The Oncologist, 2025, **30**, oyaf040
https://doi.org/10.1093/oncolo/oyaf040
Advance access publication 4 April 2025
Original Article

Retrospective analysis to validate the CTS5 in patients from *El Álamo IV* registry and GEICAM adjuvant studies

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Trial registration number
ClinTrials.gov: GEICAM/9805: NCT00121992; GEICAM/9906: NCT00129922; GEICAM/2003-02: NCT00129389, GEICAM/2003-10: NCT00129935 and *El Álamo IV*: NCT03210974

Abstract

Background: Identifying high-risk of late recurrence (beyond 10 years) in patients with hormone receptor-positive HER2-negative early breast cancer (EBC) is crucial. The Clinical Treatment Score post-5 years (CTS5) score assesses recurrence risk after 5 years of endocrine therapy (ET). This study validated CTS5 as a prognostic tool for late recurrence by examining its association with Distant Recurrence-Free Survival using GEICAM study data and evaluating model calibration.

Patients and methods: We retrospectively analyzed 5739 hormone receptor-positive HER2-negative EBC patients from the *El Álamo IV* registry ($N = 3509$, diagnosed between 2002 and 2005) and 4 adjuvant GEICAM studies ($N = 2680$, conducted between 1996 and 2006). All patients were distant recurrence-free and alive 5 years after starting adjuvant ET.

Results: The CTS5 classified 43.9% of patients as low-risk, 32.2% as intermediate-risk, and 23.9% as high-risk. Significant differences in DR were observed: hazard ratio (HR) for intermediate- vs. low-risk was 2.55 (95% CI, 1.85-3.51, $P < .0001$), and HR for high- vs. low-risk was 5.77 (95% CI, 4.28-7.78, $P < .0001$). Similar results were found across subgroups by menopausal status, duration of adjuvant ET, and prior adjuvant chemotherapy (CT). Calibration showed CTS5 overestimated DR rates in low-risk ($P = .0314$) and high-risk ($P < .0001$) patients compared to observed rates.

Conclusions: The CTS5 categorized patients based on late DR risk regardless of menopausal status, ET duration, or CT treatment. However, the model tended to overestimate events, particularly in high-risk groups, especially among those treated with ET for less than 60 months or not receiving CT.

Key words: CTS5; late-recurrence; early breast cancer (EBC); hormone receptor-positive; HER2-negative.

Received: 28 August 2024; Accepted: 10 February 2025.

Implications for practice

Clinical trials' limited follow-up hinders long-term outcomes understanding. Tools to identify patients benefiting from new therapies for preventing long-term recurrences are crucial. CTS5 estimates late distant recurrence (DR) risk. We analyzed data from a registry and 4 GEICAM trials to support CTS5's adoption in clinical practice. CTS5 effectively stratified patients by late DR risk but overestimated events in high-risk groups. Our study contributes to understand the late recurrence risk assessment in hormone receptor-positive, HER2-negative early breast cancer.

Introduction

Although treatments for early-stage breast cancer (BC) have significantly impacted mortality over the past 20 years,[1] transitioning from the advanced to potentially curative settings, recurrences remain a substantial health burden. Distant recurrence and its associated mortality imply significant costs for both our BC patients and society.[2]

BC exhibits a heterogeneous pattern of relapse, occurring at different levels either anatomically or temporally.[3-5] Focusing on the chronological dimension of recurrence, several prognostic factors are known to influence the timing of BC relapse. On this regard, hormone receptor-negative, and in particular triple-negative BC, tend to recur earlier during the follow-up,[6] while hormone receptor-positive BC maintain an extended pattern of recurrence.[7] It has been proposed that hormone receptor-positive tumors remain dormant for long periods of time regardless of available adjuvant therapies.[8] Great efforts are being made to understand the biology behind late-recurrences,[9] and translating the biological basis of dormancy into the therapeutic and surveillance field is crucial to truly impact on long-term outcomes in this population.[8,10]

The restricted follow-up periods in most clinical trials, usually up to 10 years, present a significant limitation in characterizing the long-term behavioral outcomes of BC.[11,12] The International Breast Cancer Study Group (IBCSG) trials I to V were reported with a median follow-up of 24 years, providing valuable insights into the dynamics of the hazards of recurrence over an extended period. The annual risk of BC recurrence was greater for the whole population during the first 5 years (10.4%), with a peak between 1 and 2 years after surgery (15%). Notably, among patients with hormone receptor-positive BC the risk of recurrence remained stable even beyond 10 years.[13] These observations aligned with early reports in the seventies that questioned the real curability of BC.[14]

On another level, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of tamoxifen trials confirmed that a significant number of recurrences occurred after the first 5 years of adjuvant tamoxifen treatment.[15] Interestingly, the 2017 EBCTCG meta-analysis encompassing more than 62 900 patients, confirmed that after 5 years of adjuvant endocrine therapy (ET), BC recurrences followed a steady rate from 5 to 20 years. The risk of distant recurrence strongly correlated with tumor size and lymph node involvement ranging from 10% to 41%.[7]

The Netherlands population-based registry supported the notion that the luminal A and B subtype recurrences were continuous over time with lobular tumors showing higher 10-year recurrence rates.[16] Further data coming from cancer registries such as the Danish Breast Cancer Group clinical database by Pedersen et al,[17] nicely illustrated that recurrences continued to occur even up to 32 years after primary diagnosis with highest recurrences rates occurring on years 10-12. Tumor size (>20 mm), node-positive, and estrogen receptor (ER)-positive tumors were again associated with increased cumulative incidence of recurrence.

