9P-Long term recurrence risk predictions by CanAssist Breast in a sub-cohort of TEAM

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OncoStem CanAssist Breast predicts risk of recurrence

Abstract

Background: CanAssist Breast (CAB) is an IHC based prognostic test that predicts the risk of distant recurrence in hormone receptor (HR) positive, HER2 negative early breast cancer within 5 years from diagnosis. CAB has been validated extensively on retrospective cohorts from India, USA and Europe showing its comparable performance across these divergent cohorts. The current study for the first time demonstrates the recurrence risk predictions up to 10 years in a sub-cohort of a prospective clinical trial, TEAM (Tamoxifen, Exemestane Adjuvant Multinational).

Methods: CAB has been assessed on 480 Dutch patient tumor samples (FFPE embedded) enrolled in the TEAM trial from 22 centres. TEAM is a large, international clinical trial that recruited 9766 post-menopausal women, randomized for the use of hormonal therapy, sequential (2-3 years Tamoxifen + 3-2 years exemestane) or exemestane alone (5 years) and patients were followed up for at least 10 years (median=10.4, 95% CI:10.3-10.6, range: 0.93-15.45). The investigators performing CAB were blinded to clinical outcomes. The recurrence risk predictions by CAB were compared with patient outcomes by the LUMC team. Of 480 patients, the current analysis is restricted to 434 HER2 negative patients. The performance of CAB was estimated with Kaplan-Meier survival analysis and hazard ratios (HR) by log rank test.

Results: Our study cohort had 68.4% patients with node-positive disease, 55.6% had tumors greater than 2cm (T2) and 25.8% had poorly differentiated tumors (G3). 79.3% of the cohort was treated with hormonal therapy alone, either exemestane alone or sequential therapy for a period of 5 years. CAB stratified 68% of the total cohort as low risk and 32% as high risk. All-cause mortality was 39% in CAB low risk and it was 44% in CAB high risk (HR:1.45 (0.99-2.1),p=0.04). Distant event rates and death due to breast cancer were 11% in CAB low-risk and 30% in CAB high-risk (HR: 2.91 (1.76-4.82), p=0.0001). CAB risk stratification across both the arms of hormonal therapy was significant with an HR of 4.76 (2.26-10), P<0.0001 in the exemestane arm and an HR of 2 (1-3.99), P=0.026 in the sequential arm. CAB risk stratification was not influenced by chemotherapy, and it was significant in the total cohort and across both the arms of hormonal therapy. In node-positive sub-cohort HR for CAB was significant and greater than 2 in the total cohort and in both the arms, with event (distant metastasis and death due to breast cancer) rates of 9% in the exemestane arm. CAB predicted the benefit of exemestane for low-risk (HR: 1.78 (1.07-2.94), P=0.02) and chemotherapy for high-risk patients (HR: 2.76 (1.44-5.23), P=0.016). CAB risk score had a higher and significant HR of 2.48 (1.52-4.08), P=0.0003 over clinical parameters, tumor size, node status and histological grade.

Conclusions: Data from a randomised trial show the usefulness of CAB for long term (10 years) recurrence risk predictions in early-stage HR-positive, HER2 negative breast cancer.

Clinical trial identification: ClinicalTrials.gov NCT00279448, NCT00032136, and NCT00036270; Netherlands

Introduction

- CanAssist Breast (CAB) is an immunohistochemistry based prognostic test developed using Indian breast cancer patient samples and validated on multiple cohorts from US, Spain, Germany, Austria, Italy.[2-5]
- CAB provided accurate and comparable prognostic information in South Asian and European breast cancer patients within 5 years from diagnosis[4, 5]
- CAB risk stratification was also useful in identifying patients who do not require chemotherapy from the 'clinically high-risk' patients with node-positive /luminal-B disease[3-5]
- Similarly CAB accurately identified patients requiring chemotherapy out of the "clinically low-risk patients".[4]
- CAB risk stratification was independent of age, clinical parameters, proliferative index (Ki-67) and racial/ethnic differences[2-5]
- CAB's low-risk accuracy was on par with that of Oncotype DX/MammaPrint with 83%/85% concordance in patients called low-risk[5] by both the tests.[5-6]
- **The current study for the first time assesses recurrence risk predictions at 10 years from diagnosis in a sub-cohort of a prospective randomized clinical trial, TEAM.**

