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EPIDEMIOLOGY

Comparison of the performance of four staging systems in determining the prognosis of breast cancer among women undergoing neoadjuvant chemotherapy

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Abstract

Purpose Different tumor-related factors have been proposed to assess the risk of disease progression and death in women undergoing neoadjuvant breast cancer chemotherapy. Recently, besides the classical pre-treatment clinical stage (CS) and post-treatment pathologic stage (PS), estrogen receptor status and histologic grade (CPS + EG score) and HER2 results (Neo-Bioscore) have also been added to this suite of staging systems, generating new scores. The present study aims to compare the performance of these four staging systems, namely CS, PS, CPS + EG and Neo-Bioscore, in the prognosis of breast cancer in women undergoing neoadjuvant chemotherapy.

Methods This study comprises a retrospective cohort study of female breast cancer patients diagnosed at the Brazilian National Cancer Institute, Brazil from January 2013 to December 2015. A descriptive analysis of patient characteristics was conducted, and Kaplan–Meier curves, a Cox proportional hazard analysis and Receiver Operating Characteristic (ROC) curves were developed according to the assessed staging system scores.

Results A total of 803 patients were eligible for this study. Most were under 65 years old (88.0%), presented advanced tumors (clinical stage ≥ IIB 77.1%), with positive estrogen receptor (71.2%) and negative HER2 (75.7%) results. During the follow-up, 172 patients (21.4%) evolved to death. A statistical difference ($p < 0.001$) was observed between 5 year disease-free survival and 5 year overall survival rates according to the PS, CPS + EG and Neo-Bioscore staging systems.

Conclusion The PS, CPS + EG and Neo-Bioscore staging systems were proven to be equivalent to predict the prognosis of patients undergoing neoadjuvant chemotherapy.

Keywords Breast cancer · Neoadjuvant chemotherapy · Prognosis · Pre-treatment clinical staging · Post-treatment pathological staging · CPS + EG · Neo-bioscore

Introduction

The increasingly frequent use of neoadjuvant chemotherapy as part of the primary breast cancer treatment in women makes it necessary to employ methods to assess the prognosis of these patients [1]. Initially, neoadjuvant chemotherapy was indicated only for patients presenting advanced or inoperable tumors. Currently, however, in addition to these indications, neoadjuvant chemotherapy has also been proposed for the assessment of clinical and pathological in vivo responses, as well as increasingly indicated for conservative surgeries and to avoid axillary lymphadenectomy and its complications [1–3].

Currently, several tumor-related factors are recognized as prognostic markers in patients with breast cancer. These include histological type, clinical tumor staging (cTNM),

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degree of tumor differentiation, p53 status, estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor 2 (HER2) receptors and Ki67 [4].

Tumor staging systems have been proposed as prognostic markers. A traditional system proposed by the International Union Against Cancer (UICC), is based on the size or volume of the primary tumor (T), lymph node involvement (L) and the presence of distant metastases (M). These three categories are then grouped into stages, generating two classifications: the pre-treatment clinical stage (CS), based on cTNM, and post-treatment pathologic stage (PS), based on pTNM. These two classic systems were initially brought together in the Clinical-Pathologic Scoring System (CPS) [1].

In addition to these classic systems, a staging system that includes the status of the estrogen receptor and histologic grade, as well as CPS, has demonstrated the ability to predict the risk of distant disease in women with breast cancer using neoadjuvant chemotherapy, termed CPS + EG [estrogen receptor status (E) and histologic grade (G)] [2]. Its main utility is based on the premise that locoregional recurrence impacts both disease-free survival (DFS) and overall survival (OS), since locoregional recurrence is associated with an increased risk of metastases [3]. More recently, another staging system, the Neo-Bioscore, has incorporated a new definition of ER and HER2 positivity into CPS + EG, considering that patients presenting positive HER2 display a better prognosis when receiving treatment with Trastuzumab (Mittendorf et al. 16). The American Joint Committee on Cancer (AJCC) also updated the CS and PS systems by adding ER, PR and HER2 [5]. However, little is known about the performance of these staging systems in populations outside the USA [1, 2, 12, 16] and Europe [3, 13], with the exception of studies conducted in China [10, 14]. In addition, knowledge of which of these systems can better stratify the prognosis of patients receiving neoadjuvant chemotherapy can promote better clinical decision-making.

