Risk assessment tools and adjuvant therapy for breast cancer

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Chapter 3

OVERESTIMATION OF LATE DISTANT RECURRENCES IN HIGH-RISK PATIENTS WITH ER-POSITIVE BREAST CANCER: VALIDITY AND ACCURACY OF THE CTS5 RISK SCORE IN THE TEAM AND IDEAL TRIALS

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ABSTRACT

Purpose

Most distant recurrences (DRs) in women with hormone receptor-positive breast cancer occur after five years from diagnosis. The Clinical Treatment Score post-5 years (CTS5) estimates DRs after five years of adjuvant endocrine therapy (ET). The aim of this study was to externally validate the CTS5 as a prognostic/predictive tool.

Methods

The CTS5 categorizes patients who have been disease free for five years into low, intermediate, and high risk and calculates an absolute risk for developing DRs between five and ten years. Discrimination and calibration were assessed using data from the TEAM and IDEAL trials. The predictive value of the CTS5 was tested with data from the IDEAL trial.

Results

A total of 5895 patients from the TEAM trial and 1591 patients from the IDEAL trial were included. When assessing the CTS5 discrimination, significantly more DRs were found at ten years after diagnosis in the CTS5 high- and intermediate-risk groups than in the low-risk group (hazard ratio 5.7 [95% CI 3.6 – 8.8] and 2.8 [95% CI 1.7 – 4.4], respectively). In low- and intermediate-risk patients, the CTS5-predicted DR rates were higher, although not statistically significantly so, than observed rates. However, in high-risk patients, the CTS5-predicted DR rates were significantly higher than observed rates (29% versus 19%, respectively; $p<0.001$). The CTS5 was not predictive for extended adjuvant ET duration.

Conclusion

The CTS5 score as applied to patients treated in the TEAM and IDEAL cohorts discriminates between risk categories but overestimates the risk of late DRs in high-risk patients. Therefore, the numerical risk assessment from the CTS5 calculator in its current form should be interpreted with caution when used in daily clinical practice, particularly in high-risk patients.

INTRODUCTION

The disease course of estrogen receptor (ER)–positive breast cancer can be influenced significantly by targeting ER with adjuvant endocrine therapy (ET).[1] Currently, the optimal ET regimen for postmenopausal patients consists of either five years of treatment with an aromatase inhibitor (AI) or two to three years of tamoxifen followed by two to three years of an AI.[2] Tamoxifen monotherapy for five years has been proven an inferior treatment.[3]

The majority of distant recurrences (DRs) occur after the first five years from diagnosis (i.e., after ET has been stopped).[4] Increasingly, attention is being drawn to the challenge of preventing late relapse in ER-positive breast cancer. Extending ET to a total of ten years has proven beneficial for a minority of patients, if the initial treatment consisted of tamoxifen monotherapy, both for extended treatment with tamoxifen and for switching to an AI.[5,6] However, studies so far have not shown a clinically relevant benefit of extended therapy if the initial treatment included an AI.[7-10] ET is accompanied by significant toxicity, and extended therapy should only be prescribed after carefully weighing harms and benefits.[7,11,12]

Over the past decades, the field of estimating disease recurrences has mostly shifted toward gene expression profiles. For example, gene expression profiling can be used to identify luminal A and luminal B tumors, two subtypes of ER-positive breast cancer that reflect a different tumor biology and disease prognosis. Neither subtype, however, is predictive for a better response to endocrine therapy.[13-18] Moreover, gene expression profiles are expensive and not universally available. The value of gene expression profiling in routine clinical practice and, more specifically, the identification of patient subgroups where they should be used, remains challenging.[19] With this rationale, the Clinical Treatment Score post-5 years (CTS5) has been described using data from the ATAC and BIG-1-98 trials.[20-22] The CTS5 is a prognostic tool that aims to estimate the risk for late DRs and categorizes postmenopausal patients into low-, intermediate-, and high-risk groups on the basis of commonly reported clinicopathologic parameters and is therefore cheap and easy to use.