Methods

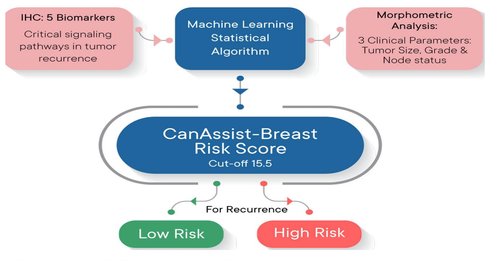
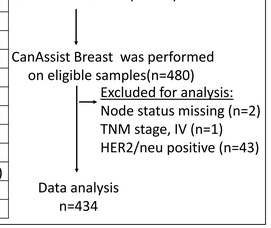


Fig 1: **Generation of CAB risk score:** IHC gradings of five biomarkers along with three clinical parameters are used by the support vector machine algorithm to generate a risk score. Based on cut-off of 15.5, each patient is categorised as either low-risk or high-risk for recurrence.

Table 1: Tumor anatomical and therapy characteristics of 434 cohort

		No. (%)
Tumor Size	T1	197 (45.4)
	T2	229 (52.8)
	T3	8 (1.8)
Node Status	N0	137 (31.6)
	N1	268 (61.8)
	N2	29 (6.6)
Grade	G1	90 (20.7)
	G2	232 (53.5)
	G3	112 (25.8)
Hormonal therapy	Exemestane	221 (50.9)
	Sequential	213 (49.1)
Chemotherapy	No	344 (79.3)
	Yes	90 (20.7)

Fig 2: Flowchart for sample selection for the current analysis



Results

Risk stratification by CanAssist Breast (CAB) at 10 years

Fig 3. CAB risk stratification is significant in total cohort

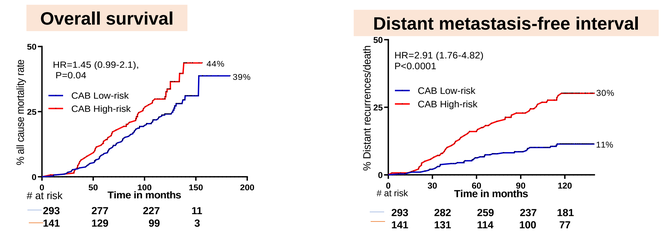


Fig 3: Kaplan-Meier curves for event rates in the total cohort: Segregation of patients into low- and high-risk groups for all cause mortality for the total time period and distant recurrences and death due to breast cancer at 10 years

Fig 4. CAB stratifies patients of both arms of hormonal therapy significantly

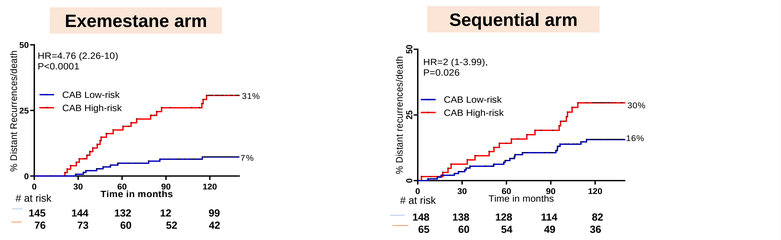


Fig 4: Kaplan-Meier curves for event rates at 10 years across both the arms of hormonal therapy: Segregation of patients into low- and high-risk groups by CAB in exemestane arm and sequential arm of TEAM trial

Fig 5. CAB risk stratification is not confounded by chemotherapy

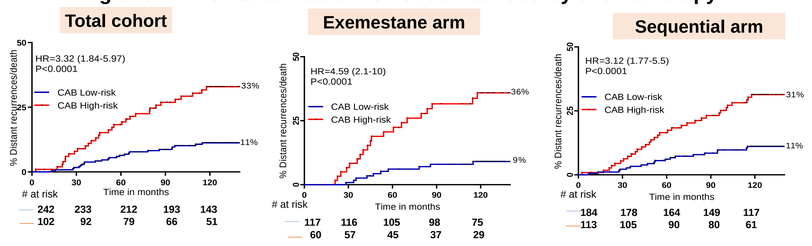


Fig 5: Kaplan-Meier event rate curves at 10 years in patients treated with endocrine therapy alone: Segregation of patients into low- and high-risk groups in total cohort, exemestane arm and sequential arm.

