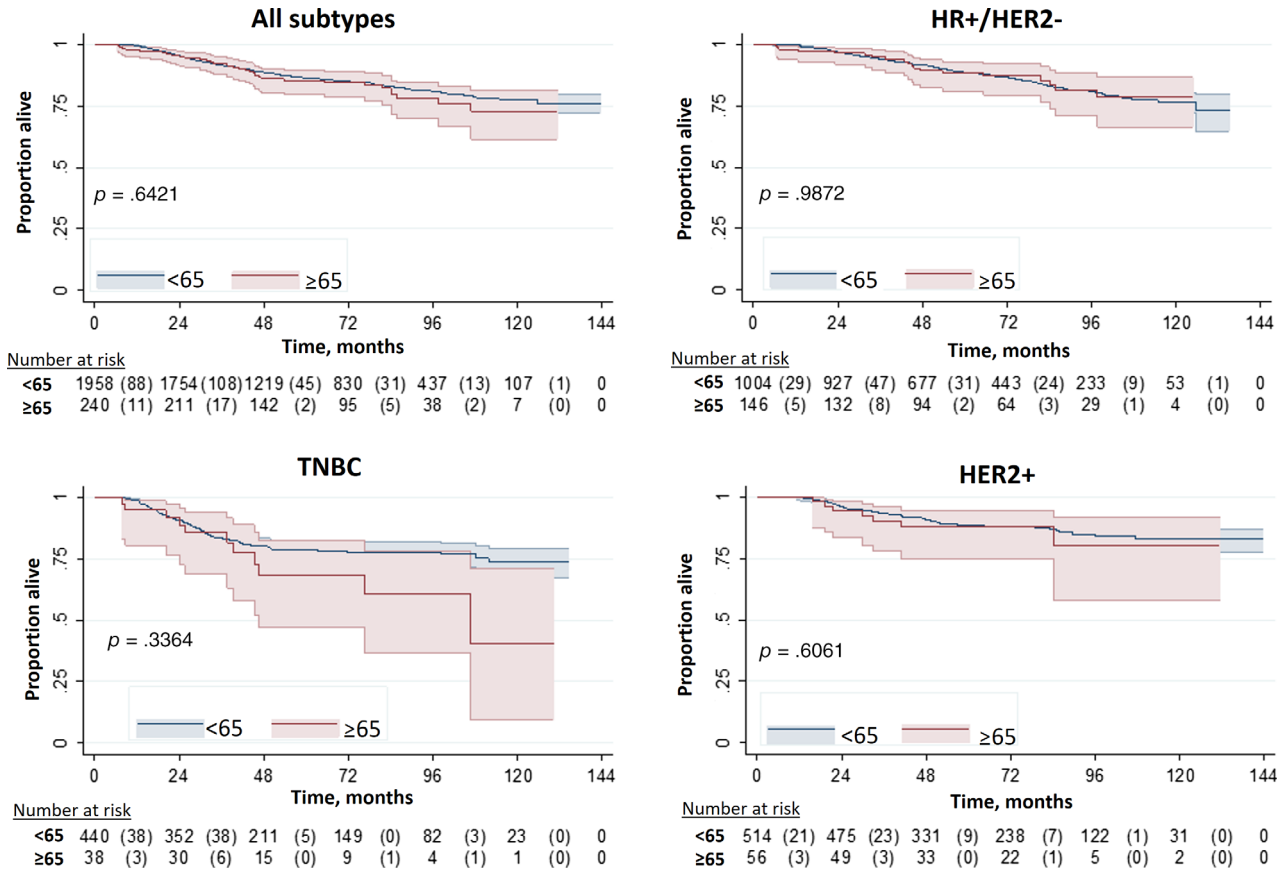

Figure 4. Overall survival by subtype and age.
Abbreviations: HER2, human epidermal growth receptor 2; HR, hormone receptor; TNB, triple-negative breast cancer.

worse OS (5-year OS for older women 85.3% vs. 86% for younger women, p = .64) when all tumor subtypes were analyzed, and this remained true for each individual subtype (Fig. 4 and Table 3). The only factor consistently associated with OS in our analysis was the achievement of a pCR.

Discussion

In this study, pCR rates among older women were significantly lower than among their younger counterparts. This difference in pCR was particularly significant for TNBC, whereas there was no difference for tumors that were HER2+ or HR+. However, despite having lower pCR rates, older adults with breast cancer had recurrence and survival rates comparable to those of younger women after receiving NACT. Importantly, achieving a pCR was significantly associated with improved survival among older women with BC, with the exception of those with HR+, HER2− disease.

NACT has become a standard of care for the treatment of locally advanced BC, and its use has been extended to early-stage disease, particularly for TNBC and HER2+ tumors, in which the response to neoadjuvant treatment may lead to modifications in adjuvant therapy [10, 23]. However, there is a lack of information regarding the use of NACT among older women with BC, and current guidelines issued by the International Society of Geriatric Oncology highlight the need for gathering additional evidence on the benefit of this strategy among older adults [16]. In a recently published meta-analysis of individual patient data from 4,756 women in ten NACT randomized trials by the Early Breast Cancer Trialists' Collaborative Group, for example, the median age of study participants was 49 years (interquartile range, 43–57), which is 13 years younger than the median age at diagnosis reported by the Surveillance, Epidemiology, and End Results Program in the U.S. [24]. Likewise, the aforementioned German pooled analysis of NACT clinical trials included a proportion of older adults of only 6.3%, even though older adults represent 44.1% of all patients with new BC cases in the U.S. [9, 24]. This situation, albeit at a lower proportion, is mirrored in real-world data from the U.S. A study examining the trends of NACT use using the National Cancer Database found that age was related with the indication for NACT, with older women less likely to receive it (16% of women aged ≥60 compared with 23% of those <60) [25].