Considering the ethnic and multi-racial characteristics of breast cancer patients in Brazil [6], the long time interval for breast cancer diagnosis [7] and the high percentage of women with breast cancer diagnosed in advanced stages [8], the applicability of these staging systems in Brazilian women is interesting to assess. In this scenario, the aim of this study was to compare the performance of these four staging systems (CS, PS, CPS + EG and Neo-Bioscore) in predicting the prognosis of women with breast cancer undergoing neoadjuvant chemotherapy.

Methods

A retrospective cohort study was carried out from January 2013 to December 2015 with women diagnosed with breast cancer enrolled at the Cancer Hospital III/INCA, in the city of Rio de Janeiro.

Patients undergoing chemotherapy followed by surgery were included in the study, according to surgeon indications. Women with bilateral breast cancer, inflammatory carcinoma, pregnant women, clinical stage IV, previous breast cancer, radiation therapy or hormone therapy prior to chemotherapy, non-epithelial tumors, clinical or cardiological contraindications for surgery, patients who did not complete neoadjuvant chemotherapy and those without complete information required to prepare the scores were excluded from the cohort.

Patients were classified according to the four staging systems. CS (I, IIA, IIB, IIIA, IIIB, IIIC) and PS (0, I, IIA, IIB, IIIA, IIIB, IIIC) were determined from the size of the primary tumor, impairment of locoregional lymph nodes and distant metastasis, as recommended by the seventh edition of the American Joint Committee on Cancer Staging Manual [9]. The CPS + EG applied scores from 0 to 2 for characteristics related to PS (stage I or IIA = 0 points, IIB or IIIA = 1 point, IIIB or IIIC = 2 points), ER status (positive = 0 points, negative = 1 point), G (degrees 1 and 2 = 0 points and 3 = 1 point) and PS (stage 0 or I = 0 points, IIA to IIIB = 1 point, IIIC = 2 points) [1]. Finally, the Neo-Bioscore considered the CPS + EG score by incorporating the HER2 status (positive = 0 points, negative = 1 point) [10]. Cases whose expression of ER or PR were < 1% in immunohistochemical analyses were considered negative for these hormone receptors. HER2 status was defined as positive in 3 + readings detected by immunohistochemical analysis. Both the CPS + EG and Neo-Bioscore systems demonstrated patient risk stratification capacity regardless of the cut-off value of 1% or 10% to define ER positivity [10].

The following adjustment variables were also studied: age, education, marital status, race/skin color, alcohol and tobacco consumption, body mass index, histopathological subtypes and pathological responses. The complete pathological response (CPR) was defined as the absence of invasive carcinoma in the breast and in the axillary region (ypT0ypN0), through the histopathological analysis of the primary site and axillary lymph nodes after the end of neoadjuvant chemotherapy. The presence of in situ carcinomas in the absence of invasive carcinoma did not exclude CPR.

The study outcomes comprised progression of the disease or death in 60 months, obtained through an active search of patient physical and electronic medical records, with the follow-up ending on May 29, 2020.

Statistical analyses

A descriptive analysis of the study population was performed, using central tendency (mean or median) and dispersion (standard deviation or interquartile value) measures for continuous variables, and absolute and relative frequency distribution for categorical variables. A Kaplan–Meier analysis was performed for the initial exploratory assessment of survival. Disease-free survival was defined as the time interval between the date of surgery until the date of the first evidence of disease progression or death from any cause and OS was defined as the time between the patient's registration at the institution until date of death or censoring. Comparison between strata were performed using the log-rank test. A Cox proportional hazards regression model was used to explore the association between the staging systems and the estimated risk of disease progression or death. The variables whose association with outcomes in Cox's univariate analyses exhibited values of $p < 0.15$ [11] were tested in sequentially constructed multivariate models, starting with the variable most strongly associated with the outcome and continuing until no other variable reached significance. Variables with $p < 0.05$ were maintained in the final model. The prognostic accuracy of the staging systems was assessed using receiver operating characteristic (ROC) curves, by comparing the areas under the curves (AUC) and their 95% confidence intervals (95% CI). Statistically significance was set at $p < 0.05$. The Statistical Package for the Social Sciences (SPSS) version 24 was used to carry out all statistical analysis.