Prognostic models, such as the CTS5, are important because they provide additional information about the disease course and can help to guide the optimal treatment strategy. A crucial aspect of implementing prognostic models into daily clinical practice is the external validation of these models because using unvalidated models could lead to inappropriate modifications of treatment regimens. The CTS5 was created with patient data from two trial cohorts and was validated using the combined patient cohorts of these two trials[20-22] and, therefore, requires further validation. This study aims to externally validate the CTS5 as a prognostic tool for late DRs and to assess it as a predictive tool for choosing the optimal duration of extended ET using patient data from two prospective randomized clinical trials: the Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) trial[2] and the Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL) trial.[7]

METHODS

Algorithm

The CTS5 categorizes postmenopausal patients with ER-positive breast cancer who are disease free after five years of standard ET into low- (< 5%), intermediate- (5% – 10%), and high- (> 10%) risk groups for developing a DR between five and ten years from diagnosis.[21] This categorization is based on the number of positive lymph nodes, grade, size and quadratic size of the tumor, and age at diagnosis. Consistent with the method used in the original CTS5 publication,[21] tumor size was capped at 30 mm. Nodal status was divided into five groups: 0, node negative; 1, 1 positive lymph node; 2, 2-3 positive nodes; 3, 4-9 positive nodes; and 4, > 9 positive nodes. The CTS5 score is calculated using the following equation:

$$CTS5\ 5 = 0.438 * nodes + 0.988 * (0.093 * size - 0.001 * size^2 + 0.375 * grade + 0.017 * age)$$

The cutoff values were established at < 3.13 for the low-risk group, 3.13 – 3.86 for the intermediate-risk group, and > 3.86 for the high-risk group.[21] The online CTS5 calculator provides both the risk category and an absolute risk of developing a late DR for individual patients.[23]

TEAM study cohort

TEAM is a phase III trial that randomly assigned postmenopausal patients with ER-positive breast cancer to either five years of exemestane or two to three years of tamoxifen followed by two to three years of exemestane. All patients were randomly assigned within one month after diagnosis. Details of the trial have been reported previously.[2,24] For the analyses of this study, all patients were included who were disease free at five years after random assignment and for whom all clinicopathologic data were available.

IDEAL study cohort

IDEAL is a phase III randomized trial that investigated the optimal duration of letrozole after standard ET in postmenopausal patients with ER-positive early breast cancer. Patients needed to be disease free after five years of standard ET before random assignment to either 2.5 or 5 years of extended treatment with letrozole. More than 90% of patients were randomly assigned within six months after stopping standard ET. No significant difference in disease-free survival was found between the treatment arms after a median follow-up of 6.6 years after random assignment. Details of the trial have been reported previously.[7] For this study, all patients were included for whom all clinicopathologic data were available.

Validation as prognostic tool

The CTS5 is validated as a prognostic tool if it is able to significantly differentiate patients into low-, intermediate-, and high-risk groups for developing DRs and if the predicted absolute risks for developing DRs correspond with the observed DR rates (i.e., is properly calibrated).

Validation as a predictive tool

The CTS5 is validated as a predictive tool for choosing between 2.5 years and 5 years extended ET if there is statistically significant interaction between the risk categories and the treatment arms of the IDEAL trial.

Statistical analyses

The primary end point for the CTS5 is a late DR, defined as the occurrence of a DR between five and ten years after diagnosis. For this study, this is translated to the occurrence of a DR at ten years after random assignment in the TEAM cohort and at five years after random assignment in the IDEAL cohort. Kaplan-Meier survival estimates and cumulative incidence survival estimates were used to determine the discriminative prognostic performance of CTS5. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) and P-values for Kaplan-Meier survival estimates were estimated from univariable Cox regression models. HRs and 95% CIs for cumulative incidence survival estimates were derived from Fine and Gray analyses.[25,26]

To examine the calibration, the observed DR rates were compared with the predicted number of DRs. To calculate the predicted late DR rates, six random patients from the TEAM cohort and six random patients from the IDEAL cohort were entered in the online CTS5 calculator.[23] The risk scores that were provided by the calculator for these patients were used to calculate the cumulative baseline hazard at five years used in the algorithm behind the online calculator, using the following equation:

$$\text{“Baseline hazard”} = (-\ln(1 - \text{“predicted risk”}))/(e^{\text{CTS5 score}})$$

