


# Pathological Response to Neoadjuvant Chemotherapy and the Molecular Classification of Locally Advanced Breast Cancer in a Latin American Cohort

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

**Key Words.** Breast neoplasm • Pathological response • Chemotherapy • Surgery

## ABSTRACT

**Background.** The majority of patients with breast cancer in Colombia are admitted into oncological centers at locally advanced stages of the disease (53.9%). The aim of this study was to describe the pathological response obtained with neoadjuvant chemotherapy (NACT) according to the molecular classification of breast cancer in patients with locally advanced tumors treated within the National Cancer Institute (NCI) Functional Breast Cancer Unit (FBCU) in Bogotá, Colombia.

**Materials and Methods.** This was an observational, descriptive, historical cohort study of patients with locally advanced breast cancer treated within the NCI FBCU.

**Results.** We included 414 patients who received NACT and surgical management. Most patients had luminal B HER2-negative tumors ( $n = 134$ , 32.4%). The overall rate of pathological complete response (pCR) ypT0/ypN0 was 15.2% ( $n = 63$ ). Tumors that presented the highest rate of pCR were pure HER2, at 40.5% ( $n = 15$ ; odds ratio [OR], 6.7); however,

with a follow-up of 60 months, only the triple negative tumors presented a statistically significant difference for event-free survival (EFS; median recurrence time, 18 months; range, 1–46) and overall survival (OS; median follow-up, 31 months; range 10–57). The molecular subtype that most recurrences presented was luminal B HER2 negative, at 38.3% ( $n = 28$ ). The majority of recurrences (93.2 %;  $n = 68$ ; OR, 5.9) occurred in patients in whom no pathological response was obtained (Chevallier 3 and 4).

**Conclusion.** Pathological response in locally advanced tumors is related to the molecular subtype of breast cancer, finding higher pCR rates in pure HER2 and triple-negative tumors. A direct relationship was found between disease recurrences and the pathological response, evidencing greater tumor recurrence in patients who did not respond to NACT (Chevallier 3 and 4). EFS and OS were greater in patients with pCR, with statistical significance only in triple-negative tumors. *The Oncologist* 2019;24:e1360–e1370

**Implications for Practice:** This research article is of scientific interest, because it describes the clinical and pathological features and analyzes the correlation between pathological response to neoadjuvant chemotherapy and the molecular classification of locally advanced breast cancer in patients treated in the National Cancer Institute in Bogotá, Colombia. It was found that pathological response is related to the molecular subtype of breast cancer. In addition, there is a direct relationship between disease recurrences and pathological response. The survival results were greater in patients with pathological complete response.

## INTRODUCTION

Breast cancer is the second most common cancer in the world and ranks first in frequency in women. Approximately 2.1 million new cases of cancer were diagnosed during

2018 (11.6% of all types of cancer). Presenting worldwide incidence of 46.3 per 100,000 people and mortality of 13.0 per 100,000 people [1].

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According to data from GLOBOCAN 2018, 13,380 new cases of breast cancer were diagnosed in Colombia within that year (an incidence of 44.1 per 100,000 people), being 13.1% of the total of patients diagnosed with cancer in the country. Among the female population, cases of breast cancer rank first in incidence, at 24.8%. Mortality in both sexes has a rate of 11.9 per 100,000 people, representing 3,702 deaths per year [1].

Breast cancer is a heterogeneous disease, with variable behavior according to the molecular subtype of each tumor. In 2016, Vasconcelos et al. classified breast cancer based on histology and immunohistochemical staining, taking into account five subtypes: luminal A (hormone-receptor-positive, human epidermal growth factor 2 [HER2] negative, low Ki67 [ $<30\%$ ]); luminal B HER2-negative (hormone-receptor-positive, HER2-negative, high Ki67 [ $>30\%$ ]); luminal B HER2-positive (hormone-receptor-positive, HER2-positive, any Ki67 value); pure HER2 tumors (hormone-receptor-negative, HER2-positive, any Ki67 value); and the basaloid or triple negative, which presents negativity for both hormone receptors and HER2 [2]. In our study, to differentiate luminal A and luminal B HER2-negative tumors, the cutoff point for the Ki67 marker was 20%, following the recommendation of the 13th International Conference on Breast Cancer in St. Gallen [3].

According to the PRECAMA study, which was coordinated by the International Agency for Research on Cancer, carried out with premenopausal women from four Latin American countries (Chile, Colombia, Costa Rica, and Mexico), it was evidenced that 72% of the tumors were hormone receptor-positive, 19% were HER2 positive, and 21% were triple negative [4]. Another study conducted at the local level, with 114 participants, showed that in Colombia the luminal A subtype is the most frequent, in 38.5% of tumors, followed by luminal B (32.4%), triple negative (15, 8%), and HER2-positive, at 13.1% [5].

Currently, the management of locally advanced breast cancer (stages IIB, IIIA, IIIB, IIIC) has neoadjuvant chemotherapy (NACT) as the first line of treatment [6]. This therapy pursues three objectives: first, decreasing tumor size to facilitate surgical management and obtain better cosmetic results; second, assessing chemosensitivity in vivo; and third, achieving the treatment of micrometastasis [7].

The meta-analysis of Cortazar et al., published in 2014, included 12 studies within a population of 11,955 patients for evaluating the benefits of NACT, thus showing that the pathological complete response (pCR), defined as absence of infiltrating tumor in both breast and axilla (ypT0-is/ypN0), was related to greater event-free survival (EFS; hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.39–0.51) and a greater overall survival (OS; HR, 0.36; 95% CI, 0.30–0.44). The association between pCR and better long-term results was stronger in patients with triple negative breast cancer (EFS: HR, 0.24; 95% CI, 0.18–0.33; OS: HR, 0.16; 95% CI, 0.11–0.25); a similar behavior was evidenced in those patients with tumors that were hormone receptor negative and HER2 positive and who were administered trastuzumab (EFS: HR, 0.15; 95% CI, 0.09–0.27; OS: HR, 0.08; 95% CI, 0.03–0.22), inferring that the prognostic value is higher in the more aggressive tumor subtypes [8].

In the meta-analysis published in 2018 by the Early Breast Cancer Trialists' Collaborative Group, within a population of 4,756 women with early breast cancer, 69% of the patients who received NACT had partial or complete clinical response. Additionally, a conservative breast surgery rate of 65% was achieved. At 15-year follow-up, a higher rate of local recurrence was observed in patients who received NACT (21.4%) versus patients who received adjuvant chemotherapy (15.9%), with an absolute difference of 5.5% (95% CI 2.4–8.6) and relative risk (RR) of 1.37 (95% CI, 1.17–1.61;  $p = .0001$ ). There were no differences regarding distant recurrences (38.2% neoadjuvant vs. 38.0% adjuvant; RR, 1.02; 95% CI, 0.92–1.14;  $p = .66$ ), death by cancer (34.4% vs. 33.7%; RR, 1.06; 95% CI, 0.95–1.18;  $p = .31$ ), or deaths from other causes (40.9% vs. 41.2%; RR, 1.04; 95% CI, 0.94–1.15;  $p = .45$ ) [9].

