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ORIGINAL RESEARCH

Late Breast Cancer Recurrence Prediction: The Role of CTS5 and Progesterone Receptor Status

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Purpose: The current study aimed to assess the recurrence rate in hormone-receptor positive, HER2 negative (HR-positive/HER2-negative) breast cancer patients from a single center in Brazil and compare it with estimates provided by the Clinical Treatment Score post-five years (CTS5).

Methods: This study comprised a retrospective analysis of patients from a national cancer center database, which began treatment between 2007 and 2008 and had no evidence of recurrence after five years of follow-up. All patients had confirmed diagnosis of HR-positive/HER2-negative early breast cancer. Disease Free-Survival (DFS) according to each CTS5 risk subgroup was the main outcome.

Results: A total of 162 patients were enrolled, 26.5% being premenopausal. The mean age at diagnosis was 60.1 years (49.8─71.6). Tumor stage: I (43.8%) and II (56.2%). Endocrine therapy consisted mainly of tamoxifen (88.0%). About 39.5%, 39.5%, and 21.0% of patients were in the low, intermediate, and high-risk (L/I/H) subgroups according to CTS5, respectively. Progesterone-receptor (PR) was ≥20% in 71.0% of tumors and 77.0%, 69.0%, and 65.0% in the L/I/H subgroups, respectively. The median follow-up was 88.9 months. DFS at 5 years (10 years since the beginning of endocrine therapy) was 100%, 96.3% (95% CI, 89.4%─100%) and 68.2% (95% CI, 48.7%─95.5%) in the L/I/H subgroups, respectively. PR was an independent prognostic factor for late recurrence in intermediate- (p=0.022) and high-risk (p=0.003) subgroup patients according to CTS5.

Conclusion: CTS5 performed well in the high-risk subset of patients from a wider population, including premenopausal women. The progesterone receptor was an independent prognostic factor for DFS in intermediate- and high-risk populations and should be further investigated in prospective multicenter studies.

Keywords: progesterone receptor, breast cancer recurrence, CTS5, prognostic factor

Introduction

In 2024, breast cancer alone is estimated to account for nearly one-third of all new cancer cases diagnosed in women.[1] Over 60% of female patients with breast cancer are diagnosed with localized disease, with up to 70% of cases classified as hormone-receptor positive (HR-positive) subtypes.[2,3] The cornerstone of treatment for these patients is antiestrogen therapy.[4] Following surgery, adjuvant endocrine therapy (ET) typically consists of tamoxifen or an aromatase inhibitor (AI). Early studies demonstrated that tamoxifen reduced the recurrence rate by approximately 50% compared to no endocrine therapy during the first 5 years of treatment, and this improvement persisted even 10 years after therapy cessation. In postmenopausal women, aromatase inhibitor has shown to be more effective than tamoxifen and are considered the preferred option for this patient population.[2]

Due to improvements in breast cancer screening, more early-stage cancers are detected. Despite recent advances in adjuvant ET, such as the addition of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors to adjuvant treatment, a significant percentage of patients still present late recurrences.[2,3] Extending the duration of ET may potentially prevent late recurrence, but to establish the optimal duration for these patients remains a challenge.[2,5]

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The Clinical Treatment Score post-five years (CTS5) is an online model used to predict late distant metastases for women with HR-positive, HER2 negative (HR-positive/HER2-negative) breast cancer who are recurrence-free after 5 years from the beginning of ET.[6] It incorporates patients' age, tumor size, grade, and number of positive lymph nodes. The recurrence risk in five to ten years is <5% in the low-, 5 to 10% in the intermediate-, and >10% in the high-risk CTS5 subgroup. As a tool to assess the risk of late distant recurrence, CTS5 was validated using data from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial and the Breast International Group 1–98 (BIG1-98) trials.[7]

Several tools integrating molecular profiling and/or clinicopathological features have been developed in recent years to predict the risk of distant recurrence. For example, the Breast Cancer Index (BCI) provides valuable information on the benefits of extending adjuvant treatment.[8] In comparison, the CTS5 has a moderate concordance rate, though it does not incorporate molecular variables.[9]