These 12 baseline hazards were then averaged. This average baseline hazard (0.00223) was used to calculate the predicted risks for the other patients, using the following equation:

$$\text{“Predicted risk”} = 1 - (e^{\wedge}(-0.00223*(e^{\text{CTS5 score}})))$$

These calculated risk scores were then cross-checked with the risk scores provided by the online calculator for another twelve random patients, six from the TEAM cohort and six from the IDEAL cohort. These were identical. The observed DR rates were determined using Kaplan-Meier survival estimates and cumulative incidence survival estimates[25] to account for death as a competing risk. To examine the calibration, the observed DR rates were compared with the predicted number of DRs for ten equal deciles.

To test the predictive value of the CTS5 for extended ET, Cox regression was used to test for interaction between the risk categories and treatment arms of the IDEAL cohort. Treatment arm and risk category were used as coefficients in the Cox regression interaction model. $P < 0.05$ was considered statistically significant. Analyses were performed using SPSS version 23.0 (IBM Corporation, Chicago, IL) and R 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) statistical software.

Ethical standards

The study was conducted in compliance with the guidelines of the Declaration of Helsinki, International Conference on Harmonization and Good Clinical Practice. The TEAM trial was approved by the medical ethics committee of the Erasmus Medical Center Rotterdam (198.231/2001/7). The IDEAL trial was approved by the medical ethics committee of the Leiden University Medical Center (P06.217).

RESULTS

Patients in the study cohorts

The TEAM trial consists of 9,779 patients. Of those patients, 2,366 were excluded because they withdrew informed consent, experienced a relapse, died, or were lost to follow-up before five years from random assignment. Another 391 patients were excluded because they continued treatment in the IDEAL trial. For 1,127 of the remaining 7,022 patients, a CTS5 and accompanying risk prediction could not be calculated because of missing clinicopathologic parameters. Thus, the cohort used in this study consisted of 5,895 patients (hereafter called the TEAM cohort; **figure 1A**). For the TEAM cohort, the observed late DR rate at ten years after random assignment was 8.7%. The IDEAL trial consists of 1,824 patients. For 233 patients, a CTS5 and risk prediction could not be calculated, which left 1,591 patients for this analysis (hereafter called the IDEAL cohort; **figure 1B**). For the IDEAL cohort, the observed late DR rate at five years after random assignment was 6.8%.

Comparison of cohorts

The observed late DR rates were 7.0% for the ATAC cohort and 5.5% for the BIG-1-98 cohort used to train and test the CTS5.[21] In the TEAM cohort, 2,113 patients (35.8%) were categorized into the low-risk group, 2,159 (36.6%) into the intermediate-risk group, and 1,623 (27.5%) into the high-risk group. Patients from the TEAM cohort were comparable to patients in the ATAC and BIG-1-98 cohorts with regard to baseline characteristics, treatment strategy (use of chemotherapy and type of ET), and overall late DR rates (**table 1**).[20-22] Patients in the TEAM cohort had slightly larger tumors (43% of patients had T21 tumors vs. 32% and 35% in the ATAC and BIG-1-98 cohorts, respectively; $P < 0.001$), and more patients had N1 disease (40% vs. 32% and 40%, respectively; $P < 0.001$).

In the IDEAL cohort, 343 patients (21.6%) were categorized into the low-risk group, 649 (40.8%) into the intermediate-risk group, and 599 (37.6%) into the high-risk group. Patients in the IDEAL cohort had some baseline characteristics that would classify them at higher risk than the patients in the ATAC and BIG-1-98 cohorts, such as age at diagnosis and number of positive lymph nodes (**table 1**). This resulted in a different distribution of patients over the risk categories and is reflected in a significantly higher proportion of patients who received chemotherapy. Nevertheless, within the three CTS5 risk categories, there were no significant differences among the cohorts in baseline characteristics and risk factors apart from age. In addition, the overall late DR rates at ten years were comparable between the IDEAL cohort and the ATAC and BIG-1-98 cohorts.

