Evaluation of Late Recurrence Risk in Premenopausal N0-N1 Breast Cancer Using the CTS5 Score

Ayumi Saito1, Tatsunori Shimoi1, Takeshi Murata2, Mai Onishi1, Masayuki Yoshida3, Ayumi Ogawa2, Ayako Nakashoji2, Hinako Maeda2, Chikashi Watase2, Kazuki Sudo1, Shin Takayama2, Kan Yonemori1
1. Department of Medical Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-Ku, Tokyo, Japan, 2. Department of Breast Surgery, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-Ku, Tokyo, Japan
3. Department of Diagnostic Pathology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-Ku, Tokyo, Japan

Introduction

- Estrogen receptor (ER)–positive, HER2-negative breast cancer carries a sustained risk of recurrence extending up to 20 years after diagnosis. While extended endocrine therapy (EET) can reduce late recurrence, the optimal duration and selection of patients who truly benefit remain unclear.
- The Clinical Treatment Score post-5 years (CTS5) is a simple risk-stratification tool based on age, tumor size, nodal status, and grade, and classifies patients into low, intermediate, and high risk of late distant recurrence. CTS5 has been validated mainly in postmenopausal women, and its clinical utility in premenopausal patients or those with N0–N1 disease is not well established.
- This study aimed to evaluate late recurrence risk using CTS5 and assess the impact of EET in a predominantly premenopausal, lower-risk N0–N1 population.

Methods

- We retrospectively reviewed patients with ER-positive, HER2-negative, non-metastatic breast cancer who underwent curative surgery at our institution between 2003 and 2017. Eligible patients had pathological N0–N1 disease and at least five years of follow-up.
- Patients with non-invasive cancer, neoadjuvant chemotherapy, or recurrence within five years were excluded. Clinical and pathological variables, treatment details, and survival outcomes were retrieved from electronic medical records.
- EET was defined as endocrine therapy continued for ≥7 years.
- The CTS5 score was calculated based on age, tumor size, nodal status, and grade, and patients were categorized into low (<3.13), intermediate (3.13–3.86), and high (>3.86) risk groups.
- Distant recurrence-free survival (DRFS) was estimated with Kaplan–Meier analysis and evaluated using Cox proportional hazards regression. DRFS was examined across CTS5 categories and further stratified by EET use. Both three-category (low / intermediate / high) and two-category (low vs. intermediate/high) CTS5 analyses were performed.

CTS5 score = 0.438×nodes+0.988×(0.093×size-0.001×size2+0.375×grade+0.017×age)

Results

Table1. Patients' characteristics

Overall (N=879).		N (%)
Age (mean (SD))		44.8 (5.75)
Histology		
	IDC	749 (85.2)
	ILC	69 (7.8)
	Others	61 (6.9)
T factor		
	pT1	629 (71.6)
	pT2	231 (26.3)
	pT3	19 (2.2)
N number		
	0	667 (75.9)
	1	132 (15.0)
	2	49 (5.6)
	3	31 (3.5)
Pathological Stage		
	Ⅰ	514 (75.9)
	ⅡA	260 (15.0)
	ⅡB	93 (5.6)
	ⅢA	12 (1.4)
Grade		
	1	268 (30.5)
	2	440 (50.1)
	3	171 (19.5)
Adjuvant radiation		523 (59.5)
Adjuvant chemotherapy		266 (30.3)
Adjuvant endocrine therapy		798 (90.8)
	SERM	674 (76.7)
	SERM/AI	108 (12.3)
	AI	15 (1.7)
	Others	1 (0.1)
Duration of Endocrine therapy		
	<7years	565 (64.3)
	>=7years	314 (35.7)
LHRH agonist use		237 (27.3)
CTS5 score groups		
	Low	670 (79.5)
	Intermediate	197 (22.4
	High	62 (7.1)

Fig1. 8y-DRFS by CTS5 score groups

Median follow up was 8.9 years.