Due to its online availability, CTS5 remains widely used, especially in low-resource settings where access to molecular profiling is limited.[6,7] In low- and middle-income countries (LMICs), CTS5 serves as a crucial tool for patient risk stratification, helping guide treatment decisions when more advanced prognostic tools are unavailable.[6,9] While retrospective studies have assessed CTS5 in broader populations, data is still scarce for Latin American patients.[10] Furthermore, there is limited research on its applicability in premenopausal women and whether incorporating additional variables could enhance its predictive value.

The goal of the current study was to assess the recurrence rate for HR-positive/HER2-negative breast cancer patients from a single center in Brazil and compare it with the estimates provided by the CTS5 for each risk subgroup. Furthermore, we present clinical characteristics, treatment profiles, and disease-free survival (DFS) according to CTS5 risk subgroups.

Methods

Study Design

This study is a single-center retrospective cohort analysis of patients with breast cancer who initiated adjuvant ET between January 2007 and December 2008 at the Instituto Nacional de Câncer (INCA), Brazil. Since data collection occurred in 2020–2021, this timeframe was selected to ensure that patients had been evaluated at least five years after completion of adjuvant ET. All included patients had a confirmed diagnosis of invasive breast cancer through pathological examination, early HR-positive disease, underwent surgical therapy, and completed at least 5 years of adjuvant ET without evidence of disease recurrence. Patients with a second primary breast tumor or HER2-positive disease (eg, HER2 IHC positivity of 3+ or 2+ with a positive ISH test) were excluded. Follow-up continued until 2020 or patients' last recorded visit to the institution.

We created an electronic clinical research form (eCRF) to collect data on sociodemographic and clinical characteristics such as age, ethnicity, body mass index (BMI), menopausal status, tumor grade, histological subtype, disease stage at diagnosis, hormone receptor status, type and duration of hormone therapy, and chemotherapy treatment. Staging was defined according to the seventh edition of the American Joint Committee on Cancer/Union for International Cancer Control[11] (AJCC/UICC). We classified post-menopausal patients as those who had experienced amenorrhea for more than 12 months due to natural causes, were older than 60 years or had undergone bilateral oophorectomy. Women who did not meet these criteria were classified as premenopausal.

The primary objective was to correlate DFS with the risk subgroups classified as low (<5%), intermediate (5–10%), and high (>10%) recurrence risk within five to ten years, as estimated by the CTS5. Secondary objectives included assessing menopausal status across risk groups and evaluating whether estrogen receptor (ER) and progesterone receptor (PR) status influenced DFS.

Statistical Analysis

Data analysis was descriptive and exploratory. Categorical variables were presented in their absolute and relative frequencies. Continuous demographic and clinical variables were presented by median and interquartile range (IQR).

Survival analysis was performed using the Kaplan-Meier method. DFS was defined as the time interval between date of diagnosis by pathological examination and recurrence. DFS was compared between low, intermediate, and high-risk subgroups. Comparisons of DFS distribution between subgroups were performed using a two-sided Log rank test. Statistical significance was indicated by p-value ≤ 0.05.

Ethical Considerations

The protocol was reviewed and approved by the local Institutional Review Board (IRB), reference number 33886820.0.0000.5274. A waiver for the informed consent was granted by the local IRB, and the study was conducted according to the principles of Good Clinical Practice guidelines.

Results

A total of 425 patients diagnosed with HR-positive/HER2-negative early breast cancer were selected from the institutional database. Patients with less than 5 years of follow-up, recurrence of disease during this period, tumor grade not available or unknown status of HER2 were not eligible. Patients with stage III disease were excluded from the analysis. In total, 162 patients met the inclusion criteria, as described in Figure 1. The main characteristics of the study population are presented in Table 1 according to CTS5 categories.