Then, late recurrences from hormone receptor-positive BC pose a real challenge. Extending the duration of ET beyond 5 years might mitigate this continuous risk of recurrence. Numerous trials have studied different sequences and durations of treatments mainly on postmenopausal patients (recently reviewed by Battisti et al[18]). However, extended ET is closely associated with undesirable adverse events ranging from musculoskeletal pain, reduced bone mineral density, increased cardiovascular risk, cognitive impairment, or impact on sexual health among others. In this context, the individualization of ET for early-stage hormone receptor-positive BC to maximize the risk/benefit balance needs validated tools to guide clinical decisions together with treatment tolerability considerations.[18,19]

Dowsett et al,[20] developed a pragmatic clinical approach to classify individual patients into different risk categories after the first 5 years of adjuvant ET, known as the *clinical treatment score at 5 years (CTS5)*. The CTS5 model is a continuous score that integrating 4 clinical variables (number of positive lymph nodes, tumor size, histological tumor grade, and age) distributes hormone receptor-positive early BC (EBC) patients into 3 risk-categories; low-risk (<3.13 with a corresponding <5% risk of distant recurrence at years 5-10), intermediate-risk (3.13-3.86 with 5%-10% 5-10-year risk) and high-risk groups (>3.86 with >10% 5-10 year risk). This tool was developed using data from the ATAC trial and validated in the BIG 1-98 (20) study dataset and the current ASCO guidelines suggest considering extended ET for postmenopausal patients with high CTS5 scores.[21]

Multiple independent validations have assessed the prognostic value of the CTS5 since 2018.[22-26] Our current analysis aims to further validate the CTS5 as a prognostic tool of late-recurrence (beyond 5 years) in a series of hormone receptor-positive Human Epidermal Growth Factor Receptor 2 (HER2)-negative BC Spanish patients included in GEICAM studies.

Methods

We included data from 4 randomized clinical trials in EBC patients and one BC registry. In the GEICAM/9805 (1999-2003),[27] patients with negative lymph nodes received 6 cycles of docetaxel/doxorubicin/cyclophosphamide (TAC) versus 6 cycles of FAC (fluorouracil/doxorubicin/cyclophosphamide). In the GEICAM/9906 (1999-2002),[28] patients with positive lymph nodes received 6 cycles of FEC (fluorouracil/epirubicin/cyclophosphamide) versus 4 cycles of FEC followed by 8 administrations of weekly paclitaxel. In the GEICAM/2003-02 (2003-2009)[29] patients with negative lymph nodes received 6 cycles of FAC versus 4 cycles of FAC followed by 8 doses of

weekly paclitaxel. In the GEICAM/2003-10 (2004-2007),[30] patients with positive lymph nodes received 4 cycles of epirubicin/cyclophosphamide followed by 4 cycles of docetaxel versus 4 cycles of epirubicin/docetaxel followed by 4 cycles of capecitabine. These studies included patients diagnosed from 1999 to 2009. *El Álamo IV* is a retrospective registry, which characterized BC cases diagnosed in Spain between 2002 and 2005 in 43 Spanish sites.

The data on ET initiation, sequence, and duration were obtained from the clinical trial and registry databases, with treatment plans established according to physicians' discretion.

The study was approved by an institutional review board.

Patients

For this analysis, we included patients with ER-positive and HER2-negative EBC, with known number of positive lymph nodes, tumor size, tumor histologic grade, and age. Furthermore, patients should have received ET (as per standard of care) and must be DR free and alive at 5 years from its initiation. Patients with prior neoadjuvant therapy were not allowed to be included in the study.

Objectives and endpoints

The primary objective was to test the validity of CTS5 as a prognostic tool, analyzing the association between CTS5 and the DR-Free Survival (DRFS). DRFS was defined as the time from the date of ET initiation to the first date of DR (defined as metastatic disease, excluding contralateral disease, and locoregional and ipsilateral recurrences).

The secondary objectives were to evaluate the calibration of the CTS5 model (comparing the expected rates of DR events by CTS5 and the observed ones) and second, to evaluate the association between CTS5 and the most relevant clinical variables (comparing the expected and observed DR events rates by menopausal status, use of prior adjuvant chemotherapy and duration of adjuvant ET).