Fig 6. CAB risk stratification is useful in node-positive patients

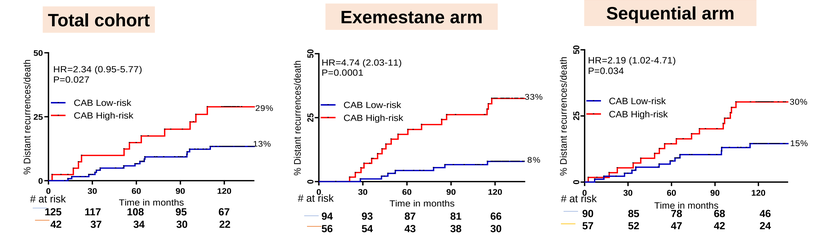


Fig 6: Kaplan-Meier event rate curves at 10 years in patients with node-positive disease: Segregation of node-positive patients into low- and high-risk groups by CAB in total cohort, exemestane arm and sequential arm.

Predictive ability of CAB at 10 years for overall survival

Fig 7. CAB predicts the benefit of exemestane in low-risk and benefit of chemotherapy for high-risk patients

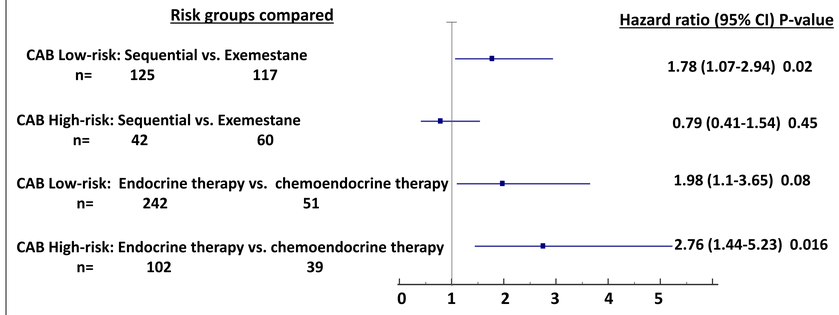


Fig 7:Univariate hazard ratios for overall survival at 10 years for CAB low and high-risk patients treated with endocrine therapy only

Table 2. CanAssist Breast risk score has higher and significant hazard ratio compared to clinical parameters

covariate	Hazard ratio	95% CI	P-value
CAB risk score: high risk, low risk	2.4872	1.52- 4.08	0.0003
Grade: G2+G3, G1	1.895	0.84-4.26	0.1216
T size: T2+T3, T1	1.3171	0.81- 2.14	0.2647
Node status: N+, N0	1.1993	0.69-2.08	0.516

Table 2: Multivariate table for hazard ratios for CanAssist Breast risk score and clinical parameters

Conclusions:

- ❖ CanAssist Breast recurrence risk predictions are useful till 10 years of disease diagnosis in post-menopausal, hormone receptor-positive, HER-2 negative women
- ❖ CanAssist Breast risk stratification is significant in both types of hormonal therapy
- ❖ CanAssist Breast recurrence risk predictions are useful to plan therapy in women with the node-positive disease
- ❖ CanAssist Breast predicts the overall survival benefit of exemestane, but not for tamoxifen, for low-risk and the benefit of chemotherapy for high-risk patients

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Acknowledgments

We thank Mr Ramu Kolli, Dr Naveen Krishnamoorthy and Dr Manjula Adinarayan from OncoStem Diagnostics, Bangalore for helping us with IHC experimentation, histopathological work. We thank Geeske Dekker-Ensink from the LUMC for preparing the slides.

Disclosure statement: The first and presenting author, Xi Zhang has no conflict of interest.