Median age (IQR) at diagnosis was 60.1 (49.8─71.6) years, and 26.5% (43 patients) of women were premenopausal. At baseline, 43.8% (71 patients) of the patients had tumor stage I and 56.2% (91 patients), stage II. There were 39.5% (64 patients), 39.5% (64 patients) and 21.0% (34 patients) of patients with tumors in the low, intermediate, and high-risk (L/I/H) subgroups, respectively.

Patients with high-risk CTS5 were more likely to be older (median 67.1 years, IQR 59.3─77.4), post-menopausal (30 patients, 88.2%), and to have higher-grade tumors (17 patients, 50.0%), larger tumor sizes (median 31.0 mm, IQR 28.5─43.8), and lymph node involvement (median 1.0, IQR 1.0─2.0) compared to the overall cohort. ER status was higher than 10% in most cases (154 patients, 95.1%), while PR status was above 20% in 71.0% (115 patients) of tumors. Most patients in the high-risk group (18 patients, 52.9%) received chemotherapy, as compared to 21.9% (14 patients) in the low-risk group. Adjuvant ET included tamoxifen in 87.7% of cases (142 patients), anastrozole in 6.2% (10 patients), and a switch between these therapies in 6.2% (10 patients).

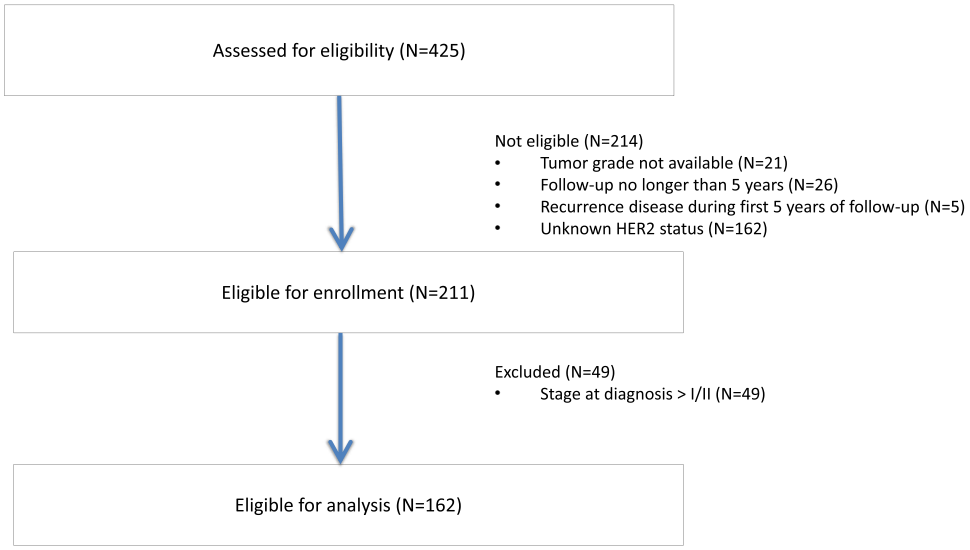

Figure 1 Flow diagram of the study.

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Table 1 Patient and Tumor Characteristics According to CTS5 Subgroups