Statistical analysis

Patients were stratified into the 3 risk groups (low-, intermediate-, and high-risk) using the CTS5 cutoffs with the formula described by Dowsett et al.[20] The Cox proportional hazard regression model was used to calculate the hazard ratios (HR) and their corresponding 95% confidence intervals (CI), from the continuous CTS5 and the categorical CTS5 scores defined by the risk groups. Kaplan-Meier survival estimates were used to determine the prognosis performance of CTS5, and the survival curves between the risk groups were compared using the log-rank test.

To determine the calibration of the model, expected and observed DR rates were used. The predicted risk for each patient was derived from the baseline hazard and the CTS5 score, as previously done by Noordhoek et al[22] The observed DR rates were calculated using the Kaplan-Meier survival estimates, with their corresponding 95% CI. The baseline hazard was adjusted for 20 randomly selected patients, using the CTS5 scores calculated from the CTS5 online tool (https://cts5-calculator.com). The expected and observed DR rates were compared in the 3 risk groups, and independently in 10 equal deciles of the expected DR rates. To compare the expected and observed rates, a chi-square test was used in each of the 3 risk groups, and in each decile of the expected risk.

A sensitivity analysis using ET duration, including missing data was performed.

P values < .05 were considered statistically significant. The R package version 4.1 was used for the statistical analyses (https://www.r-project.org).

Results

Patients characteristics

We selected a total of 5739 patients for the analysis, comprising 338 from the GEICAM/9805, 484 from the GEICAM/9906, 1073 from the GEICAM/2003-02, and 785 from the GEICAM/2003-10 clinical trials (Figure 1). From 2002 to 2005, more than 3000 patients per year were included in the *El Álamo IV registry:* 3052 patients in 2002, 3254 in 2003, 3461 in 2004, and 3335 in 2005. These patients were recruited from 43 institutions across Spain, covering 13 of the 17 Spanish regions. According to national registries, the total number of BC cases diagnosed in Spain during this period was 84 280, *El Álamo IV* registry represents 15.5% of them, from which 3059 patients were included in this analysis.

Baseline demographic and disease characteristics are described in Table 1. The median age was 54 years (19-90), with 40.4% and 59.6% being pre- and post-menopausal women, respectively. Additionally, 58.5% had negative lymph nodes, 62.9% had a tumor size <2 cm, 23.7% presented with histological tumor grade 3, and 7.2% with lobular BC. Adjuvant chemotherapy was administered to 78.5% of patients. With a median follow-up time of 11.3 years, the median exposure time to adjuvant ET was 60 months (range: 0-180 months), with 35.3% of patients receiving more than 60 months of treatment. ET in combination was administered to 37.3% of patients (97.2% sequentially, 1.4% concomitantly and 1.4% unknown).

CTS5 score validation

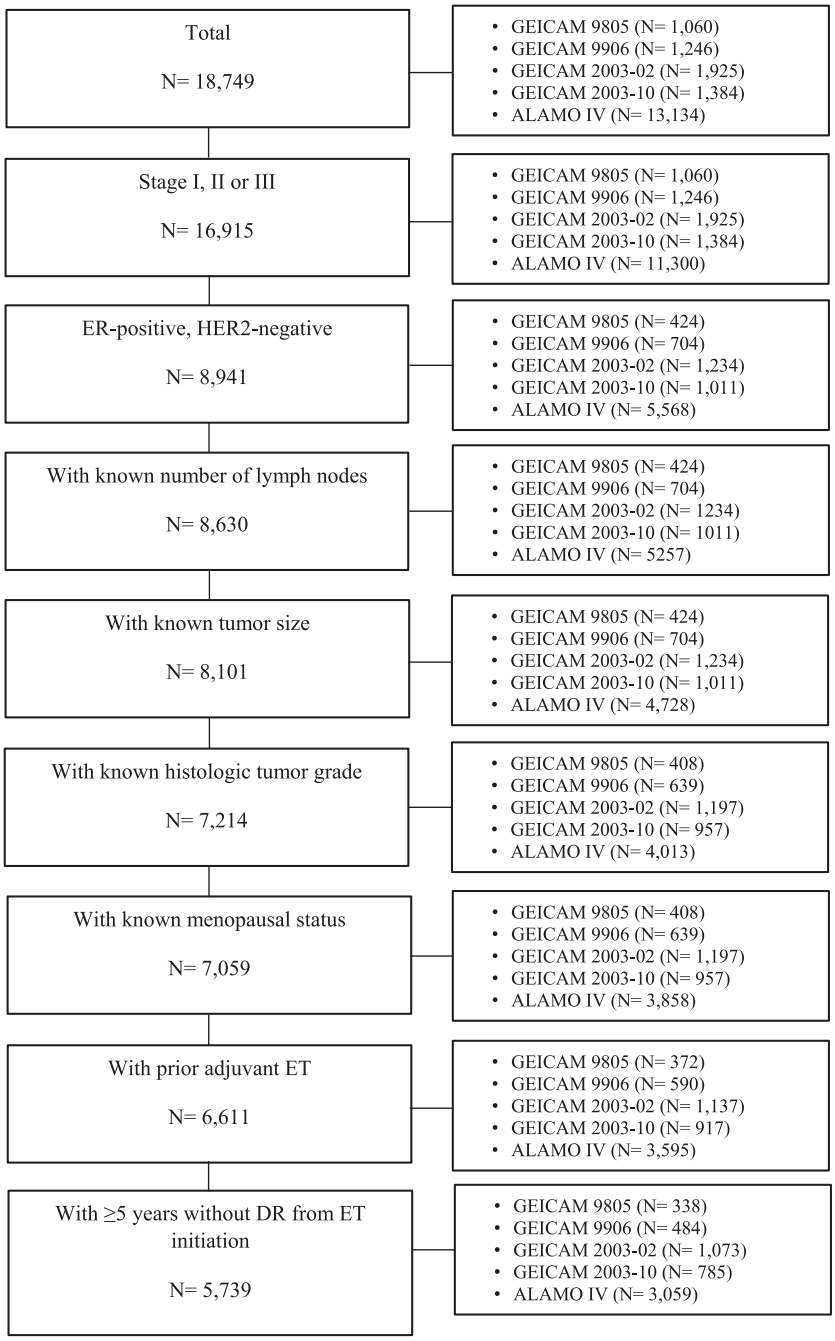
The median of CTS5 score was 3.26 (range 1.2-6.06); 43.9% of patients were classified as low-risk, 32.2% as intermediate-risk, and 23.9% as high-risk category. The distribution was not uniform by study due to the distinct inclusion criteria of each one. Specifically, clinical trials GEICAM/9805 and GEICAM/2003-02 included patients with negative lymph nodes, whereas studies GEICAM/9906 and GEICAM/2003-10 enrolled patients with positive lymph nodes.