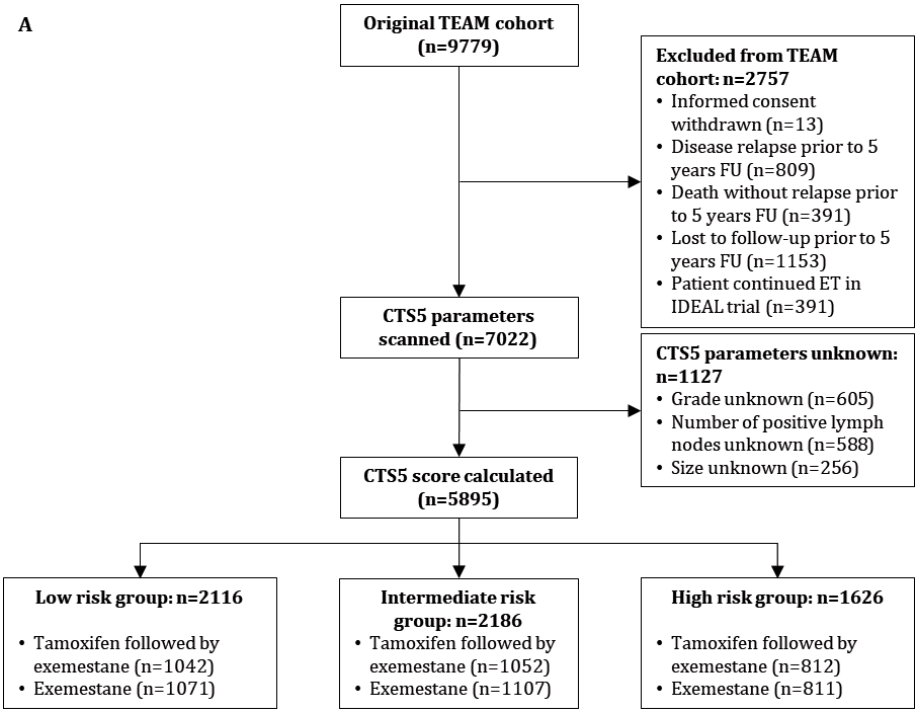


Figure 1: CONSORT diagram to account for missing patients in the TEAM cohort[2] (A) and in the IDEAL cohort[7] (B).

CTS5 = Clinical treatment score post-5 years.[21] DR = distant recurrence. ET = endocrine therapy.

The TEAM cohort	Total	Low-risk	Intermediate-risk	High-risk
Total	**5895**	**2113 (35.8)**	**2159 (36.6)**	**1623 (27.5)**
Age (years) Median	63	61	63	66
Interquartile range	57 – 70	56 – 66	58 – 70	59 – 74
Tumor size (mm) < 10	376 (6.4)	343 (16.2)	30 (1.4)	3 (0.2)
10 – 20	2968 (50.3)	1688 (79.9)	1037 (48.0)	243 (15.0)
> 20	2551 (43.3)	82 (3.9)	1092 (50.6)	1377 (84.8)
Histological grade I	1163 (19.7)	757 (35.8)	304 (14.1)	102 (6.3)
II	3176 (53.9)	1195 (56.6)	1221 (56.6)	760 (46.8)
III	1556 (26.4)	161 (7.6)	634 (29.4)	761 (46.9)
Positive lymph nodes 0	3501 (59.4)	1855 (87.8)	1359 (62.9)	287 (17.7)
1	1182 (20.1)	239 (11.3)	572 (26.5)	371 (22.9)
2 – 3	722 (12.2)	19 (0.9)	208 (9.6)	495 (30.5)
4 – 9	377 (6.4)	-	20 (0.9)	357 (22.0)
> 9	113 (1.9)	-	-	113 (7.0)
Prior chemotherapy yes	1929 (32.7)	398 (18.8)	789 (36.5)	742 (45.7)
Allocated ET 5 years EXE	2989 (50.7)	1071 (50.7)	1107 (51.3)	811 (50.0)
2-3 years TAM, 2-3 years EXE	2906 (49.3)	1042 (49.3)	1052 (48.7)	812 (50.0)