The study was approved by the INCA Research Ethics Committee on December 10, 2012 (CAAE 06,794,512.3.0000.5274; opinion 166.838).

Results

A total of 1106 patients enrolled at INCA between January 2013 and December 2015 and undergoing neoadjuvant chemotherapy were eligible for this study. Patients with bilateral breast cancer (45), inflammatory carcinoma (17), non-epithelial tumors (01), occult breast carcinoma (01), pregnant women (07), previous cancer (09) and previous cancer treatment (15), contraindication for surgery (02), evolution to stage IV in the presence of neoadjuvancy (57), submitted to other neoadjuvant chemotherapy protocols (32), presenting sentinel lymph node biopsy before neoadjuvant chemotherapy (02), patients who did not complete chemotherapy (67) or who presented no information on histologic grade, hormone receptors or HER2 (48) were excluded. After applying these exclusion criteria, a total of 803 patients were included (Fig. 1).

Most patients were under 65 years old (88.0%), non-white (66.1%), reported 8 or more years of schooling (69.6%) and were overweight or obese (72.6%) (Table 1).

Most patients presented advanced tumors at the time of diagnosis (clinical stage ≥ IIB 77.1%). The most frequent histological type was invasive ductal carcinoma (ICD) (92.7%). Most patients presented positive estrogen receptor (71.2%) and HER2-negative (75.5%) tumors. Regarding type of surgery, Madden's modified radical mastectomy was the most performed (71.0%), with sentinel lymph node biopsy carried out in 28.5% of the cases. During the follow-up period, 191 patients (23.8%) died (Table 2).

Disease-free and overall 5-year survival were statistically different ($p < 0.001$) between the strata in the assessed four staging systems (Table 3).

The factors identified in the Cox univariate analyses with $p < 0.15$ (Supplementary Tables 1 and 2) were used as the adjusting variables in order to identify the risks for disease progression (Table 4) and death (Table 5) in 60 months according to each assessed staging system. For both outcomes, PS IIA to IIIC, CPS + EG ranging from 2 to 6 and Neo-Bioscore from 3 to 6 indicated worse prognoses for breast cancer patients, although only clinical IIIB staging was associated with worse DFS.

The comparison of prognostic accuracy according to the evaluated staging systems (Table 6) showed that CS performed worse both in estimating disease progression and death in 60 months, while the other three staging systems performed similarly.

Discussion

This study compared the ability of four staging systems to stratify the prognosis of patients with breast cancer undergoing neoadjuvant chemotherapy. In relation to CS, the PS, the CPS + EG and the Neo-Bioscore staging systems were able to better predict the risk of disease and death progression.

A high frequency of invasive ductal carcinomas was observed in the present study (92.7%), similar to that reported by Abdelsattar et al. (82.1%) [12] and Marmé et al. (87.8%) [13]. Regarding histologic grade, grade 3 was the most frequently detected by Abdelsattar et al. (59%) [12], while grade 2 was the most prevalent (64.5%) herein, in agreement with Marmé et al. (54.9%) [13]. Abdelsattar et al. [12] and Marmé et al. [13] reported similar data regarding the positive estrogen receptor (61.9%), while its frequency was of 71.2% in this study.

Unlike the data found in the present study concerning type of surgery, Xu et al. [14] reported a 56.8% rate of conservative surgery and 43.2% of mastectomies, while Madden's modified radical mastectomy was performed in 71.0% of the patients of the cohort of this study. Abdelsattar et al.