Characteristics		CTS5 Subgroups			Total
		Low N (%)	Intermediate N (%)	High N (%)	
Number of patients		64 (39.5)	64 (39.5)	34 (21.0)	162 (100.0)
Age at diagnosis	Median (IQR)	52.5 (46.6–66.0)	65.2 (52.4–71.7)	67.1 (59.3–77.4)	60.1 (49.8–71.6)
Ethnicity	White	40 (62.5)	42 (65.6)	18 (52.9)	100 (61.7)
	Black + brown	22 (34.4)	20 (31.3)	16 (47.0)	58 (35.8)
	Missing	2 (3.1)	2 (3.1)	0 (0.0)	4 (2.5)
BMI	Median (IQR)	26.0 (24.0–29.6)	27.4 (24.5–31.4)	27.4 (24.6–29.2)	26.9 (24.2–30.3)
Menopausal status	Pre-	27 (42.2)	12 (18.8)	4 (11.8)	43 (26.5)
	Post-	37 (57.8)	52 (81.2)	30 (88.2)	119 (73.5)
Grade	Low	26 (40.6)	7 (10.9)	0 (0.0)	33 (20.4)
	Intermediate	31 (48.4)	39 (60.9)	16 (47.1)	86 (53.1)
	High	4 (6.2)	12 (18.8)	17 (50.0)	33 (20.4)
	Missing	3 (4.7)	6 (9.4)	1 (2.9)	10 (6.2)
Tumor size (mm)	Median (IQR)	11.5 (7.0–15.0)	24.0 (15.0–30.0)	31.0 (28.5–43.8)	20.0 (13.0–30.0)
Lymph nodes	Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.0 (1.0–2.0)	0.0 (0.0–1.0)
Stage	I	53 (82.8)	18 (28.1)	0 (0.0)	71 (43.8)
	II	11 (17.2)	46 (71.9)	34 (100.0)	91 (56.2)
Histology	Ductal	57 (89.1)	49 (76.6)	29 (85.3)	135 (83.3)
	Lobular	2 (3.1)	9 (14.1)	2 (5.9)	13 (8.0)
	Missing	5 (7.8)	6 (9.4)	3 (8.8)	14 (8.6)
Estrogen receptor (ER)	<10%	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.6)
	≥10%	62 (96.9)	59 (92.2)	154 (95.1)	0 (0.0)
	Missing	2 (3.1)	5 (7.8)	7 (4.3)	71 (43.8)
Progesterone receptor (PR)	<20%	13 (20.3)	15 (23.4)	12 (35.3)	40 (24.7)
	≥20%	49 (76.6)	44 (68.8)	22 (64.7)	115 (71.0)
	Missing	2 (3.1)	5 (7.8)	0 (0.0)	7 (4.3)
Endocrine therapy	Tamoxifen	58 (90.6)	55 (85.9)	29 (85.3)	142 (87.7)
	Anastrozole	3 (4.7)	5 (7.8)	2 (5.9)	10 (6.2)
	Switch	3 (4.7)	4 (6.2)	3 (8.8)	10 (6.2)
Chemotherapy	No	29 (45.3)	29 (45.3)	7 (20.6)	65 (40.1)
	Yes	14 (21.9)	15 (23.4)	18 (52.9)	47 (29.0)
	Missing	21 (32.8)	20 (31.2)	9 (26.5)	50 (30.9)

Abbreviations: BMI, body mass index; ER, estrogen receptor; IQR, interquartile range; PR, progesterone receptor.

The median follow-up was 88.9 months. DFS at 5 years (10 years since the beginning of ET) was 100%, 96.3% (95% CI, 89.4%─100%), and 68.2% (95% CI, 48.7%–95.5%) in L/I/H subgroups, respectively, as presented in Figure 2, and still not reached for the total study population, as presented in Supplemental Figure 1.

Specifically in the intermediate- and high-risk patient subgroups according to CTS5, PR status was an independent prognostic factor for late recurrence, with p values of 0.022 and 0.003, respectively, demonstrating that PR expression lower than 20% in these subgroups leverages the risk of recurrence. The DFS by PR level for the total population is presented in Supplemental Figure 2, and the DFS by PR level for the intermediate- and high-risk patient subgroups is presented in Figures 3 and 4.

Discussion

We performed a retrospective analysis of 162 patients with HR-positive/HER2-negative early breast cancer, selected from an institutional database, and evaluated clinicopathological features and outcomes based on CTS5 risk categories. Our main finding was that PR status <20% was a significant independent prognostic factor for late recurrence in intermediate- and high-risk patients (p = 0.022 and p = 0.003, respectively). This finding aligns with previous studies