The purpose of this study is to describe the pathological response obtained with NACT according to the molecular classification of breast cancer in patients with locally advanced tumors treated within the National Cancer Institute (NCI) Functional Breast Cancer Unit (FBCU) in Bogotá, Colombia. Colombia is known for being a country with a mestizo and multicultural population; it is for this reason that the results could be extrapolated to the rest of the countries of the region, and treatment guidelines could be developed for breast cancer based on the findings presented in this article.

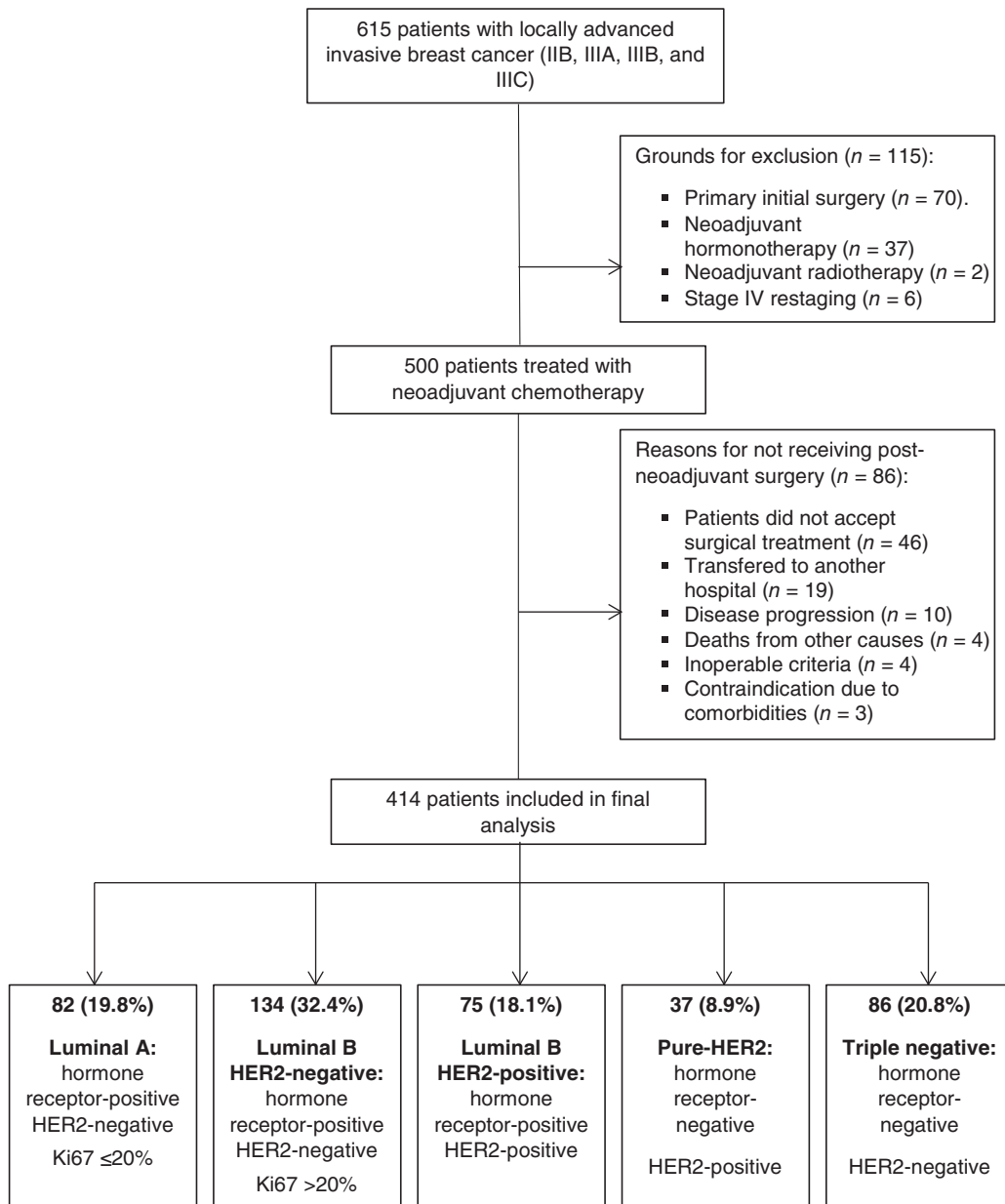
## MATERIALS AND METHODS

An observational, descriptive, historical cohort study was carried out, approved by the NCI Institutional Ethics Committee. This study included 414 patients with confirmed diagnosis of invasive breast cancer at locally advanced stages who received NACT and surgical management of the breast and axilla within the NCI FBCU in Bogotá, Colombia, during the period between September 1, 2013, and August 31, 2017. Patients who received neoadjuvant hormone therapy, surgery as initial treatment, or neoadjuvant radiotherapy; those who restaged as clinical stage IV; and those who for some reason did not receive surgical management after neoadjuvant therapy were excluded (Fig. 1).

The information on clinical and sociodemographic characteristics of the patients was taken from data recorded in the FBCU database and the NCI SAP electronic health records system. Data were collected by three of the authors and then compiled in an electronic database based on the REDCap platform, and the quality was evaluated under supervision of an NCI research monitor.

The variables analyzed in this study were age in completed years, body mass index, menopausal status, histopathological characteristics of the biopsy, initial clinical stage of the disease, NACT regimen administered, clinical response obtained according to scale of the World Health Organization [10], type of surgical intervention, pathological response according to Chevallier criteria, (defining pCR as ypT0/ypN0) [11], adjuvant treatment offered, presence of recurrence and disease progression, treatment thereof, and follow-up.

The statistical analysis of categorical and nominal variables was carried out using absolute and relative frequency



**Figure 1.** Flow diagram of patient inclusion. Ki67, proliferation marker. 20% cut-off point, recommendation of the 13th International Breast Cancer Conference of St. Gallen [3].

measurements, whereas for continuous variables, measures of central tendency and measures of dispersion were used.

Response of the various tumor molecular subtypes and their clinical behavior with respect to the NACT administered, the surgical treatment performed, and adjuvant management offered were assessed.

