Validation of Late Distant Recurrence Prediction Model in Premenopausal Women with ER(+)/HER2(-) BC

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Introduction

- The CTS5 model was originally developed to estimate the risk of late distant metastasis (DM) in ER-positive/HER2-negative breast cancer survivors who completed five years of endocrine therapy (ET). However, its performance is limited in premenopausal women, and the model may underestimate late-recurrence risk as it was derived from historical trial cohorts.
- To overcome these issues, **we previously developed a machine-learning–based risk model to predict late DM risk for premenopausal women,** incorporating eight clinicopathologic variables—age, tumor size, nodal status, nuclear grade, histologic grade, progesterone receptor status, ovarian function suppression, and chemotherapy **(Fig. 1)**
- In the present study, **we aimed to externally validate our model** using independent institutional and trial-based cohorts and to compare its predictive performance with that of CTS5.

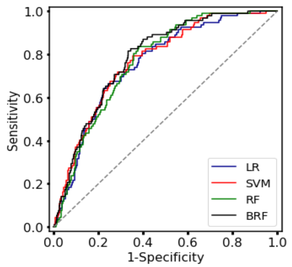


Fig 1. Performance of the machine learning–based prediction model in the development cohort.
Our model previously demonstrated strong discriminative ability with an AUC of 0.783, using the Balanced Random Forest (BRF) algorithm. The model effectively separated high- and low-risk groups, with the high-risk group showing significantly worse DMFS (p < 0.001; HR 8.15; 95% CI, 4.82–13.81).

Methods and Materials

- We **retrospectively** reviewed **premenopausal women (≤45 years) with ER (+) /HER2 (-) breast cancer** who underwent primary surgery **between 2000 and 2013** at Asan Medical Center, Severance Hospital, Boramae Medical Center, and in the ASTRRA trial.
- Patients who received neoadjuvant chemotherapy, discontinued endocrine therapy before 4.5 years, or developed distant metastasis within five years were excluded.
- Patients were **classified as high- or low-risk using a probability cut-off of 0.48**. The primary endpoint was distant metastasis–free survival (DMFS) between five and ten years after surgery.

Results

- A total of 1,465 patients were included in this study **(Table 1)**
- Median f/u duration: **157.7 months** (IQR: 137.6-185.6)
- **Based on risk classification and the use of ET extension**, patients were classified into four groups
  - **Low risk without ET extension**: 820 patients
  - **Low risk with ET extension**: 362 patients
  - **High risk without ET extension**: 131 patients
  - **High risk with ET extension**: 152 patients

Variables	Cohort data (n = 1465) No.	(%)
Age, years		
median	41	
IQR	38-43	
Breast Surgery		
BCS	835	(57.0)
TM	630	(43.0)
Nodal status (No. of positive nodes)		
Negative	897	(61.2)
1-3	419	(28.6)
4-9	100	(6.8)
9+	49	(3.3)
Nuclear grade		
Well	130	(8.9)
Intermediate	1060	(72.4)
Poor	275	(18.8)
Histologic grade		
I	166	(11.3)
II	1036	(70.7)
III	263	(18.0)
Tumor size, mm		
<10	245	(16.7)
10-19	585	(39.9)
20-29	379	(25.9)
≥30	256	(17.5)
Progesterone receptor		
Positive	1268	(86.6)
Negative	197	(13.4)
Chemotherapy		
No	599	(40.9)
Yes	866	(59.1)
ET extension		
No	1182	(80.7)
Yes	283	(19.3)
Ovarian function suppression		
No	928	(63.3)
Yes	537	(36.7)

Table 1. Baseline characteristics of patients in the external validation cohort

- Among 1,182 patients who did not undergo ET extension, **the high-risk group had significantly worse DMFS than the low-risk group** (p<0.001, HR 2.71; 95% CI, 1.60–4.58).
- When including those who extended ET, **high-risk patients appeared to significantly benefit from ET extension** (p=0.008, HR 4.36; 95% CI, 1.33–14.29), **whereas low-risk patients did not (p=0.238) (Fig.2)**

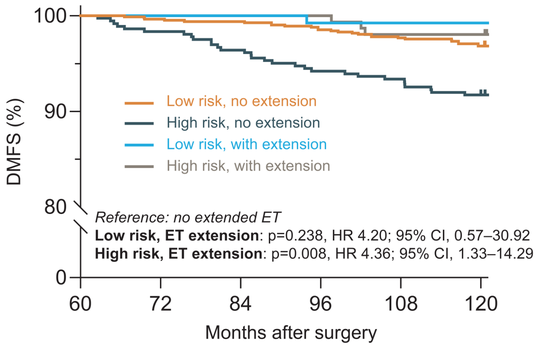


Fig. 2. Kaplan–Meier Curves of late DMFS stratified by our model

- **In comparison with CTS5**, our model achieved a **slightly better AUC (0.701 vs. 0.654) and sensitivity (0.536 vs. 0.429)**
- When analyzing for those who did not receive extended ET, the CTS5 high-risk group demonstrated significantly worse DMFS (p<0.001, HR, 3.39; 95% CI, 1.91–6.00). However, **the intermediate-risk group did not show a distinct survival pattern compared with the low-risk group (p = 0.885). (Fig.3)**
- **Finally, we developed our model using the combined development and validation datasets (n=2,395) (Fig.4).** The updated model demonstrated robust performance, with an **AUC of 0.744,** accuracy of 0.718, sensitivity of 0.615, specificity of 0.725, positive predictive value of 0.128, and negative predictive value of 0.966.

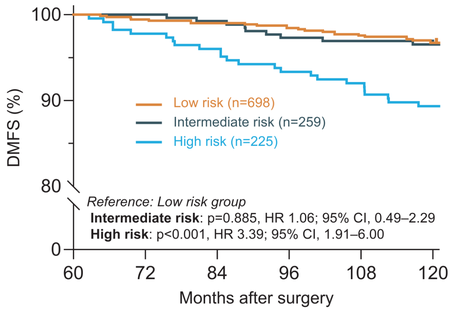


Fig. 3. Kaplan–Meier Curves of late DMFS stratified by CTS5 model

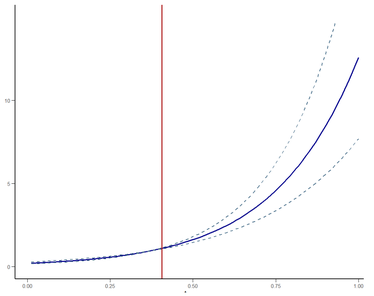


Fig. 4. Updated model using the combined development and validation datasets (n=2,395)

5-10yr DM risk (%)	Probability score
0.5	0.222
1	0.391
1.5	0.481
2	0.551
2.5	0.611
3	0.651
3.5	0.691
4	0.721
4.5	0.750
5	0.770
5.5	0.800
6	0.820
6.5	0.840
7	0.860
7.5	0.870
8	0.890
8.5	0.910
9	0.920
9.5	0.930
10	0.950
10.5	0.960
11	0.970
11.5	0.980
12	0.990

Conclusions

- **Our machine learning–based model** provides valuable prognostic information on the **risk of late distant recurrence between 5-10 years of treatment in premenopausal, ER (+)/HER2 (-) BC patients.**
- This model would assist clinicians in **personalizing decisions regarding the duration of ET and the need for OFS** in patients who remain recurrence-free at five years postoperatively.

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