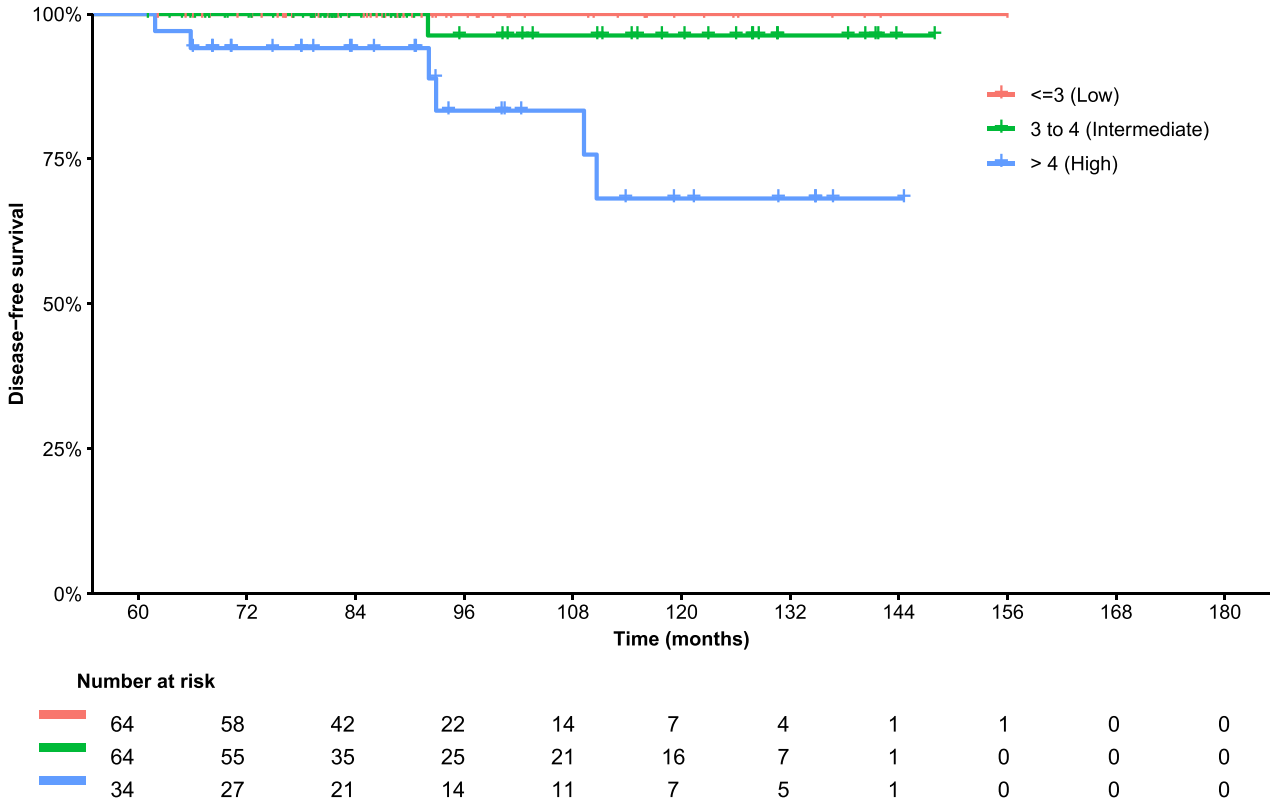

Figure 2 DFS by CTS5 subgroups.