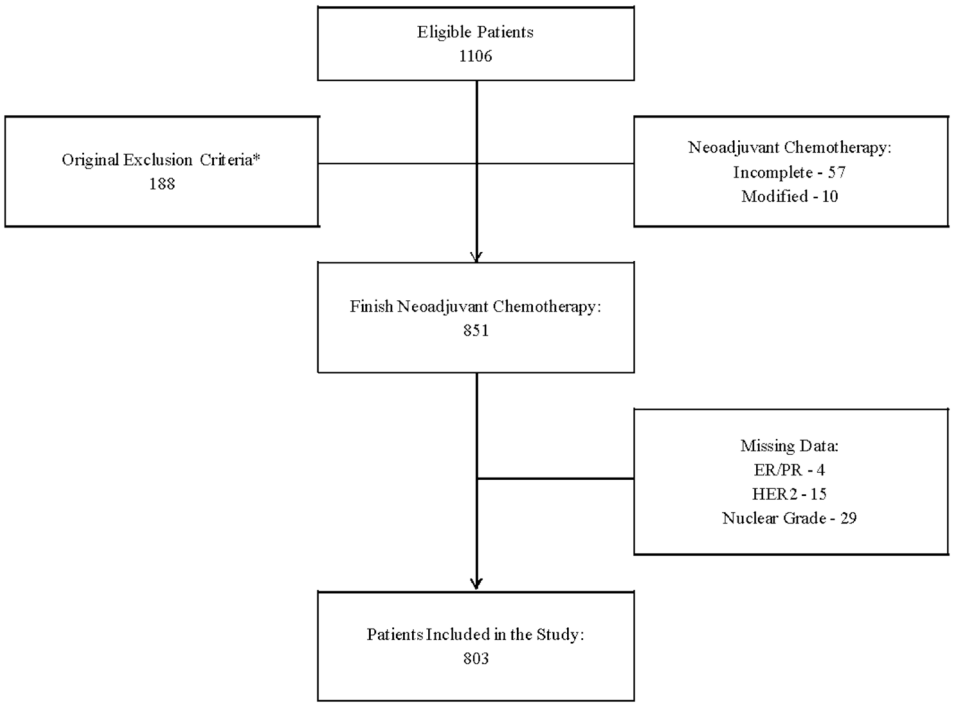

Fig. 1 Flow diagram indicating patient selection for the present study. The original exclusion criteria (*) were: bilateral breast cancer (45), inflammatory carcinoma (17), non-epithelial tumors (01), occult breast carcinoma (01), pregnant women (07), previous cancer (09) and previous cancer treatment (15), contraindication for surgery (02), evolution to stage IV in the presence of neoadjuvancy (57), submitted to other neoadjuvant chemotherapy protocols (32), presenting sentinel lymph node biopsy before neoadjuvant chemotherapy (02) (total = 188). From the remaining 918 patients those who did not complete neoadjuvant chemotherapy (67) and those with missing data on key variables (48) were excluded. The remaining 803 were selected for the analysis. *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor 2

reported data similar to that described herein with mastectomy being performed in 71% of cases [12].

The CPR reported by Marmé et al. was of 21.2%, while in the present study, CPR occurred in 115 patients (14.3%) [13]. Michel et al. found data similar to those indicated by Marmé et al. with CPR in 22.5% of cases [3]. Although it is known that only 22% of patients treated with Neoadjuvant chemotherapy reach CPR, patients with CPR, in general, show better survival compared to patients without CPR [15].

At enrollment, most patients presented with advanced tumors (CS ≥ IIB 77.1%). Conversely, much lower percentages were found by Xu et al., who demonstrated that the most frequent clinical stage (34.7%) was the IIA [11]. Michel et al. in 2019, also described a higher percentage of patients in stage II (72.5%), while only 24.1% were in stage III [3].

The application of the CPS + EG score showed results similar to those reported by Abdelsattar et al. [12] who described a high frequency of patients in the groups with the highest score (11.7% in group 5 and 0.4% in group 6), while in the present study 4.2% were categorized as group 5 and 0.1%, as group 6. Similarly, Jeruss et al. classified 5.6% of their patients as group 5 and 1.0% as group 6 [1]. Michel et al. described a much lower number of patients in these groups, with only three (0.7%) in group 5 and none in group 6 [3]. Unlike what was found in the study, in which OS was of 38.6% in groups 5 and 6, Xu et al. described a OS of 28.9% in these groups [14], while Marmé et al. observed 27% in group 5 and 6% in group 6 [13]. On the other hand, Marmé et al. demonstrated a DFS of 21% in group 5, while in this study a 27.1% rate was noted [13]. Such discrepancies may be due to differences in chemotherapy indication, since patient selection was carried out at very different times, due to changes in the profile of patients for whom treatment was indicated (previously, chemotherapy was indicated in most cases for inoperable and advanced tumors) and the implementation of new hormonal or monoclonal antibody therapies.