For the survival analysis, events corresponding to death from any cause and disease-free period were quantified. For EFS and OS, date of diagnosis was taken as the moment of admission to the cohort. OS analysis was performed based on 406 patients, because 8 patients were lost during follow-up. Regarding EFS, this was calculated on a total of 412 patients, as two patients who had disease progression during treatment with NACT were excluded.

The events were taken as numerators to estimate incidence rates, taking as a denominator the total time

contributed by patients of the cohort. These rates were estimated by taking into account the risk of bias caused by the presence of differential monitoring. Survival functions were estimated for each of the two outcomes (OS and EFS) using the Kaplan-Meier method. These functions took into account the loss of follow-up and were handled as censoring on the right. In addition, survival functions were compared using the log-rank test.

In addition, two logistic regression models were designed to calculate the odds ratios (OR): in the first one, the variable of interest was pathological response according to clinical variables (age, histological grade, histological type, lymph node involvement, molecular subtype); and in the second one, the variable of interest was tumor recurrence according to clinical variables (molecular subtype of the tumor and pathological response).

Statistical analysis of the information was made through The R Project software v.3.5.1, with a free license for its use.

## RESULTS

Out of 1,293 patients who were admitted to the NCI FBCU between September 1, 2013, and August 31, 2017, 615 (47.6%) were in locally advanced stages (IIB, IIIA, IIIB, and IIIC), 460 (35.5%) were in early stages (I and IIA), and 218 (16.9%) patients were in the metastatic stage (IV).

Of the 615 patients with locally advanced tumors, 115 patients were excluded for the following reasons: 70 (11.4%) had initial management with surgery, 37 (6.0%) patients were treated with neoadjuvant hormone therapy, 2 (0.3%) were treated with neoadjuvant radiotherapy, and 6 patients were restaged because of distant metastasis.

A total of 500 patients received the complete NACT regimen. Nonetheless, for the analysis of this study, only the 414 patients who were taken to surgical management of the primary tumor in the NCI were included. The 86 excluded patients were not submitted to surgery of the primary tumor for the following reasons: 46 patients did not accept surgical treatment, 19 patients were transferred to another institution by their insurer, 10 patients presented disease progression and did not receive any surgical treatment, 4 died from a cause different than the disease, 4 were deemed as inoperable by the surgeon who evaluated them, and the remaining 3 patients had comorbidities that prevented surgical management. These last seven patients were referred to treatment with radiotherapy for local control of the disease (Fig. 1).

In total, 414 patients were included (median age, 54 years; range, 23–81); 63.0% ( $n = 261$ ) of the patients were postmenopausal (Table 1).

With respect to the initial clinical stage, most patients were classified in clinical stage IIIB (51.0%,  $n = 211$ ), and the most frequent tumor histological type was the ductal carcinoma not-otherwise-specified (NOS), identified in 257 patients (62.1%). A total of 230 (55.6%) patients had size T4b tumors, and 378 (91.3%) patients had clinical lymph node involvement (cN+); grade 2 tumors were the most frequent, found in 53.1% ( $n = 220$ ) of biopsies (Table 1).

Regarding classification by molecular subtypes of breast cancer, luminal A tumors were 19.8% of cases, with 82 patients; luminal B HER2-negative was described in 134 patients (32.4%); luminal B HER2 positive was 18.1%, with 75 patients; 37 patients presented pure HER2 tumors (8.9%); and the triple-negative tumors reached 20.8%, with 86 patients. The cut-off point for the Ki67 marker was 20% to differentiate between luminal A and luminal B, taking the recommendation of the 13th St. Gallen International Breast Cancer Conference [3], which was in force at the time of start of collection of patients included in this study (Fig. 1).

As a neoadjuvant treatment, the most frequently administered chemotherapy was that of adriamycin + cyclophosphamide – taxane in 58.2% ( $n = 241$ ) of patients. Of the 414 patients in the study, 26.1% ( $n = 108$ ) were given anti-HER2 therapy with trastuzumab (Table 2).

Regarding the clinical response to neoadjuvant, disease control was achieved (partial response + complete

response + stable disease) in 392 (94.7%) patients, whereas there was disease response (partial response + complete response) in 318 (76.8%) patients. Only in 18.6% ( $n = 77$ ) of the patients was a clinical complete response (cCR) obtained (Table 3).

Conservative surgical management was performed in 36.7% ( $n = 152$ ) of patients, and modified radical mastectomy was performed in 262 (63.3%) patients. Because their tumors were locally advanced tumors, all patients ( $n = 414$ , 100%) were taken to axillary lymphadenectomy. Only 24.4% ( $n = 64$ ) of the patients taken to radical surgical management underwent immediate breast reconstruction (Table 2); reconstruction with tissue expander or implant was the most frequent, occurring in 53.1% ( $n = 34$ ) of the cases.

The overall pCR ypT0/ypN0 rate was 15.2% ( $n = 63$ ), and the ypT0-is/ypN0 rate was 22.2% ( $n = 92$ ). Taking luminal A tumors as a reference category, it was found that tumors with the highest pCR rate were pure HER2 tumors, at 40.5% ( $n = 15$ ; OR, 6.7; 95% CI, 2.1–24.8), and triple negative, at 23.2% ( $n = 20$ ; OR, 3.7; 95% CI, 1.3–12.4). Thirdly, there are the luminal B HER2-positive tumors, at 20% ( $n = 15$ ; OR, 3.4; 95% CI, 1.1–11.6); the luminal A and luminal B HER2-negative tumors achieved pCR in 6.1% ( $n = 5$ ) and 6.0% ( $n = 8$ ; OR, 1.1; 95% CI, 0.3–4.0), respectively (Table 3). Patients at stage IIIA achieved pCR 20.9% ( $n = 18$ ) of the time; rates for those with stages IIB and IIIB were 16.0% ( $n = 15$ ) and 14.2% ( $n = 30$ ), respectively, and no patient with stage IIIC achieved pCR.

Of the cN+ patients, 43.9% ( $n = 166$ ) were reported as ypN0. A total of 32.5% ( $n = 63$ ) of patients who were ypN0 presented pCR. Among the patients who achieved pCR (ypT0), 98.4% ( $n = 62$ ;  $p = .00001$ ) had negative lymph nodes in the axillary dissection (ypN0).

The highest rate of pCR was evidenced in grade 3 tumors, at 21.3% ( $n = 37$ ), and the adriamycin + cyclophosphamide – taxane + trastuzumab (AC–TH) regimen achieved the highest pCR rate, with 29.9% ( $n = 26$ ).

Pathological complete response was obtained in 17.1% ( $n = 44$ ) of the ductal NOS tumors, 12.1% ( $n = 14$ ) for pure ductal tumors, 8.3% ( $n = 1$ ) for lobular tumors, and 13.8% ( $n = 4$ ) for other histological types.