After 5 years from the start of ET, 5.73% of patients had an event of DR. The Kaplan-Meier DRFS curves by risk groups are depicted in Figure 2. A significant difference in DR was seen among the 3 groups, HR for intermediate- versus low-risk, 2.55 (95% CI, 1.83-3.51; *P*-value < .0001) and HR for high- versus low-risk, 5.77 (95% CI, 4.28-7.78; *P*-value < .0001).

Subgroups analyses were conducted based on menopausal status (pre-menopausal and postmenopausal), duration of adjuvant ET (≤60 months and >60 months) and prior administration of adjuvant chemotherapy (yes and no). The results were generally consistent across subgroups, except for the comparison of intermediate- versus low-risk in patients not receiving adjuvant chemotherapy, as shown in Table 2.

CTS5 score calibration

In the low-risk group, the expected (by CTS5) and observed DR rates were 3.2 and 2.4, respectively (95% CI, 1.8-3.1), *P*-value = .0314. For the intermediate-risk group, the



ER denotes estrogen receptor; N denotes lymph nodes; ET denotes endocrine therapy; DR denotes distant recurrence.

Figure 1. Flowchart.

corresponding rates were 7.1 and 6.1 (95% CI, 4.9-7.2), *P*-value = .1036, and in the high-risk group 19.3 and 13.3 (95% CI, 11.4-15.2), *P*-value < .0001. For a detailed comparison between the expected and observed DR rates by deciles refer to Supplementary Table 1 and Figure 3

The comparison between the expected and observed DR rates by CTS5 risk groups in the aforementioned subgroups showed an overestimation of DR events in high-risk patients, except for those treated with >60 months of adjuvant ET as indicated in Table 3.

A sensitivity analysis, including data from patients whose ET duration was not available (*N* = 1889), was performed (Supplementary Table 2). We categorized ET duration into 3 groups: less than 5 years (*N* = 1823 patients), 5-7 years (*N* = 1716 patients), and more than 7 years (*N* = 311 patients). This analysis revealed a consistent tendency to overestimate DR events in high-risk patients, except for those on extended ET regimens. However, the interpretation of these findings is limited by the small sample size in these categories.

In particular, this model tends to overestimate the risk in the highest deciles (deciles 8-10).

Association of CTS5 score and relevant clinical variables

This analysis confirmed some well-established factors associated with poor prognosis, including the number of

Table 1. Baseline characteristics of patients.