The Neo-Bioscore staging system's ability to better stratify patients into prognostic subgroups compared to CS,

Table 1 Sociodemographic characteristics of the population ($N=803$)

Variables	N (%)
Age at diagnosis	
< 65 years	707 (88.0)
≥ 65 years	96 (12.0)
Marital status	
Living with a companion	329 (41.0)
Living alone	465 (57.9)
Missing	9 (1.1)
Race/skin color	
White	268 (33.4)
Non-white*	531 (66.1)
Missing	4 (0.5)
Years of study	
0–8	329 (41.0)
> 8	460 (57.3)
Missing	14 (1.7)
Alcohol consumption	
Current/past	179 (22.2)
Never	573 (71.4)
Missing	51 (6.4)
Tobacco consumption	
Current/past	220 (27.4)
Never	535 (66.6)
Missing	48 (6.0)
Body mass index	
< 18.5	3 (0.4)
18.5–24.9	214 (26.7)
25–29.9	291 (36.2)
30–34.9	177 (22.0)
35–39.9	83 (10.3)
≥ 40	33 (4.1)
Missing	2 (0.2)

*Non-white = Black (147), Mulatto (382), Asian-Brazilians (1), Indigenous (1)

Table 2 Clinical and therapeutic variables of the population ($N=803$)

Variables	N (%)
Histological subtype	
Non-special-type invasive carcinoma	744 (92.7)
Others	59 (7.3)
Histologic grade	
Grade 1	48 (6.0)
Grade 2	518 (64.5)
Grade 3	237 (29.5)
Estrogen receptor	
Positive	572 (71.2)
Negative	231 (28.8)
Progesterone receptor	
Positive	467 (58.2)
Negative	336 (41.8)
HER2	
Positive	197 (24.5)
Negative	606 (75.5)
Type of surgery	
Radical Madden mastectomy	570 (71.0)
Conservative surgery	140 (17.4)
Total mastectomy	71 (8.8)
Radical Patey mastectomy	17 (2.1)
Radical Halsted mastectomy	5 (0.6)
Sentinel lymph node biopsy	
No	574 (71.5)
Yes	229 (28.5)
Axillary lymph node dissection	
Yes	664 (82.7)
No	139 (17.3)
Complete pathological response	
Yes	115 (14.3)
No	688 (85.7)
Progression of the disease in 60 months	
Yes	268 (33.4)
No	535 (66.6)
Death in 60 months	
Yes	172 (21.4)
No	631 (78.6)

HER2 human epidermal growth factor 2

PS and CPS + EG was demonstrated in the study where it was first applied, at the MD Anderson Cancer Center. Specific 5-year survival rates ranged from 76 to 96% according to the score obtained in the CS, 64% to 97% according to the score obtained in the PS, 52% to 98% according to the score obtained in the CPS + EG systems, and from 48 to 99% according to the Neo-Bioscore system [16]. In another study, carried out in China, Xu et al. (2018) demonstrated that the CPS + EG and Neo-Bioscore staging systems also exhibited better risk stratification than the CS for DFS, Specific Survival and OS [14]. Unlike previous studies, only the initial clinical stage showed worse performance in stratifying the risk of disease progression and death in 60 months in the present study. The PS, CPS + EG and Neo-Bioscore staging systems showed equivalent performance in stratifying the risk of disease progression or death.

Unlike the Neo-Bioscore score used in the present study (1 point for HER2-negative cases), the modified Neo-Bioscore, which will be validated in a multicenter cohort

Table 3 Disease-free and overall 5-year survival according to the four assessed staging systems