Adjuvant chemotherapy was administered to 17 (4.1%) patients, most of them with triple-negative tumors ( $n = 11$ , 64.7%) with evidence of residual tumor in the surgical specimen. All of the patients were treated with adjuvant radiotherapy; however, only 92.3% ( $n = 382$ ) of the patients received it at the NCI. The remaining 32 patients did not receive adjuvant radiotherapy for the following reasons: 13 of them abandoned the treatment, 13 had disease progression, 3 were transferred to other hospitals, 2 died, and 1 patient did not receive it because of pulmonary comorbidity. For the hormonal treatment of patients with hormone-receptor-positive, tamoxifen was the drug of greatest choice 41.9% ( $n = 127$ ) of the time (Table 2).

With a follow-up of 60 months, the overall recurrence rate (local, regional, and systemic) was 17.6% ( $n = 73$ ), with a median recurrence time of 18 months (1–46 months). Distant recurrence occurred in 68.5% ( $n = 50$ ) of these patients, 21.9% ( $n = 16$ ) of patients relapsed locally, and 9.6% ( $n = 7$ ) relapsed at a regional level. Taking luminal A

**Table 1.** Demographic and clinical characteristics of patients included in the study

Characteristics	Total of patients ( <i>n</i> = 414), <i>n</i> (%)
Median age (range), yr	54 (23–81)
Gender	
Female	412 (99.5)
Male	2 (0.5)
Menopausal status	
Menopausal	261 (63.0)
Premenopausal	153 (37.0)
Body mass index, kg/m <sup>2</sup>	
Low weight (<18)	4 (1.0)
Normal (18–25)	155 (37.4)
Overweight (25.1–29.9)	173 (41.8)
Class I obesity (30–34.9)	62 (15.0)
Class II obesity (35–39.9)	14 (3.4)
Class III obesity (>40)	6 (1.4)
Tumor size	
Tx	1 (0.2)
T1	3 (0.7)
T2	107 (25.8)
T3	71 (17.1)
T4a	1 (0.2)
T4b	230 (55.6)
T4c	1 (0.2)
T4d	–
Lymph node involvement	
N0	36 (8.7)
N1	193 (46.6)
N2a	159 (38.4)
N2b	3 (0.7)
N3a	2 (0.5)
N3b	4 (1.0)
N3c	17 (4.1)
Clinical stage	
IIB	94 (22.7)
IIIA	86 (20.8)
IIIB	211 (51.0)
IIIC	23 (5.6)
Tumor histology	
Ductal not-otherspecified	257 (62.1)
Pure ductal	116 (28.0)
Lobular	12 (2.9)
Other types	29 (7.0)
Tumor grade (SBR)	
1	20 (4.8)
2	220 (53.1)
3	174 (42.0)

(continued)

**Table 1.** (continued)

Characteristics	Total of patients ( <i>n</i> = 414), <i>n</i> (%)
Estrogen receptors	
Positive	285 (68.8)
Negative	129 (31.2)
Progesterone receptors	
Positive	249 (60.1)
Negative	149 (36.0)
No data	16 (3.9)
Human epidermal growth factor 2	
Positive (3+)	99 (23.9)
Equivocal (2+)	40 (9.7)
Negative (0/1+)	274 (66.2)
No data	1 (0.2)
Ki67	
≤20%	99 (23.9)
>20%	307 (74.2)
No data	8 (1.9)

Ki67, cellular marker for proliferation; SBR; Scarff-Bloom-Richardson.

tumors as a reference category, the molecular subtype that showed the most relapses was luminal B HER2 negative, at 38.3% (*n* = 28; OR, 2.7; 95% CI, 1.2–7.1), followed by the triple negative, at 31.5% (*n* = 23; OR, 4.3; 95% CI, 1.8–11.6), and the luminal B HER2 positive, in 11 (15.1%; OR, 2.4; 95% CI 0.9–6.8) cases, whereas luminal A presented seven (9.6%) relapses and pure HER2 presented four relapses (5.5%; OR, 2.3; 95% CI 0.5–8.5). A total of 93.2% (*n* = 68; OR, 5.9; 95% CI, 2.0–25.2) of relapses occurred in patients in whom no pathological response was obtained (Chevallier 3 and 4); the reference group was that of patients with pCR (Chevallier 1; Table 4).

The organs most frequently affected by metastatic involvement were bones, with 25.8% (*n* = 25), followed by lungs and central nervous system, with 16.5% (*n* = 16) each. Regarding the 16 patients who presented local recurrence, 6 of them underwent conservative surgery and 10 underwent radical surgery. Of the 73 patients who relapsed (*n* = 28), 38.3% received single therapy and (*n* = 45) 61.6% received combined therapy; 15.1% (*n* = 11) of patients received chemotherapy in monotherapy, whereas among those who received combined treatment, 13 (17.8%) patients were treated with radiotherapy plus chemotherapy, and 4.1% (*n* = 3) of patients did not receive any recurrence management because they died before starting treatment. Despite having received some type of treatment for recurrence, 42.5% (*n* = 31) of these patients had disease progression.

A total of 41 deaths were recorded, representing 10.1% of the total patients, with a median follow-up time of 31 months (10–57 months). A total of 78.0% (*n* = 32) of these deaths were due to the disease, whereas the remaining nine deaths (22.0%) were due to other causes



**Table 2.** Treatments administered to cohort patients

Treatment	Total of patients, n (%)
Neoadjuvant chemotherapy regimen (n = 414)	
AC-T	241 (58.2)
AC-TH	87 (21.0)
AC-TC	18 (4.3)
TC	21 (5.1)
AC	3 (0.7)
Other	44 (10.6)
Surgical treatment (n = 414)	
Conservative surgery	152 (36.7)
Radical surgery	262 (63.3)
Immediate breast reconstruction (n = 262)	
Yes	64 (24.4)
No	198 (75.6)
Adjuvant treatments received (n = 414)	
Hormonotherapy	303 (73.2)
Chemotherapy	17 (4.1)
Radiotherapy	377 (91.1)
Target therapy	115 (27.8)
None	13 (3.1)

Abbreviations: AC, adriamycin + cyclophosphamide; AC-T, adriamycin + cyclophosphamide – taxane; AC-TH, adriamycin + cyclophosphamide – taxane + trastuzumab; AC-TC, adriamycin + cyclophosphamide – taxane + carboplatin; TC, taxane + carboplatin.

(eight patients suffered acute myocardial infarction and the remaining died from infectious pulmonary process).