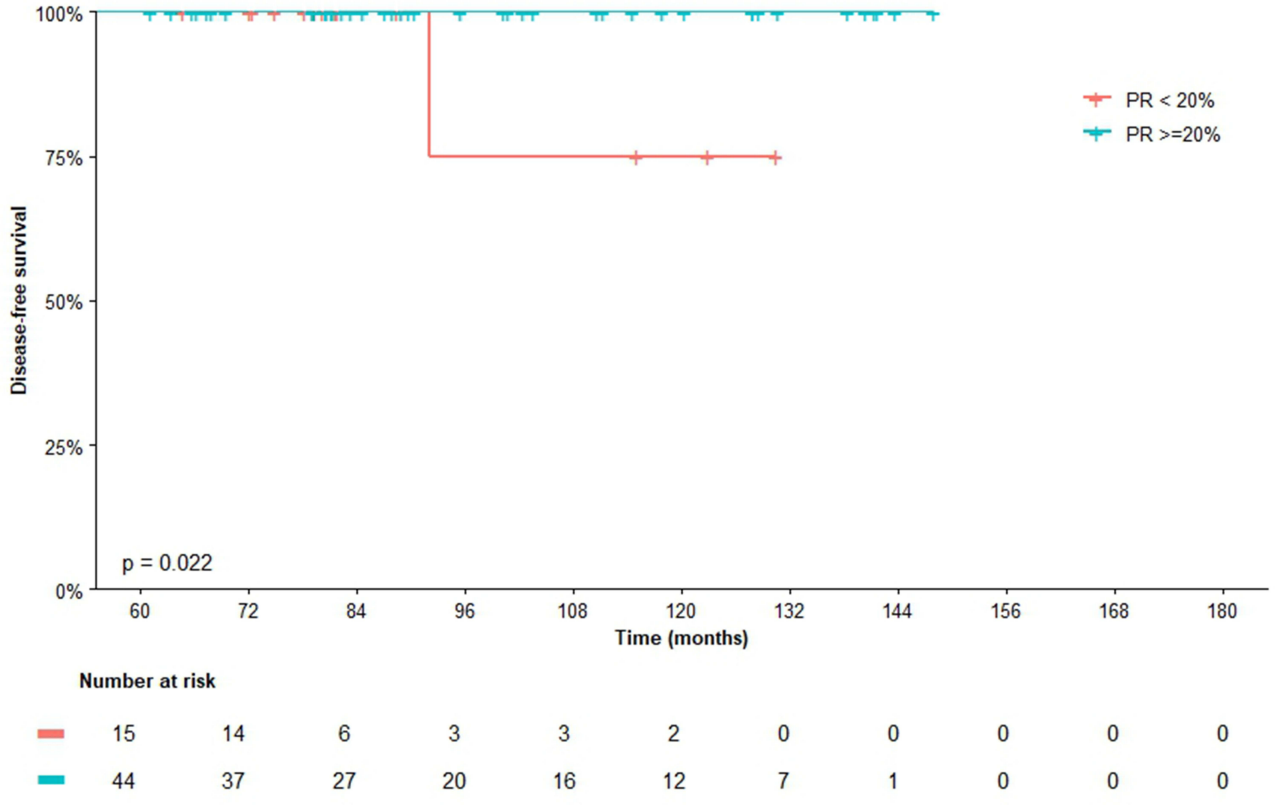

Figure 3 DFS by PR level for the intermediate-risk patient subgroup.