The IDEAL cohort	Total	Low-risk	Intermediate-risk	High-risk
Total	**1591**	**343 (21.6)**	**649 (40.8)**	**599 (37.6)**
Age (years) Median	55	52	55	56
Interquartile range	49 – 61	47 – 58	48 – 62	50 – 62
Tumor size (mm) < 10	56 (3.5)	47 (13.7)	8 (1.2)	1 (0.2)
10 – 20	607 (3.5)	251 (73.2)	267 (41.1)	89 (14.9)
> 20	928 (58.3)	45 (13.1)	374 (57.6)	509 (85.0)
Histological grade I	277 (17.4)	128 (37.3)	105 (16.2)	44 (7.3)
II	760 (47.8)	161 (46.9)	310 (47.8)	289 (48.2)
III	554 (34.8)	54 (15.7)	234 (36.1)	266 (44.4)
Positive lymph nodes 0	614 (38.6)	236 (68.8)	344 (53.0)	34 (5.7)
1	388 (24.4)	94 (27.4)	192 (29.6)	102 (17.0)
2 – 3	301 (18.9)	13 (3.8)	98 (15.1)	190 (31.7)
4 – 9	220 (13.8)	-	14 (2.2)	206 (34.4)
> 9	68 (4.3)	-	1 (0.2)	67 (11.2)
Prior chemotherapy yes	1085 (68.2)	230 (67.1)	403 (62.1)	452 (75.5)
Initial ET 5 years TAM	180 (11.3)	44 (12.8)	82 (12.6)	54 (9.0)
5 years AI	465 (29.2)	85 (24.8)	189 (29.1)	191 (31.9)
2-3 years TAM, 2-3 years AI	946 (59.5)	214 (62.4)	378 (58.2)	354 (59.1)
Allocated extended ET 2.5 years	785 (49.4)	172 (50.1)	336 (51.8)	278 (46.4)
5 years	805 (50.6)	171 (49.9)	313 (48.2)	321 (53.6)

Table 1: Overview of clinicopathologic and demographic characteristics of the patients in the TEAM and IDEAL cohorts. All values are N (%).

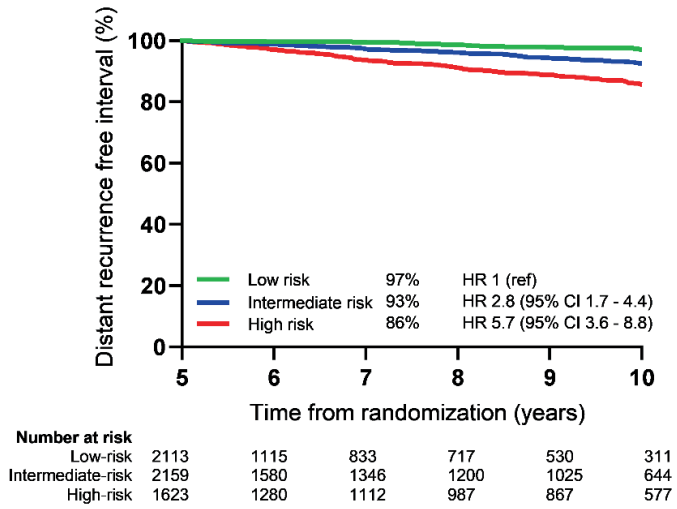
AI = aromatase inhibitor. ET = endocrine therapy. EXE = exemestane. TAM = tamoxifen.

Prognostic validation

Discrimination. In the TEAM cohort, the DR-free interval (DRFi) was 97% (95% CI 96% – 98%) in the low-risk group, 93% (95% CI 91% – 94%) in the intermediate-risk group, and 86% (95% CI 84% – 88%) in the high-risk group. The DRFi was significantly lower in the high-risk group (HR 5.7; 95% CI 3.6 – 8.8; log-rank P < 0.001) and the intermediate-risk group (HR 2.8; 95% CI 1.7 – 4.4; log-rank P < 0.001) compared with the low-risk group (**figure 2A**).

In the IDEAL cohort, the DRFi was 98% (95% CI 96% – 99%) in the low-risk group, 95% (95% CI 93% – 97%) in the intermediate-risk group, and 89% (95% CI 87% – 92%) in the high-risk group. The DRFi was significantly lower in the high-risk group (HR 4.8; 95% CI 2.3 – 10.2; log-rank P < 0.001) and intermediate-risk group (HR 2.2; 95% CI 1.0 – 4.8; log-rank P = 0.037) compared with the low-risk group as well (**figure 2B**).