The EFS and OS functions were calculated with the non-parametric Kaplan-Meier estimator. Figures 2 and 3 show graphics and *p* value associated with the log-rank test on the hypothesis of equality of the EFS and OS curves, respectively. The triple-negative molecular subtype (EFS: 87.5%; *p* = .01; OS: 93.3%; *p* = .02) was the only one with statistical significance in the presence of pCR.

## DISCUSSION

According to the 2015 statistical yearbook published by the NCI, 53.9% of patients treated for breast cancer are in locally advanced stages of the disease [12]. In this study, it was identified that 47.6% (*n* = 615) of the patients were in such clinical stages; this percentage was lower because the NCI FBCU had lack of prior treatment as a criterion for the inclusion of patients in the study. This study is unique because it collects patients with breast cancer exclusively in locally advanced stages, whereas similar studies have taken as a population patients with breast cancer in early stages of the disease, and some have included a portion of patients in locally advanced stages, but only IIB and IIIA [13].

The biological behavior of breast cancer is variable so, to properly characterize tumors to evaluate pathological responses to treatment with NACT, has repercussions with

respect to the survival of patients because pCR is a prognosis factor for both OS and EFS [11, 14, 15].

Based on Perou's classification, the incidence of tumors varies depending on the molecular subtype; luminal A tumors are described as 30%–40% of all invasive cancers, luminal B HER2-negative tumors represent 20%–30%, tumors that overexpress HER2 reach 12%–20%, and triple negatives become 15%–20% of the total of tumors [16]. The data obtained in this study in terms of incidence according to molecular subtypes are similar to those of the international literature; only a decrease in the incidence of luminal A tumors was found, which made up 19.8% of the cases. The other tumor subtypes had similar incidences to those reported by Fragomeni et al. at the Surgical Oncology Clinics of North America in 2018 [16].

In this study, the pathological response was taken according to Chevallier's criteria [11], which define pCR as the absence of invasive and in situ carcinoma in the breast and axillary nodes (ypT0/ypN0); other authors define it as the absence of invasive cancer in breast and axillary nodes, regardless of the presence of carcinoma in situ (ypT0-is/ypN0). It can also be defined as the absence of invasive carcinoma in the breast, regardless of the presence of carcinoma in situ or axillary node involvement (ypT0/is) [17].

The overall rates of pCR were 15.2% (*n* = 63) for ypT0/ypN0 and 22.2% (*n* = 92) for ypT0-is/ypN0, which were similar to those obtained by Cortazar et al., with ypT0/ypN0 13.0%, ypT0-is/ypN0 18.0%, and ypT0-is22.0% [8], whereas Cirier et al. obtained a pCR ypT0/ypN0 rate of 16.0% [18].

HER2-positive tumors have an aggressive behavior but present better rates of pCR compared with other molecular subtypes of breast cancer, achieving pCR rates of up to 66.7%, described by Buzdar [19]. In this study, we divided the HER2-positive tumors into two groups: luminal B HER2 positive and pure HER2; thus, we obtained pCR rates of 20% (*n* = 15) and 40.5% (*n* = 15), respectively. These data are comparable to those by Pierga et al., who identified a pCR rate of 26.0% in this tumor subtype [20].

The NOAH study, with a 3-year follow-up for the treatment of patients with neoadjuvant trastuzumab and until completing 52 weeks in adjuvant therapy, showed an EFS percentage of 71%, whereas patients in the control group had 56%. In addition, patients who received anti-HER2 treatment presented a better pCR rate (RR, 2.07; 95% CI, 1.41–3.03) and a reduction in the risk of relapse by 33% (RR, 0.67; 95% CI, 0.48–0.94). However, there was no benefit in the OS (RR, 0.67; 95% CI, 0.39–1.15) [21]. Valachis et al. also concluded that patients receiving neoadjuvant treatment with trastuzumab had higher pCR rates (RR, 1.85; 95% CI, 1.39–2.46) [22].

A pCR rate of 23.2% was obtained for triple-negative tumors (*n* = 20), which was lower than that reported by other authors. The GeparSixto study, which included 315 patients who received NACT with paclitaxel plus liposomal doxorubicin plus bevacizumab, with or without weekly carboplatin, found pCR in 53.2% of patients treated with carboplatin compared with 36.9% in those who did not receive this drug (*p* = .005) [23]. Wang-Lopez et al. also

**Table 3.** Specific pathological and clinical response for each molecular subtype of breast cancer in patients included in the cohort

Subtype	Pathological response (Chevallier criteria), <i>n</i> (%)				Clinical response (WHO criteria), <i>n</i> (%)			
	Class 1	Class 2	Class 3	Class 4	Complete response	Partial response	Stable disease	Disease progression
Luminal A ( <i>n</i> = 82, 19.8%)	5 (6.1)	4 (4.9)	25 (30.5)	48 (58.5)	6 (7.3)	50 (61.0)	25 (30.5)	1 (1.2)
Luminal B HER2 negative ( <i>n</i> = 134, 32.4%)	8 (6.0)	6 (4.5)	44 (32.8)	76 (56.7)	21 (15.7)	81 (60.4)	27 (20.1)	5 (3.7)
Luminal B HER2 positive ( <i>n</i> = 75, 18.1%)	15 (20.0)	10 (13.3)	16 (21.3)	34 (45.3)	21 (28.0)	42 (56.0)	9 (12)	3 (4.0)
Pure-HER2 ( <i>n</i> = 37, 8.9%)	15 (40.5)	6 (16.2)	8 (21.6)	8 (21.6)	13 (35.1)	24 (64.9)	0 (0)	0 (0)
Triple negative ( <i>n</i> = 86, 20.8%)	20 (23.2)	3 (3.5)	28 (32.6)	35 (40.7)	16 (18.6)	44 (51.2)	13 (15.1)	13 (15.1)
Total ( <i>n</i> = 414, 100%)	63 (15.2)	29 (7.0)	121 (29.2)	201 (48.6)	77 (18.6)	241 (58.2)	74 (17.9)	22 (5.3)

Abbreviations: HER2, human epidermal growth factor 2; WHO, World Health Organization.