Staging system	*N*	(%)	5-year disease-free survival Rate (±SD)	5-year overall survival Rate (±SD)
Clinical stage				
I	20	(2.5)	89.5 (±7.0)	94.1 (±5.7)
IIA	164	(20.4)	71.4 (±3.9)	83.3 (±3.1)
IIB	192	(23.9)	69.3 (±3.8)	82.9 (±2.9)
IIIA	168	(20.9)	64.0 (±4.0)	75.8 (±3.5)
IIIB	251	(31.3)	50.9 (±3.5)	68.3 (±3.1)
IIIC	8	(1.0)	75.0 (±15.3)	72.9 (±16.5)
p value (log-rank test)			<0.001	0.001
Pathologic stage				
0	123	(15.3)	84.5 (±3.6)	92.5 (±2.6)
I	147	(18.3)	80.5 (±3.6)	89.3 (±2.8)
IIA	190	(23.7)	65.8 (±4.0)	79.9 (±3.1)
IIB	113	(14.1)	58.5 (±5.1)	71.1 (±4.4)
IIIA	133	(16.6)	43.5 (±4.7)	62.3 (±4.5)
IIIB	45	(5.6)	37.8 (±9.4)	61.0 (±7.4)
IIIC	52	(6.5)	40.8 (±7.1)	61.8 (±7.0)
p value (log-rank test)			<0.001	<0.001
CPS + EG				
0	50	(6.2)	87.9 (±5.2)	97.9 (±2.1)
1	134	(16.7)	80.4 (±3.8)	91.8 (±2.5)
2	229	(28.5)	67.2 (±3.6)	80.5 (±2.8)
3	257	(32.0)	61.1 (±3.2)	75.5 (±2.8)
4	98	(12.2)	37.2 (±5.4)	54.9 (±5.5)
5/6*	35	(3.8)	27.1 (±10.0)	38.6 (9.1)
p value (log-rank test)			<0.001	<0.001
Neo-Bioscore				
0	33	(4.1)	81.7 (±7.6)	96.9 (±3.1)
1	115	(14.3)	85.0 (±3.9)	94.1 (±2.4)
2	207	(25.8)	67.9 (±3.8)	83.4 (±2.7)
3	245	(30.5)	62.0 (±3.3)	75.1 (±2.9)
4	150	(18.7)	47.3 (±4.5)	67.5 (±4.0)
5/6*	52	(5.8)	37.1 (7.4)	43.6 (7.8)
p value (log-rank test)			<0.001	<0.001
Total	803	(100.0)	63.2 (±1.9)	77.0 (±1.6)

SD standard deviation, *CPS + EG* clinical-pathologic scoring system + estrogen receptor status and tumor grade

*Given the small number of cases in subcategory 6 of the CPS + EG (one case) and Neo-Bioscore (six cases), and in order to ensure their representativeness in the analyses, these cases were grouped with category 5. No patient totaled 7 points on Neo-Bioscore

study in China [10], computes 2 points for HER2-positive patients who did not receive anti-HER2 treatment. The authors assume that, in China, most HER2-positive cases have difficulty in accessing anti-HER2 treatment. Therefore, the modified Neo-Bioscore could perform better than Neo-Bioscore and CPS + EG staging systems [10], especially in areas with difficult access to hormonal therapy and immunomodulators, creating the expectation that new staging

Table 4 Risk of disease progression in 60 months according to the four assessed staging systems

Staging system	*N*	cHR	95% CI	*p* value	aHR	95% CI	*p* value
Clinical stage*							
I	20	Ref					
IIA	164	2.6	(0.6–10.9)	0.181			
IIB	192	2.7	(0.7–11.2)	0.165			
IIIA	168	3.5	(0.8–14.2)	0.084			
IIIB	251	5.2	(1.3–20. 9)	0.021			
IIIC	8	2.7	(0.4–19.0)	0.324			
Pathologic stage*							
0	123	Ref					
I	147	1.2	(0.7–2.3)	0.492			
IIA	190	2.3	(1.4–4.0)	0.002			
IIB	113	3.1	(1.7–.4)	< 0.001			
IIIA	133	4.8	(2.8–8.2)	< 0.001			
IIIB	45	5.8	(3.1–10.8)	< 0.001			
IIIC	52	5.3	(2.9–9.6)	< 0.001			
CPS + EG**							
0	50	Ref					
1	134	1.7	(0.7–4.5)	0.274	1.6	(0.6–4.2)	0.333
2	229	3.0	(1.2–7.4)	0.018	2.8	(1.1–7.0)	0.025
3	257	4.2	(1.7–10.4)	0.002	3.9	(1.6–9.6)	0.003
4	98	8.0	(3.2–20.1)	< 0.001	7.2	(2.9–18.1)	< 0.001
5/6	35	12.3	(4.7–32.3)	< 0.001	10.3	(3.9–27.1)	< 0.001
Neo-Bioscore**							
0	33	Ref					
1	115	0.8	(0.3–2.2)	0.639	0.7	(0.3–2.0)	0.558
2	207	1.9	(0.8–4.8)	0.155	1.8	(0.7–4.5)	0.202
3	245	2.6	(1.0–6.4)	0.039	2.5	(1.0–6.1)	0.048
4	150	4.2	(1.7–10.3)	0.002	3.9	(1.6–9.6)	0.003
5/6	53	6.1	(2.4–15.6)	< 0.001	5.5	(2.1–14.2)	< 0.001

Chr crude hazard ratio, *aHR* adjusted hazard ratio, *CI* confidence interval

*No model adjustment

**Model adjusted for complete pathological response

systems consider the increasing incorporation of these treatments in neoadjuvancy [17].