One of the main reasons for the use of other strategies instead of NACT among older women with BC is the finding that older adults are less likely to present with more aggressive subtypes such as TNBC or HER2+ disease, for which NACT has been shown to be more effective [26]. The incidence of luminal tumors increases with age, whereas the proportion of basal-like tumors (which are more likely to be HR−) decreases, and this might affect responses to NACT, as shown in our study [27]. Additionally, the efficacy and safety of the use of adjuvant chemotherapy or targeted therapies for older adults who do not achieve a pCR after NACT is relatively unknown because a very low proportion of older women were included in RCTs exploring this strategy. The median age of patients enrolled in the CREATE-X RCT of adjuvant capecitabine in women with TNBC without a pCR after NACT was of 48 years (range, 25–74) [28], whereas in the KATHERINE RCT of adjuvant trastuzumab emtansine in women with HER2+ BC without a pCR after NACT, the median age was of 49 years (range, 24–79; 8.4% aged ≥65) [29]. Of note, neither RCT has reported on the efficacy or safety of the treatment in patients aged ≥65 years.

Another explanation for the lack of information regarding the real-world use of NACT for the treatment of older women with BC in developed countries is that most cases among older adults present at early stages. Large cohort studies from the U.S. and Western Europe have shown that the prevalence of stage III disease among older women presenting with localized BC is <15%, which is partially attributable to screening programs and to appropriate access to timely medical care [30]. Therefore, when treating older women with BC in developed countries, there is usually no need to decrease the tumor burden in order to make surgery possible or to achieve breast conservation, which is one of the strongest indications for NACT. Unfortunately, this is not the case in LMICs such as Mexico, where most women present with locally advanced disease [11, 31]. We have previously shown that almost half of older adults with BC treated in Mexico present with stage III or IV disease and therefore are not candidates for treatment with upfront surgery followed by adjuvant chemotherapy or hormonal treatment [32]. Interestingly, in our study very few older women receiving NACT were treated with breast conservation, which may reflect both local surgical practices and patient barriers for accessing radiotherapy after breast-conserving surgery, which may lead to the decision to perform mastectomy [33].

In our study, we found no difference in the rate of pCR between older and younger women with BC, with the exception of those with TNBC, in which younger women had higher pCR rates. A potential explanation for this finding is that intrinsic BC subtypes may differ according to age, even among women considered to have TNBC by IHC. Older women with TNBC are less likely to have basal-like disease than younger women and are more likely to have HER2-enriched, luminal, and normal-like tumors after undergoing PAM50 testing [27]. Because basal-like tumors are more likely to respond to chemotherapy, this might explain the lower pCR rate in older women in our study. Another potential explanation, which we did not measure, is that older women may be less likely to complete full NACT courses or may have more dose reductions and reduced dose intensity [34].

This study has limitations, including its retrospective design, the lack of a centralized pathology review of all cases, and the fact that subtype characterization was made using IHC instead of more advanced assays such as Ki67 staining or PAM50. In addition, the follow-up is relatively short, and more recurrences could take place with a longer follow-up, particularly among women with HR+ disease. Importantly, we had no detailed information regarding the complete treatment provided, including radiotherapy dosing, adherence to hormonal treatment, type of chemotherapy, or NACT dose intensity. Finally, we have no information on more detailed patient characteristics, including a

geriatric assessment, in order to understand if the patients that were treated with NACT had specific characteristics, such as a low prevalence of geriatric syndromes. However, our study also has several strengths. Most data on the use of NACT in older women come from RCTs, which usually include a highly selected population of older individuals, and thus our study provides information on a more heterogeneous, "real-world" patient population. Even though our patients were not included in an RCT and received varying treatment schedules, our results are fairly comparable to those previously reported, showing that older women with BC with indications for NACT benefit from this strategy as much as their younger counterparts [9]. Additionally, our data demonstrate that providing evidence-based treatment for older women with locally advanced BC in a LMIC is feasible and that older women should not be denied NACT if clinically indicated. This is particularly relevant because this issue is shared by many LMICs, and thus our results could prove useful for oncologists working across various settings globally.

Conclusion

Our results show that although older women have a lower rate of pCR (which is mostly due to the lower proportion of TNBC), they have similar outcomes to their younger counterparts when treated with NACT in a real-world clinical setting. Our results are relevant because they provide information about a clinical scenario that has not been examined thoroughly in clinical trials and because they highlight the feasibility of administering NACT among older adults. Furthermore, our results highlight the relevance of better understanding the management of TNBC in older patients with BC and of evaluating further strategies to improve response rates and survival among older persons.

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Disclosures

The authors indicated no financial relationships.

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For Further Reading:
Temidayo Fadelu, Ruth Damuse, Joarly Lormil et al. Patient Characteristics and Outcomes of Nonmetastatic Breast Cancer in Haiti: Results from a Retrospective Cohort. ***The Oncologist*** 2020;25:e1372–e1381.

Implications for Practice:
Patients with breast cancer in Haiti have poor outcomes. Prior studies show that most Haitian patients are diagnosed at later stages. However, there are no rigorous studies describing how late-stage diagnosis and other prognostic factors affect outcomes in this population. This study presents a detailed analysis of survival outcomes and assessment of prognostic factors in patients with nonmetastatic breast cancer treated in Haiti. In addition to late-stage diagnosis, other unfavorable prognostic factors identified were young age and estrogen receptor-negative disease. The study also highlights that the availability of basic breast cancer treatment in Haiti can lead to promising early patient outcomes.