**Table 4.** Absolute and relative frequencies (%) of molecular subtypes of breast cancer, the pathological response, and recurrence

Recurrence	Luminal A	Luminal B HER2 negative	Luminal B HER2 positive	Pure HER2	Triple negative
Total ( <i>n</i> = 73, 100%), <i>n</i> (%)	7 (9.6)	28 (38.3)	11 (15.1)	4 (5.5)	23 (31.5)
Local ( <i>n</i> = 16, 21.9%)	1 (6.2)	5 (31.2)	3 (18.8)	2 (12.5)	5 (31.3)
Regional ( <i>n</i> = 7, 9.6%)		3 (42.8)	2 (28.6)	1 (14.3)	1 (14.3)
Distant ( <i>n</i> = 50, 68.5%)	6 (12.0)	20 (40.0)	6 (12.0)	1 (2.0)	17 (34.0)
Class 1 ( <i>n</i> = 3, 4.1%), <i>n</i> (%)				2 (66.7)	1 (33.3)
Local				2 (66.7)	
Regional					
Distant					1 (33.3)
Class 2 ( <i>n</i> = 2, 2.7%), <i>n</i> (%)		1 (50.0)			1 (50.0)
Local					1 (50.0)
Regional					
Distant		1 (50.0)			
Class 3 ( <i>n</i> = 15, 20.5%), <i>n</i> (%)	2 (13.3)	6 (40.0)	1 (6.7)		6 (40.0)
Local		1 (6.7)			1 (6.7)
Regional					
Distant	2 (13.3)	5 (33.3)	1 (6.7)		5 (33.3)
Class 4 ( <i>n</i> = 53, 72.6%), <i>n</i> (%)	5 (9.4)	21 (39.6)	10 (18.9)	2 (3.8)	15 (28.3)
Local	1 (1.9)	4 (7.5)	3 (5.7)		3 (5.7)
Regional		3 (5.7)	2 (3.8)	1 (1.9)	1 (1.9)
Distant	4 (7.5)	14 (26.4)	5 (9.4)	1 (1.9)	11 (20.8)

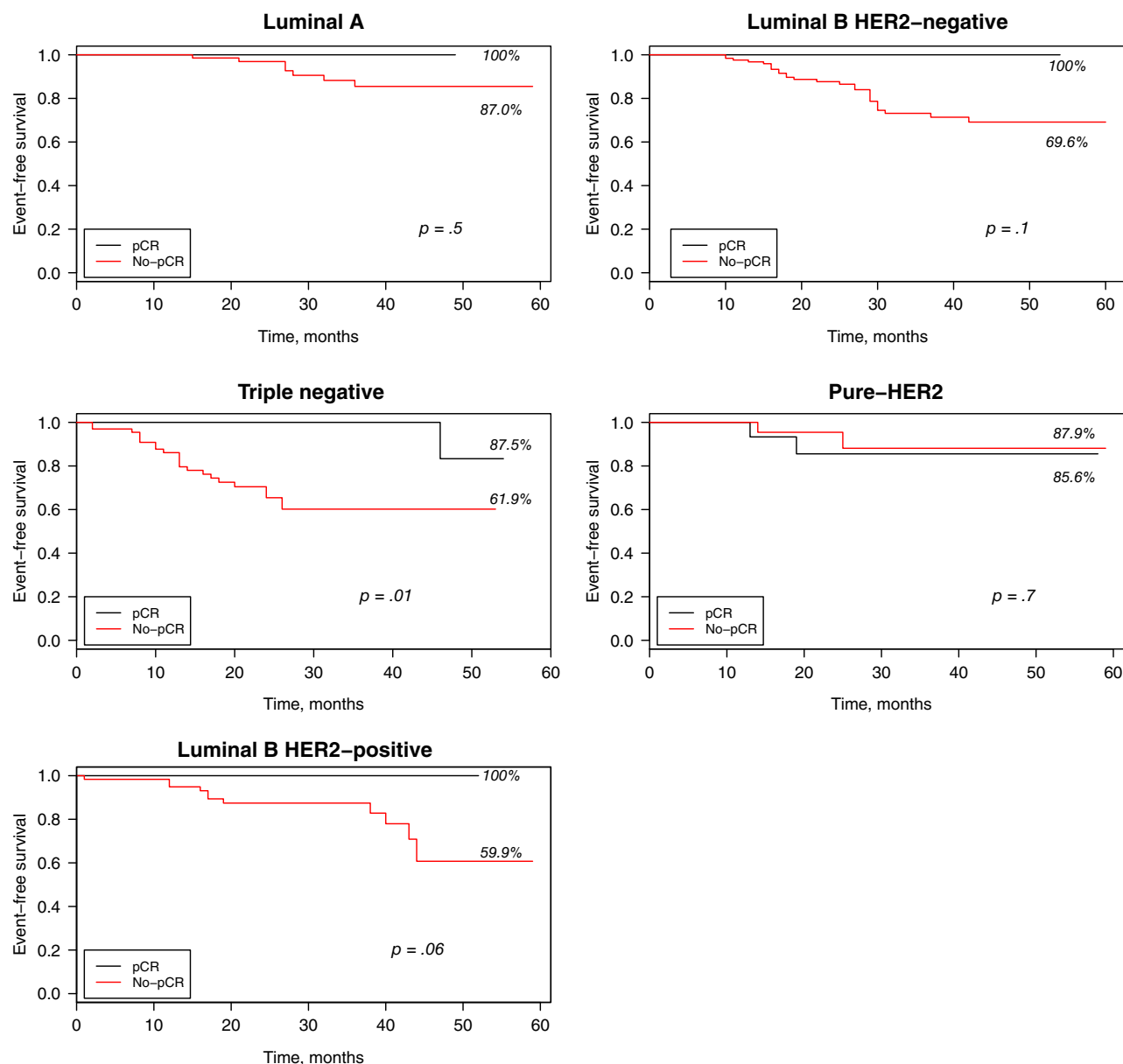
Abbreviation: HER2, human epidermal growth factor 2.

reported higher rates of pCR for triple-negative tumors, which vary within a range of 20% to 62% [17].

In 2009, Byrski et al. published a study (10 patients with *BRCA 1* mutation) in which they evaluated four cycles of cisplatin in the neoadjuvant treatment, reporting a 90% pCR rate [24]. The preliminary report of a study carried out in the NCI, conducted by Díaz et al., which included all patients with triple-negative tumors seen within the FBCU,

reported pCR rates of 22.6%, concordant with those obtained in the current study [25].

Luminal A and luminal B HER2-negative tumors are the least chemosensitive; in our cohort they achieved pCR rates of 6.1% (*n* = 5) and 6.0% (*n* = 8), respectively. In 2012, von Minckwitz et al. reported pCR rates of 6.4% for luminal A tumors and 11.2% for luminal B HER2-negative ones [26]. International literature reports pCR rates for these subtypes of



**Figure 2.** Association between pCR and event-free survival, by molecular subtype of breast cancer. Abbreviation: pCR, pathological complete response.

tumors of around 10% [8], which is comparable to the results obtained in this retrospective study, and it is for this reason that the worldwide trend is toward the use of hormone therapy alone as a systemic treatment in this group of patients [27].