This study presents certain limitations, such as its retrospective design, the limited number of patients in the CPS + EG group 6 and the short follow-up time. However, similar limitations have been found in other studies [12, 14]. The strengths of this study are the fact that it was carried out in a single cancer treatment center specialized in breast cancer, the good quality of medical records, the strict inclusion and exclusion criteria and the size of the analyzed population, which was considerable when compared to other studies with lower case numbers (Xu et al. in 2018: 403 patients [14], Michel et al. in 2019: 432 patients [3]).

In conclusion, this pioneer study in Brazil, confirms the benefit of using the PS, the CPS + EG and the Neo-Bioscore staging systems for the stratification of patients undergoing neoadjuvant chemotherapy to predict disease progression and death. These three staging systems showed equivalent performance in determining the prognosis of these patients.

Table 5 Risk of death in 60 months according to the four assessed staging systems

Staging system	*N*	cHR	95% CI	*p* value	aHR	95% CI	*p* value
Clinical stage*							
I	20	Ref					
IIA	164	3.2	(0.4–23.8)	0.251			
IIB	192	3.2	(0.4–23.6)	0.249			
IIIA	168	4.9	(0.7–35.7)	0.116			
IIIB	251	6.6	(0.9–47.7)	0.060			
IIIC	8	5.5	(0.5–61.0)	0.163			
Pathologic stage*							
0	123	Ref					
I	147	1.5	(0.6–3.5)	0.391			
IIA	190	2.9	(1.4–6.3)	0.006			
IIB	113	4.6	(2.1–10.1)	< 0.001			
IIIA	133	6.2	(2.9–13.0)	< 0.001			
IIIB	45	7.5	(3.2–17.4)	< 0.001			
IIIC	52	6.3	(2.8–14.4)	< 0.001			
CPS + EG**							
0	50	Ref			Ref		
1	134	3.7	(0.5–28.8)	0.213	3.5	(0.4–27.0)	0.237
2	229	9.0	(1.2–65.2)	0.030	8.4	(1.2–61.4)	0.035
3	257	12.8	(1.8–92.4)	0.011	11.6	(1.6–83.5)	0.015
4	98	26.4	(3.6–192.1)	0.001	23.2	(3.2–169.2)	0.002
5/6	35	48.4	(6.5–361.1)	< 0.001	39.9	(5.3–297.9)	< 0.001
Neo-Bioscore**							
0	33	Ref			Ref		
1	115	1.7	(0.2–14.2)	0.618	1.6	(0.2–13.3)	0.664
2	207	5.6	(0.8–41.0)	0.089	5.2	(0.7–38.2)	0.103
3	245	8.5	(1.2–61.5)	0.034	8.1	(1.1–58.7)	0.038
4	150	12.2	(1.7–88.7)	0.013	11.3	(1.6–81.6)	0.017
5/6	53	23.2	(3.1–170.8)	0.002	20.6	(2.8–152.1)	0.003

cHR crude hazard ratio, *aHR* adjusted hazard ratio, *CI* confidence interval

*No model adjustment

**Model adjusted for complete pathological response

Table 6 Comparison of the prognostic accuracy according to the four assessed staging systems

Staging system	Progression of the disease*		Death*	
	AUC	(± SD)	AUC	(± SD)
clinical stage	60.4	(± 2.1)	60.7	(± 2.4)
Pathologic stage	69.7	(± 1.9)	69.2	(± 2.2)
CPS + EG	67.4	(± 2.0)	69.9	(± 2.2)
Neo-Bioscore	66.2	(± 2.0)	67.9	(± 2.2)

AUC area under the curve, *SD* standard deviation

*In 60 months

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was approved by the INCA Research Ethics Committee on December 10, 2012 (CAAE 06794512.3.0000.5274; opinion 166.838).

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