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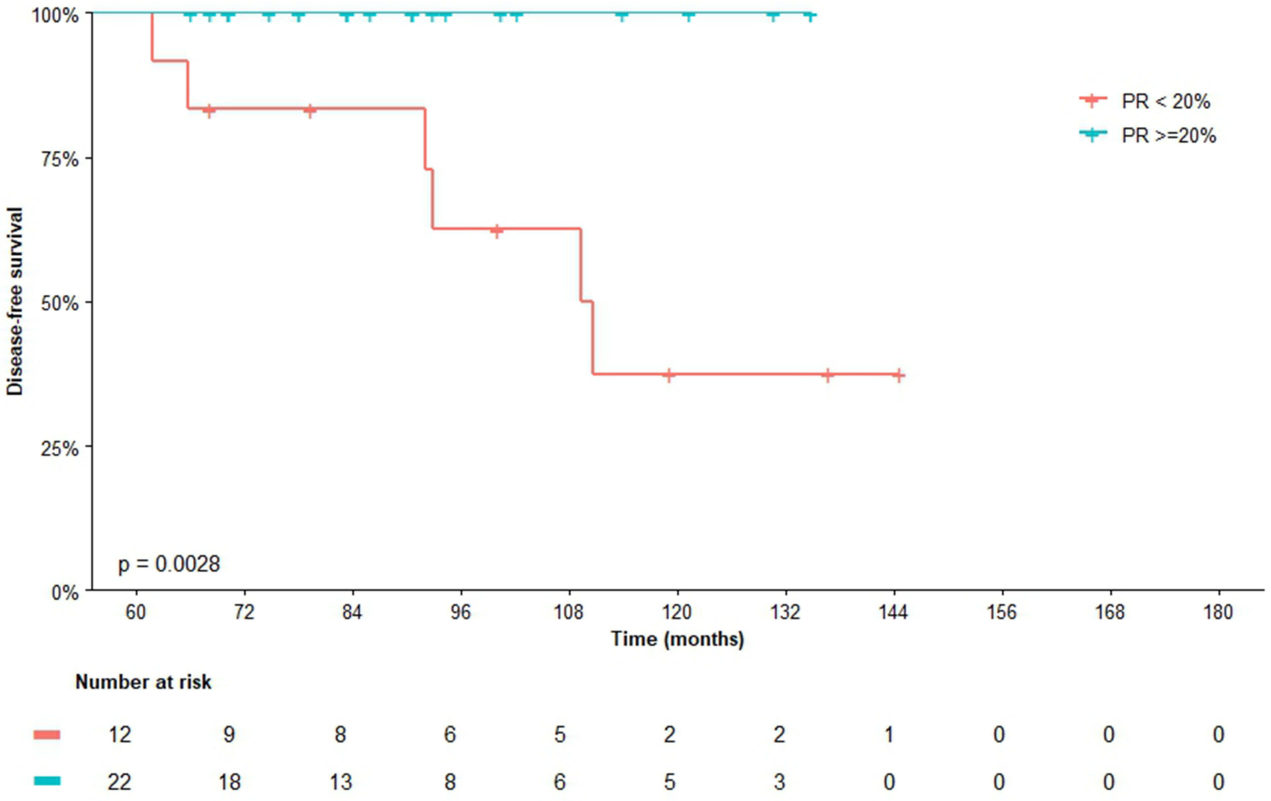

Figure 4 DFS by PR level for the high-risk patient subgroup.

demonstrating that negative or low PR expression is associated with worse DFS and OS compared to strong PR-positive breast cancer, particularly in premenopausal patients.[12,13]

Given that PR expression can be easily evaluated through IHC in clinical practice, it may serve as a valuable marker to identify patients, otherwise classified as having a good prognosis, who could benefit from additional adjuvant treatments, including extended ET. As a widely available and cost-effective marker, PR could enhance risk stratification in breast cancer.[12–14] However, further prospective studies are needed to validate its role in refining risk assessment models.

Although PR status is not currently included in CTS5 assessment, it is well established as a marker of poor prognosis.[12,14] Future investigations should explore whether incorporating PR into CTS5 could enhance its predictive accuracy and guide treatment decisions. In this context, it is also important to acknowledge the methodological limitations of Kaplan–Meier, such as its inability to adjust for covariates, oversimplification of continuous variables, and potential bias from censored data.[15] Alternative statistical approaches – such as multivariable Cox regression models, restricted mean survival time (RMST), and machine learning-based survival models – may offer more precise and individualized risk stratification.[16] In resource-limited settings, where access to genomic assays and novel targeted therapies remains constrained, optimizing CTS5 with additional biomarkers like PR could represent a pragmatic and impactful approach to improving long-term outcomes.[6,9,10]

In our cohort, DFS at 5 years (10 years since the beginning of ET) was 100%, 96.3% (95% CI, 89.4%–100%), and 68.2% (95% CI, 48.7%–95.5%) in L/I/H CTS5 subgroups, respectively. As presented by Dowsett et al in the ATAC cohort, the mean recurrence risk 5 to 10 years after completion of ET was 2.5% (95% CI, 1.8%–3.4%) in the low-risk subgroup, 7.7% (95% CI, 6.3%–9.5%) in intermediate-risk subgroup, and 20.3% (95% CI, 17.2%–24.0%) in high-risk subgroup, according to the CTS5 risk calculator.[7] In the BIG I-98 cohort, the mean risk of distant recurrence at 5 to 10 years was 3.6% (95% CI, 2.7%–4.9%), 6.9% (95% CI, 5.6%–8.5%), and 17.3% (95% CI, 14.8%–20.1%), respectively.[6]