	Total
	N = 5739
Median age, years (range)	54 (19-90)
Menopausal status, *n* (%)	
Postmenopausal	3420 (59.6%)
Premenopausal	2319 (40.4%)
Histologic tumor type, *n* (%)	
Invasive ductal carcinoma	5059 (88.2%)
Invasive lobular carcinoma	415 (7.2%)
Other	249 (4.3%)
Unknown	16 (0.3%)
Number of positive axillary lymph nodes, *n* (%)	
0	3359 (58.5%)
1-3	1670 (29.1%)
≥ 4	710 (12.4%)
Tumor size, *n* (%)	
≤ 2 cm	3608 (62.9%)
> 2 cm and ≤5 cm	1987 (34.6%)
> 5 cm	144 (2.5%)
Histopathological tumor grade, *n* (%)	
G1, well differentiated	1335 (23.3%)
G2, moderately differentiated	3044 (53.0%)
G3, poorly differentiated	1360 (23.7%)
Ki-67 level, *n* (%)	
≥20%	1808 (31.5%)
<20%	343 (6.0%)
Unknown	3588 (62.5%)
Prior chemotherapy, *n* (%)	
No	1237 (21.5%)
Yes	4502 (78.5%)
Median duration of ET, months (range)	60 (0-180)
Duration of ET, *n* (%)	
≤60 months	1823 (31.8%)
> 60 months	2027 (35.3%)
Unknown	1889 (32.9%)
Type of ET, *n* (%)[†]	
SERM + aromatase inhibitors	2136 (37.2%)
SERM	2110 (36.7%)
Aromatase inhibitors	1484 (25.9%)
SERD + aromatase inhibitors	1 (0.1%)
Other	8 (0.1%)

[†]ET in combination was administered in 37.3 % of patients (97.2% sequentially, 1.4% concomitantly and 1.4% unknown).
ET, endocrine therapy; G, grade; SERD, Selective Estrogen Receptor Degrader, SERM, Selective Estrogen Receptor Modulator

lymph nodes involved, tumor size, and histological tumor grade, outlined in Supplementary Table 3. The CTS5 score was higher for patients with 1-3 and >3 positive lymph nodes compared to negative lymph nodes, for patients with tumor size >2 cm to ≤5 cm and >5 cm compared to <2cm, as well as for patients with histological tumor grade 2 and 3 compared to grade 1.

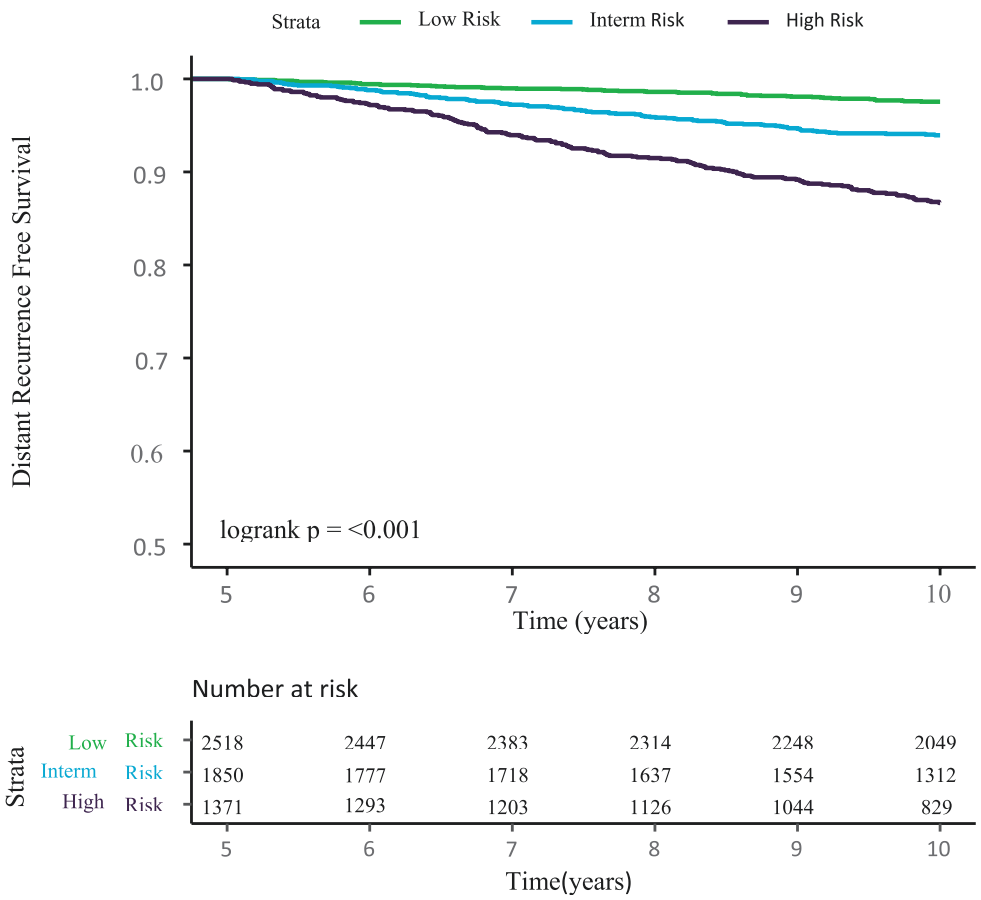
Discussion

Validated tools are crucial for tailoring systemic treatment strategies for patients with early-stage hormone receptor-positive HER2-negative BC, in which late recurrences represent a major challenge for cure.[7,8,13,16-18] In this GEICAM analysis, our goal was to validate the prognostic value of the CTS5 multivariate predictor for estimating DR beyond 5 years of ET in a cohort of patients enrolled in academic clinical trials of adjuvant chemotherapy along with participants in our national retrospective *El Álamo IV* registry (1996-2006). The CTS5 effectively classified our patients into different late DR risk categories, regardless of menopausal status, ET duration or chemotherapy treatment. However, the model tended to overestimate the number of events, particularly in the high-risk group, and this overestimation was more pronounced among patients treated with ET for less than 60 months and those not receiving adjuvant chemotherapy.