A



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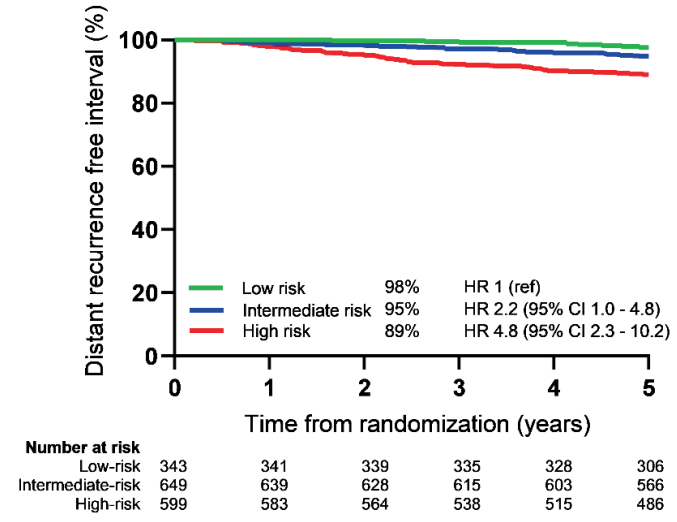

Figure 2: Kaplan-Meier survival estimates of observed late distant recurrence (DR) rates with accompanying risk table, indicating discriminatory prognostic value of the Clinical Treatment Score post-5 years (CTS5) for DRs in patient from the TEAM (A) and IDEAL (B) cohorts.

Calibration. In patients from the TEAM cohort with a predicted late DR risk up to 7%, the observed late DR rates corresponded with the predicted rates. However, in patients with higher predicted risks, the observed late DR rates were significantly lower than the predicted rates (**table 2**; **figure 3A**). In the highest decile, the absolute difference between the predicted DR rate and the observed rate was 10% (29.0% vs 19.3% [95% CI, 15.3 – 23.0], respectively; **figure 4A**).

In patients from the IDEAL cohort with predicted risk up to 8%, the predicted rate was higher than the observed rates, although not statistically significant. However, in patients with a higher predicted risk, the predicted rate was significantly higher than the observed rates (**table 2**; **figure 3B**). In the patients with the highest predicted risk, the predicted DR rate was 31.6%, while the observed rate was only 15.5% (95% CI, 9.6 – 21.0; **figure 4B**).

The observed late DR rates using the cumulative incidence method did not differ significantly from the rates obtained with the Kaplan-Meier method (data not shown).

The TEAM cohort	**Predicted** %	**Observed** % (95% CI)
Low-risk group	3.4	3.0 (1.6 – 4.3)
Intermediate-risk group	7.2	7.4 (5.8 – 86)
High-risk group	19.0	14.2 (12.1 – 16.3)
The IDEAL cohort	**Predicted** %	**Observed** % (95% CI)
Low-risk group	3.6	2.4 (0.8 – 4.1)
Intermediate-risk group	7.2	5.2 (3.5 – 6.9)
High-risk group	19.5	10.9 (8.4 – 13.4)

Table 2: Observed and predicted probability of late distant recurrences with accompanying 95% confidence intervals in the three risk categories in the TEAM and IDEAL cohorts.

CI = confidence interval.

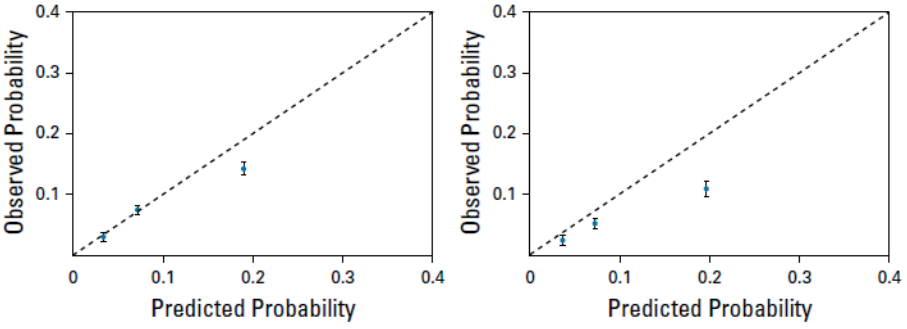

Figure 3: Observed and predicted probability of distant recurrences with accompanying 95% confidence intervals in the three risk categories in the TEAM (A) and IDEAL (B) cohorts.