In the current study, it is noteworthy that the recurrence rate after 5 years was 31.8% in the high-risk subgroup. Given that HR-positive breast cancer can recur late, patients should be followed for a longer period, which is a limitation of our study. However, even within our 5-year follow-up analysis, we emphasize the elevated recurrence rate in the high-risk subgroup, which was even higher than that reported in the BIG I-98 and ATAC cohorts over a longer follow-up period.[7] This discrepancy may be partially explained by differences in access to healthcare resources, treatment adherence, and availability of advanced prognostic tools in a public hospital setting. Genomic tools, such as Breast Cancer Index, have been developed to identify who may benefit from extended adjuvant ET.[17] However, these tools are not routinely available in Brazil, which may limit treatment optimization in high-risk patients.

Despite 73.5% of women being postmenopausal, 88.0% received tamoxifen as adjuvant ET. Although tamoxifen remains an effective therapy, AI are now the preferred option for postmenopausal patients, as they provide greater reduction in recurrence risk.[18] The reliance on tamoxifen in our cohort was primarily due to its greater availability, and lower cost at the time treatment was initiated, reflecting resource constraints within our institution. This treatment limitation may have contributed to the lower DFS observed in our study, particularly in the high-risk subgroup, when compared to cohorts where AI-based regimens were more frequently used.

Data concerning extension of ET for premenopausal women are still scarce in literature.[18] In our cohort, 26.5% of women were premenopausal. Interestingly, in a survival analysis stratified by CTS5 risk groups, PR status demonstrated prognostic value in the intermediate- and high-risk patient subgroups according to CTS5. When classified by CTS5 subgroups, the number of patients with PR expression lower than 20% was directly related to the risk of disease recurrence. However, since the study did not specifically explore the combined efficacy of CTS5 and PR in predicting DFS, these results should be interpreted with caution. Additionally, the modest size of the cohort and the relatively short follow-up time for an HR-positive breast cancer population further limit the generalizability of these findings.

At last, it is important to recap that this is a retrospective, single-center study based on data retrieved from patients' medical records. Despite these limitations, our analysis provides valuable insights into a previously underrepresented patient population and reinforces the prognostic value of the CTS5 score, including its applicability to premenopausal patients. Moreover, our findings underscore the potential relevance of PR status as an additional prognostic factor, warranting further investigation.

Conclusion

CTS5 is a valid tool for identifying early-stage breast cancer patients who may benefit from extended adjuvant ET, particularly those in high-risk subgroups. Our findings reinforce its applicability in a distinct population, including premenopausal women, and highlight progesterone receptor (PR) status as an independent prognostic factor for DFS in the intermediate- and high-risk subgroups according to CTS5. However, the combined efficacy of CTS5 and PR for predicting DFS was not explored in this study and warrants further investigation. Given the importance of accessible and cost-effective prognostic tools in resource-limited settings, CTS5, potentially enhanced by additional biomarkers such as PR, offers a pragmatic and impactful strategy for optimizing long-term breast cancer management. Further studies are warranted to validate these findings and explore the integration of PR status into risk assessment models.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

The current investigation was subjected to ethical scrutiny and received approval from the Ethics in Human Research Committee of INCA, Rio de Janeiro, Brazil, with registration number CAAE 33886820.0.0000.5274, adhering to the principles of Good Clinical Practice guidelines.

Informed Consent

Considering the retrospective nature of this observational study, which involved the use of anonymized data for analysis, the Institutional Review Board (IRB), also known as the Ethics in Human Research Committee of the Instituto Nacional de Câncer (Comitê de Ética em Pesquisa do Instituto Nacional de Câncer; CEP-INCA), deemed it appropriate to waive the requirement for informed consent from participants.

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Disclosure

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