Notably, while the retrospective validation of the score based on the Royal Marsden records did not detect an excess in predicted versus observed events in the high-risk group,[24] the CTS5 post-5 years was applied to more than 6000 patients treated in the TEAM and IDEAL trials.[22] This validation revealed an overestimation of the late distant relapse risk in the high-risk patient category. The ABCSG-06 and 06a joint analysis[26] recently reported a similar trend in the high-risk category, suggesting the use of the continuous CTS5 score instead. Our dataset (comprising patients from 4 adjuvant systemic chemotherapy trials and a registry) showed similar results. The CTS5 demonstrated reduced effectiveness in the top risk deciles, with a 10.2% risk difference, aligning with previous calibrations in this controversial field.

The recent update of ASCO guidelines on the use of biomarkers for adjuvant chemotherapy and ET in early-stage BC suggests that additional calibration of the CTS5 predictor may be required.[21] Based on this recommendation and from a clear clinical perspective, we sought to retrospectively assess the model in our cohort, encompassing a significant number of patients along different risk-categories (58.5% node negative), histologic tumor types (7.2% lobular BC), and menopausal status (40.4% premenopausal patients). In fact, in our cohort patients were younger (median age 54 years) than in most of the previously reported sets participating in clinical trials.[20,26] This cohort also provides demographic diversity within a European context, comprising patients from diverse regions across Europe and add up to the previously published validations, on clinical trials, institutional series and national registries.[22-25,31,32] To expand the global implementation of this ready-to-use and cost-effective tool, local validations, such as this study, add value to locally adopt the general international recommendations and integrate them into our daily clinical practice.[21]

Consequently, to translate our findings into clinical practice, patients with a low/intermediate CTS5 score might consider skipping an extension of ET given their more favorable BC prognosis. In contrast, we should be cautious in the decision-making process with women with a high CTS5 score who will require more effective treatment strategies due to their poorer prognosis to prevent late distant-recurrences; biomarker-guided approaches will be crucial to optimize their therapeutic journey. Thus, while some institutional cohorts have suggested that CTS5 appeared to predict response to extended ET,[33] to discriminate in these upper deciles which



Kaplan-Meier curves for Distant Recurrence-Free Survival (DRFS) were represented for low, intermediate and high risk.

Figure 2. DRFS curves by risk groups.

Table 2. Comparison of HR of DR by subgroups.

	Intermediate-risk vs low-risk	High-risk vs low-risk
Premenopausal	1.87 (95% CI, 1.16-3.00) *P*-value = .0103	4.79 (95% CI, 3.12-7.37) *P*-value < .0001
Postmenopausal	3.31 (95% CI, 2.11-5.19) *P*-value < .0001	6.95 (95% CI, 4.52-10.66) *P*-value < .0001
ET ≤ 60 months	3.09 (95% CI, 1.80-5.29) *P*-value < .0001	4.75 (95% CI, 2.82-7.99) *P*-value < .0001
ET > 60 months	2.24 (95% CI, 1.23-4.06) *P*-value = .0081	8.61 (95% CI, 5.15-14.41) *P*-value < .0001
Yes CT	2.41 (95% CI, 1.68-3.43) *P*-value < .0001	5.39 (95% CI, 3.85-7.53) *P*-value < .0001
No CT	2.07 (95% CI, 0.87-4.94) *P*-value = .1	4.9 (95% CI, 2.26-10.62) *P*-value = .0001

CT, denotes chemotherapy, DR, denotes distant recurrence; ET, denotes endocrine therapy; HR, denotes hazard ratio

patients truly benefit from extended treatment approaches (which is the current strategy we could offer to high-risk patients) we would likely need to rely on more sophisticated genomic tools such as the Breast Cancer Index (BCI)[34] that could add more granularity based on tumor biology beyond classic clinical-pathological variables.