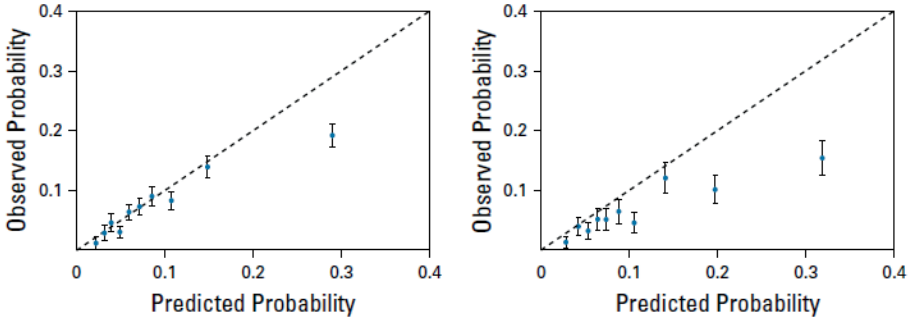

Figure 4: Observed and predicted probability of distant recurrences with accompanying 95% confidence intervals in ten equal deciles in the TEAM (A) and IDEAL (B) cohorts.

Predictive validation

In the IDEAL cohort, there was no statistically significant interaction between the risk categories and the treatment allocation (P = 0.5). No difference in observed DR rates was seen between 2.5 and 5 years of extended ET in the low-risk (HR 0.6; 95% CI 0.1 – 2.5), intermediate-risk (HR 1.7; 95% CI 0.8 – 3.3), or high-risk (HR 1.2; 95% CI 0.7 – 1.9) groups (**table 3**). Thus, there was no risk category in which the treatment allocation had a significant effect on the occurrence of late DR.

	2.5 years extended ET	5 years extended ET	P-value
Low-risk group	3.4	3.0 (1.6 – 4.3)	0.49
Intermediate-risk group	7.2	7.4 (5.8 – 86)	0.15
High-risk group	19.0	14.2 (12.1 – 16.3)	0.50

Table 3: Absolute late distant recurrence rates in the IDEAL cohort stratified by treatment arm and risk group.

P-values are derived from univariable Cox regression models.

DISCUSSION

Considering the substantial risk of late DRs for patients with ER-positive breast cancer, even after five years of ET, and the potential benefit of extended ET, there is a demand for prognostic and predictive models.[4,27] The CTS5 was developed for this purpose. It aims to estimate the DR rate between five and ten years from diagnosis for postmenopausal patients with ER-positive breast cancer who remain disease free after five years of standard ET.[21]

As applied to the TEAM and IDEAL cohorts, the CTS5 is able to discriminate postmenopausal patients with ER-positive breast cancer into three risk categories with respect to late DR. In the two large cohorts of trial patients used in these analyses, the risk of late DR as predicted by the CTS5 corresponded to the observed DR rates in low-risk patients, but the CTS5 overestimated the observed risk of DR in patients with a higher

predicted risk. Furthermore, the CTS5 could not predict benefit of 5 years over 2.5 years of extended ET using data from the IDEAL cohort.

The discrimination of the CTS5 has also been tested and validated in one retrospective cohort of non-trial patients with ER-positive breast cancer; however, the calibration was not tested in that study.[28] Although our study is one of the first that aimed to externally validate it, the CTS5 is already being used in clinical practice through the online calculator.[23]

Patients in the TEAM cohort, who had ER-positive breast cancer and were disease free for five years on either exemestane monotherapy or tamoxifen followed by exemestane, were comparable to patients in both cohorts used to create the CTS5 with regard to most risk factors, treatment strategy, and overall DR rates. The proportional distribution of patients into the three risk categories was also similar.[20-22] Because there was no difference in the definition of DR, it was expected that the predicted late DR risk would not differ from the observed DR rates. This was confirmed in low- and intermediate-risk patients. However, in the high-risk patients, the predicted risk was significantly higher than the observed late DR rate (19% and 14%, respectively). Although 14% would still be categorized as high risk, a more valid numerical estimation can lead to more accurately tailored treatment advice.