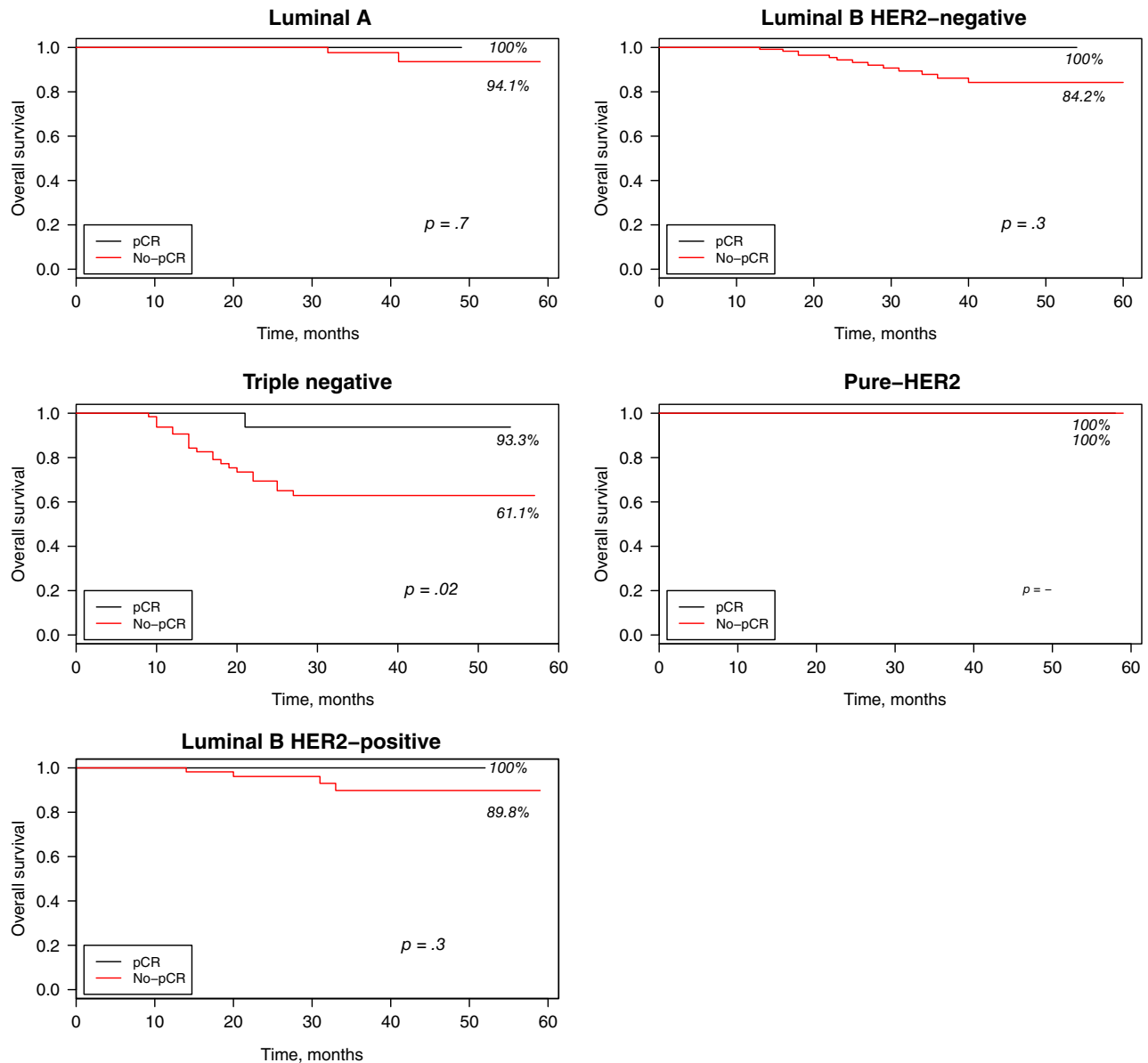
Several prognostic factors for pCR have been identified, among which the axillary node involvement, status of hormone receptor, and HER2, tumor grade, and the NACT regimen administered to patients are described [13, 28, 29]. In this study, we identify that 43.9% ( $n = 166$ ) of cN+ patients were reported as ypN0, and only 32.5% ( $n = 63$ ) of ypN0 patients achieved pCR, whereas 98.4% ( $n = 62$ ) of patients who had pCR presented no axillary node involvement (ypN0). Samiei et al. showed that cN0 patients who achieve pCR after NACT have high probabilities of reaching ypN0, especially in the hormone receptor-positive HER2-positive, hormone receptor-negative HER2-positive, and triple-negative subtypes of breast cancer [13].

Within the grade 3 tumors of differentiation, a pCR rate of 21.3% was presented ( $n = 37$ ), comparable to that reported by Ring et al. [28], who showed rates of 15.6%, and Guarneri et al., who showed rates of 18.2%, for tumors with this grade of differentiation [29].

It is a fact that pCR is directly related to the NACT regimen administered [30]. Patients who were administered anthracycline-based regimens plus trastuzumab (AC-TH) showed pCR rates of 29.9% ( $n = 26$ ), which are concordant with findings obtained by the GeparQuattro study that reported benefits in pCR for chemotherapy combined with these agents; the AC-TH group achieved pCR in 31.7% patients versus 15.5% in the control group [31].

The other NACT regimen that obtained acceptable pCR rates was based on taxanes plus platinum (TC), achieving pCR in 28.6% ( $n = 6$ ) of patients. However, the response was lower if we compare it with the one obtained in the CALGB 40603





**Figure 3.** Association between pCR and overall survival, by molecular subtype of breast cancer. Abbreviation: pCR, pathological complete response.

study, which found an increase of 14.0% in the pCR rate in favor of the group of patients who received carboplatin [32].

Of the total number of patients included in the study, only 36.7% ( $n = 152$ ) were taken to treatment with conservative surgery after receiving NACT, which is well below the conservative surgical management rate reported in NSABP B-18, which reached 67% of the cases [33]; it is noteworthy in this cohort that only patients with locally advanced breast cancer were included. In contrast, the meta-analysis of Valachis et al. did not find benefit for treatment with conservative surgery (RR, 0.98; 95% CI, 0.8–1.19) [22].

Cortazar et al. [8] showed that the pure HER2 molecular subtype with pCR obtained better long-term results (EFS: HR, 0.15; 0.09–0.27; OS: HR, 0.08; 0.03–0.22), and just like Cirier et al. [18], they found statistical significance for OS ( $p = .035$ ) but not for EFS ( $p = .09$ ). In our study, the pure HER2 subtype, despite obtaining the highest pCR rate, did not present statistically significant differences in terms of

EFS ( $p = .7$ ) or OS ( $p = 0$ ). However, the triple-negative subtype that obtained pCR had statistical significance for both EFS (87.5%;  $p = .01$ ) and OS (93.3%;  $p = .02$ ).