In this study, we provide pooled data on a representative cohort of mainly Spanish patients with notable follow up across several clinical trials and a registry. This comprehensive dataset allows us to focus on the long-term outcomes of hormone receptor-positive HER2-negative BC patients in both the controlled clinical trial and real-word settings. Data quality, particularly in coding the events of interest and disease characteristics, improves the robustness of our cohort. Nevertheless, we must acknowledge several limitations of our analysis. First, we did not control for ET duration in this

cohort of patients included either in clinical trials testing different adjuvant chemotherapy regimens or in a real-world registry in which ET duration was decided as per physician's criteria. As a result, we could not fully assess the controversial predictive value of the CTS5 tool for selecting candidates for extended ET regimens.[22,34] To address this limitation, we conducted a sensitivity analysis considering different intervals of ET duration (less than 5 years, 5-7 years, and more than 7 years), without finding any significant difference. However, in our cohort, the number of patients with ET durations exceeding 6 years was limited. Additionally most of our patients underwent adjuvant chemotherapy and with the current integration of multigene predictors (such as OncotypeDx, Mammaprint, Prosigna, or Endopredict) as valuable biomarkers in decision-making, some of these patients could have foregone chemotherapy in favor of exclusive ET adjuvant approaches. Finally, this retrospective analysis lacks representation of adjuvant treatments with newer CDK4/6 and PARP inhibitors, as these therapies have only recently been integrated into the treatment algorithm. Moreover, their impact on late distant recurrences requires further investigation in future studies. Germline BRCA1/2 mutation status was not available for these patients, as its assessment was not part of the standard of care at the time of enrollment. However, its low prevalence in unselected hormone receptor-positive/HER2-negative patients is unlikely to have significantly influenced the overall results. Further research on new biomarkers based on *t* accumulated knowledge about the biology of dormancy and the intricate dynamics between tumor cells and their microenvironment is highly needed to predict the long-term evolution of BC. Importantly, beyond the prognosis, we still lack reliable predictors of response to emerging adjuvant therapies such as PARP inhibitors, CDK4/6 inhibitors, new endocrine agents, their sequences, or combinations, to truly individualize the long-term treatment of our patients.

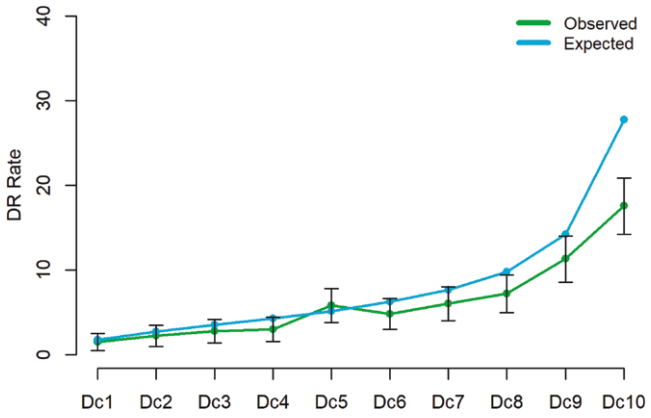


Figure 3. Comparison by deciles between the DR rates expected by CTS5 and observed.

Acknowledgments

We acknowledge the patients who participated in the analysis and their families and all the participating investigators. We also acknowledge the support of the GEICAM staff.

Author contributions

Sara Lopez-Tarruella, Marina Pollán, and Eva Carrasco conceived the study design. Sara Lopez-Tarruella, Marina Pollán,

Table 3. Comparison by risk groups between the DR rates expected by CTS5 and observed by subgroups.

CTS5 and DR		Number of patients	DR rates expected	DR rates observed	*P*-value
Low-risk	All patients	2,518	3.2	2.4 (1.8-3.1)	.0314
	Premenopausal	1144	3.1	2.9 (1.9–3.9)	.6999
	Postmenopausal	1374	3.3	2 (1.3–2.8)	.0099
	ET ≤ 60 months	883	3	2.5 (1.5–3.6)	.4024
	ET > 60 months	912	3.2	2.1 (1.1–3)	.0681
	Prior adjuvant CT	1698	3.5	2.7 (1.9–3.5)	.0996
	No prior adjuvant CT	820	2.7	1.8 (0.9–2.8)	.1414
Intermediate-risk	All patients	1850	7.1	6.1 (4.9–7.2)	.1036
	Pre-menopausal	707	7	5.3 (3.6–7)	.0854
	Post-menopausal	1143	7.1	6.5 (5–8)	.4875
	ET ≤ 60 months	513	7.2	7.5 (5.1–9.9)	.758
	ET > 60 months	628	7.1	4.6 (2.9–6.3)	.0179
	Prior adjuvant CT	1606	7.1	6.4 (5.1–7.6)	.3153
	No prior adjuvant CT	244	7.1	3.7 (1.1-6.2)	.0436
High-risk	All patients	1371	19.3	13.3 (11.4-15.2)	<.0001
	Pre-menopausal	468	18.3	13.3 (10–16.4)	.0106
	Post-menopausal	903	19.8	13.4 (11-15.7)	<.0001
	ET ≤ 60 months	427	19.4	11.4 (8.1–14.5)	.0002
	ET > 60 months	487	20	16.7 (13.2–20.1)	.1063
	Prior adjuvant CT	1198	19.3	13.9 (11.8-15.9)	<.0001
	No prior adjuvant CT	173	19.5	8.6 (3.7-13.2)	.0012

CT, denotes chemotherapy; ET denotes endocrine therapy.