Patients in the IDEAL cohort who had ER-positive breast cancer and were disease free for five years on any ET had comparable baseline characteristics within the risk categories to both CTS5 cohorts and had comparable overall DR rates. However, IDEAL patients differed from the CTS5 cohorts with regard to treatment strategy; patients in the IDEAL cohort were treated with extended ET for either 2.5 or 5 years. Preliminary results from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis on extended ET showed that extending ET beyond the first five years may yield an absolute risk reduction of late DR of 1%-5% at ten years after diagnosis, with the effect size depending on the type of ET given during the first five years.[29]

When applying the CTS5 to the IDEAL cohort, the predicted DR rates were similar to the observed DR rates in low-risk patients, but in the highest risk decile, the CTS5 predicted a DR rate of 31.6%, while we observed a DR rate of 15.5% (95% CI, 9.6% to 21.0%). It is possible that the difference in treatment strategy led to a slight reduction in late DR rates (up to 5% according to the preliminary data of the EBCTCG), but extended treatment is unlikely to account for the 16% risk difference that was observed in this analysis.

A potential explanation for the difference in observed and predicted DR rates is the discrepancy in the years of diagnosis between the cohorts. While patients in the ATAC and BIG-1-98 cohorts were diagnosed between 1996 and 2003, patients in the TEAM and IDEAL cohorts were diagnosed between 2001 and 2006. Over this period, significant improvements in diagnostic accuracy (reliability of hormone receptor and human epidermal growth factor receptor 2 [HER2] status determination[30]) and systemic therapy (chemotherapy regimens and anti-HER2 medication) were made. Moreover, in the ATAC and BIG-1-98 cohorts, 20% and 24% of patients were treated with chemotherapy, while this was 33% and 68% in the TEAM and IDEAL cohorts, respectively. This could explain

the observation that the largest difference between observed and predicted late DR rates was seen in high-risk patients.

The most common reason for excluding patients from the TEAM and IDEAL trial cohorts to create the cohorts used in this study was unknown grade (**figure 1**). This was mostly due to the difficulty in scoring the histologic grade of lobular carcinomas.[31] Because there were no differences in late DR rates between the included patients and patients who were excluded on the basis of unknown grade (data not shown), this is not likely to bias the results of our analyses.

Furthermore, an aspect to keep in mind is the difference between prognostic and predictive tools.[32] Prognostic tools aim to distinguish patients with an inherently worse prognosis from those with a better prognosis, while predictive tools aim to distinguish those patients who will respond well to treatment from those who will not. Often, prognostic tools are not predictive and should not be used as such because patients with a worse prognosis are not necessarily the same patients who benefit from more extensive therapy.[33] In patients treated in the IDEAL trial, the CTS5 was not able to select patients who benefit from 5 years of extended ET as opposed to 2.5 years. Because of the design of the IDEAL trial, it was not possible to investigate whether the CTS5 is predictive of the type of extended ET (i.e., tamoxifen v AI v no extended ET).

Future prognostic and predictive models will most likely focus on genetic and/or functional profiles, and although these have shown promising results so far, accessibility and availability in daily clinical practice need to be prioritized as well.[19] This is one major advantage of the CTS5 because it is based on clinicopathologic parameters that are available for all patients and is cheap and easy to implement across all health care settings.

In conclusion, the CTS5 as applied to patients treated in the TEAM and IDEAL cohorts categorizes patients into low-, intermediate-, and high-risk groups. In low-risk patients, the predicted late DR risks correspond with the observed DR rates, but the CTS5 overestimates the risk of late DRs in high-risk patients from the TEAM and IDEAL cohorts. Using patient data from the IDEAL cohort, the CTS5 cannot be validated as a predictive tool for extended ET either. Especially in high-risk patients, an unrealistic assessment of the risk to develop a late DR could potentially lead to overtreatment. Therefore, the numerical risk assessment from the CTS5 calculator in its current form should be interpreted with caution when used in daily clinical practice, particularly when used in high-risk patients.

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