The strength of this study is evidenced in the quality of the information obtained, having been derived from a detailed anamnesis in the medical records, a rigorous process of data collection, verification, and analysis. These results will be taken into account for the approach and treatment of patients with locally advanced breast cancer at the NCI FBCU.

#### Limitations of the Study

The limitations found in this study are those derived from retrospective studies, mainly the difficulty of establishing a causal relationship. In the context of Colombia, the principal risk of bias is the loss of follow-up due to changes in contracting by insurers and the difficult access of patients to health services.

## CONCLUSION

Pathological response in locally advanced tumors is related to the molecular subtype of breast cancer, with higher pCR rates in *pure HER2* and triple negative tumors. A direct relationship was found between disease recurrence and pathological response, with greater tumor recurrence in patients who did not respond to neoadjuvant chemotherapy (Chevallier 3 and 4). EFS and OS were higher in patients with pCR, with a statistical significance only in triple negative tumors.

## ACKNOWLEDGMENTS

We thank National Cancer Institute in Bogotá for the funding support.

## REFERENCES

- Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
- Vasconcelos I, Hussainzada A, Berger S et al. The St. Gallen surrogate classification for breast cancer subtypes successfully predicts tumor presenting features, nodal involvement, recurrence patterns and disease free survival. *Breast* 2016;29:181–185.
- Goldhirsch A, Winer EP, Coates AS et al. Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 2013;24:2206–2223.
- Romieu I, Biessy C, Carayol M et al. Reproductive factors and molecular subtypes of breast cancer among premenopausal women in Latin America: The PRECAMA study. *Sci Rep* 2018;8:13109.
- Bonilla-Sepúlveda O, Matute-Turizo G, Severiche C. Clasificación en subtipos intrínsecos de los carcinomas de mama analizados en un centro de patología de Medellín en el año 2011. *CES Medicina* 2015;29:12.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology - Breast Cancer 2019. Available from: [https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). Accessed April 22, 2019.
- Kaufmann M, Hortobagyi GN, Goldhirsch A et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: An update. *J Clin Oncol* 2006;24:1940–1949.
- Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. *Lancet* 2014;384:164–172.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: Meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol* 2018;19:27–39.

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## DISCLOSURES

The authors indicated no financial relationships.

- Miller AB, Hoogstraten B, Staquet M et al. Reporting results of cancer treatment. *Cancer* 1981;47:207–214.
- Chevallier B, Roche H, Olivier JP et al. Inflammatory breast cancer. Pilot study of intensive induction chemotherapy (FEC-HD) results in a high histologic response rate. *Am J Clin Oncol* 1993;16:223–228.
- Instituto Nacional de Cancerología-ESE. Anuario Estadístico 2015. Bogotá, Colombia: Instituto Nacional de Cancerología-ESE, 2018. Available from <https://www.cancer.gov.co/files/libros/archivos/2015>. Accessed April 22, 2019.
- Samiei S, van Nijnatten TJA, de Munck L et al. Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy. *Ann Surg* 2018 [Epub ahead of print].
- Sataloff DM, Mason BA, Prestipino AJ et al. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: A determinant of outcome. *J Am Coll Surg* 1995;180:297–306.
- Penault-Llorca F, Abrial C, Raoelfils I et al. Comparison of the prognostic significance of Chevallier and Sataloff's pathologic classifications after neoadjuvant chemotherapy of operable breast cancer. *Hum Pathol* 2008;39:1221–1228.
- Fragomeni SM, Sciallis A, Jeruss JS. Molecular subtypes and local-regional control of breast cancer. *Surg Oncol Clin N Am* 2018;27:95–120.
- Wang-Lopez Q, Chalabi N, Abrial C et al. Can pathologic complete response (pCR) be used as a surrogate marker of survival after neoadjuvant therapy for breast cancer? *Crit Rev Oncol Hematol* 2015;95:88–104.
- Cirier J, Body G, Jourdan ML et al. Impact of pathological complete response to neoadjuvant chemotherapy in invasive breast cancer according to molecular subtype [in French]. *Gynecol Obstet Fertil Senol* 2017;45:535–544.
- Buzdar AU, Ibrahim NK, Francis D et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive

operable breast cancer. *J Clin Oncol* 2005;23:3676–3685.

- Pierga JY, Delaloge S, Espié M et al. A multicenter randomized phase II study of sequential epirubicin/cyclophosphamide followed by docetaxel with or without celecoxib or trastuzumab according to HER2 status, as primary chemotherapy for localized invasive breast cancer patients. *Breast Cancer Res Treat* 2010;122:429–437.
- Gianni L, Eiermann W, Semiglazov V et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): A randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet* 2010;375:377–384.
- Valachis A, Mauri D, Polyzos NP et al. Trastuzumab combined to neoadjuvant chemotherapy in patients with HER2-positive breast cancer: A systematic review and meta-analysis. *Breast* 2011;20:485–490.
- von Minckwitz G, Schneeweiss A, Loibl S et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): A randomised phase 2 trial. *Lancet Oncol* 2014;15:747–756.
- Byrski T, Huzarski T, Dent R et al. Response to neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients. *Breast Cancer Res Treat* 2009;115:359–363.
- Díaz-Casas S, Lancheros E, Sánchez-Campo A. Descripción de una cohorte de pacientes con cáncer de mama triple negativo en la Unidad Funcional de Mama del Instituto Nacional de Cancerología. 2019 [Epub ahead of print].
- von Minckwitz G, Untch M, Blohmer JU et al. Definition and impact of pathological complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012;30:1796–1804.
- Semiglazov VF, Semiglazov VV, Dashyan GA et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. *Cancer* 2007;110:244–254.
- Ring AE, Smith IE, Ashley S et al. Oestrogen receptor status, pathological complete response

and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer. *Br J Cancer* 2004;91:2012–2017.

**29.** Guarneri V, Broglio K, Kau SW et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. *J Clin Oncol* 2006;24:1037–1044.

**30.** Mieog JS, van der Hage JA, van de Velde CJ. Preoperative chemotherapy for women with

operable breast cancer. *Cochrane Database Syst Rev* 2007:CD005002.

**31.** Untch M, Loibl S, Bischoff J et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): A randomised phase 3 trial. *Lancet Oncol* 2012;13:135–144.

**32.** Sikov WM, Berry DA, Perou CM et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week

paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol* 2015;33:13–21.

**33.** Rastogi P, Anderson SJ, Bear HD et al. Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008;26:778–785.