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Funding

The trial sponsor is GEICAM Spanish Breast Cancer Group, and it was not financed by any third party. GEICAM is responsible for data collection, analysis, interpretation of the data, writing the report and decision to submit the paper for publication. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The content is solely the responsibility of the authors.

Conflicts of interest

Dr. Sara Lopez-Tarruella has received advisory by AstraZeneca, Novartis, Roche, Pfizer, Pierre Fabre, Lilly, Seagen, Daiichi Sankyo Europe GmbH, Gilead Sciences, MSD, GlaxoSmithKline, Veracyte and speaker honoraria by Lilly. Eva Carrasco has stock and other ownership interests from Lilly, has received travel and accommodations support from Roche and her husband has participated in consulting and advisory board activities with Bristol-Myers Squibb, Novartis, Celgene, Roche Pharma, Janssen, Amgen, Incyte, Abbvie and Pfizer, has received travel and accommodations support from Celgene, Novartis and Bristol-Myers Squibb. His institution has received research funding from Celgene, Janssen, Bristol-Myers Squibb, Novartis, Celgene, Roche/Genentech, Amgen, Pfizer and Abbvie. GEICAM has received research funding from Roche/Genentech, Bristol-Myers Squibb, Novartis, Pfizer, Celgene, AstraZeneca, Merck Sharp & Dohme, Pierre Fabre and Takeda. Raquel Andrés has received research funding from Roche/Genentech, Bristol-Myers Squibb, Novartis, Pfizer, Celgene, AstraZeneca, Merck Sharp & Dohme, Pierre Fabre and Takeda. Miguel Martín has received consulting fees from AstraZeneca, Amgen, Taiho Oncology, Roche/Genentech, Novartis, PharmaMar, Eli Lilly, PUMA, Taiho Oncology and Pfizer; speakers' honoraria from AstraZeneca, Amgen, Roche/Genentech, Novartis, Daiichi Sankyo, and Pfizer; and contracted research fees from Roche, Novartis, and PUMA. Sonia Servitja has received speaker honoraria by Daiichi-Sankyo, AstraZeneca, Roche Pharma and Novartis and advisory by Seagen, Genomic Health, MSD and Daiichi-Sankyo. Begoña Bermejo has received speaker honoraria by Pfizer, Roche, MSD, Palex, Eisai, Daichii-Sankyo, AstraZeneca and Seagen and advisory by MSD, Roche, Pierre Fabre, Novartis, AstraZeneca and Seagen. Antonio Antón has received speaker honoraria by Astrazeneca-Daiichi-Sankyo, Eli Lilly and Seagen, advisory by AstraZeneca-Daichii-Sankyo, Eli Lilly, Gilead and personal grant by AstraZeneca-Daiichi-Sankyo, Eli Lilly, Gilead, Pfizer and Seagen. Ángel Guerrero-Zotano has received institutional grant by Pfizer, advisory by AstraZeneca, Novartis, MSD, Pierre-Fabre, Exact Science, Menarini-Stemline, Daiichi Sankyo travel grant by Roche, Novartis, Pfizer, Gilead and Pierre Fabre and speaker honoraria by Roche, AstraZeneca, Daichi-Sankyo, Novartis, MSD, Pfizer and Menarini-Stemline. Montserrat Muñoz: Consulting/advisory relationship NO Research Funding NO Employment NO Expert Testimony Menarini, Novartis Honoraria NO Ownership Interests NO Intellectual Property Rights/inventor/patent holder NO Scientific Advisory Board Seagen Other (Please define) Travel Grants Roche, Gilead, Daiichi, Lilly, Pfizer. Luis Antonio Fernández has received speaker honoraria by BMS, MSD, Pierre-Fabre, Roche, Novartis and Pfizer and advisory by Novartis and Pfizer. Isabel Álvarez has received speaker honoraria by Roche Pharma, advisory by AstraZeneca, Pfizer, Novartis, Roche Pharma and Gilead and research funding by AstraZeneca, Pfizer, Novartis and Roche Pharma. Álvaro Rodríguez-Lescure has received speaker honoraria by Roche, Pfizer, Novartis, Lilly, AstraZeneca, Gilead, Daiichi-Sankyo, Eisai, MSD and Seagen, advisory by Roche, Pfizer, Novartis, Lilly, AstraZeneca, Daiichi-Sankyo, Gilead, MSD and Seagen. Encarna Adrover has received speaker honoraria from Pfizer, Lilly, AstraZeneca. Diana Moreno: Gilead and Novartis (honoraria for training session). The rest of the authors have no conflicts of interest.

Data availability

The studies from which the patients were selected were completed and closed, except *El Álamo IV* registry which is in data cleaning process. The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study protocols of the original clinical trials were approved by the corresponding institutional review boards and Regulatory Agencies. Informed consent was obtained from all individual participants included in the clinical trials. The current study was approved by an institutional review board.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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