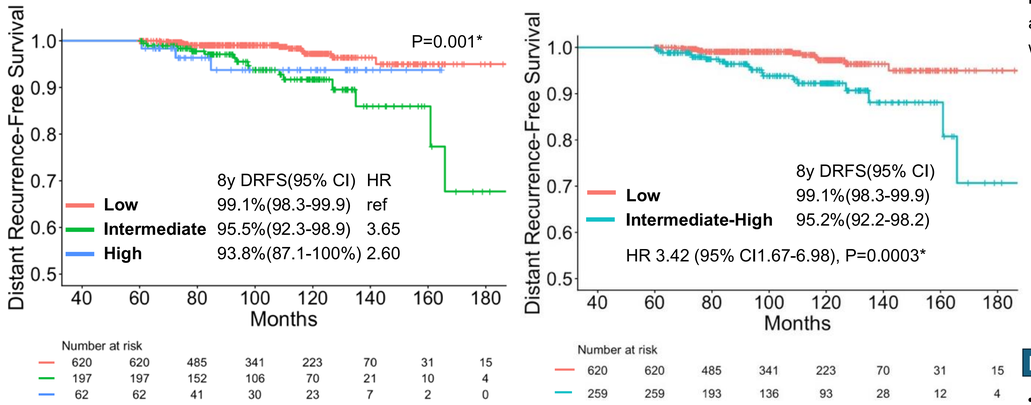


Fig2. 8y-DRFS by CTS5 score groups and extended endocrine therapy(EET)

Median follow up was 8.9 years.

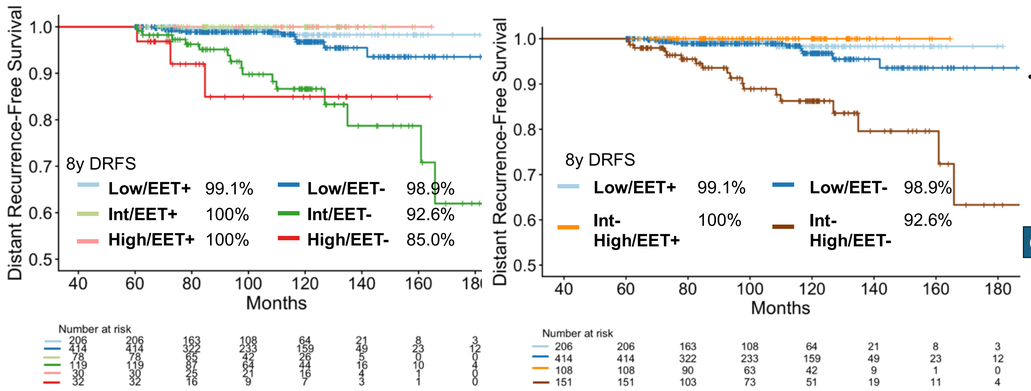


Table2. Multivariate analysis of distant recurrence

Based on DR analysis, the intermediate/high groups showed a tendency toward a larger DRFS difference, whereas the low group did not. Therefore, multivariable analysis was used the two-category CTS5. Sensitivity analyses were performed with and without the EET variable(Table2A, Table2B).

A.

		HR	Lower_CI	Upper_CI	p_value
CTS5 Group	Low	Ref			
	Intermediate/High	4.13	1.82	9.34	<0.001*
LHRH agonist use		1.28	0.57	2.82	0.542
Adjuvant chemotherapy		0.65	0.26	1.61	0.353

B.

		HR	Lower_CI	Upper_CI	p_value
CTS5 Group	Low	Ref			
	Intermediate/High	4.15	1.85	9.32	<0.001*
LHRH agonist use		1.05	0.47	2.35	0.898
Adjuvant chemotherapy		1.05	0.47	2.35	0.561
Extended Endocrine therapy		0.19	0.06	0.62	0.006*

Discussion

- CTS5 successfully stratified the risk of late distant recurrence even in this predominantly premenopausal N0–N1 population—an important setting in which its utility has not been well established. Patients with intermediate and high CTS5 scores exhibited a significantly greater risk of late recurrence, suggesting that CTS5 may help identify those most likely to benefit from extended endocrine therapy. In contrast, patients within the low CTS5 category achieved excellent long-term outcomes, and extended therapy did not appear to provide additional benefit, highlighting the potential to avoid unnecessary treatment and long-term adverse effects.
- The simplicity and low cost of CTS5 make it suitable for widespread use, including in resource-limited settings. However, this study is limited by its retrospective single-institution design, the relatively small number of recurrence events, and the potential influence of immortal time bias when evaluating extended therapy. Larger prospective studies are needed to confirm the clinical utility of CTS5 for guiding extended endocrine therapy decisions in premenopausal patients.

Conclusion

- **CTS5 effectively stratified late recurrence risk even in predominantly premenopausal N0–N1 patients.**
- **Intermediate and high CTS5 scores were associated with substantially higher late-recurrence risk and showed potential benefit from EET.**
- **Patients in the low CTS5 group experienced excellent long-term outcomes and showed no clear benefit from extended therapy, suggesting that treatment extension may be safely omitted.**

Contact information

Ayumi Saito. MD
Department of medical oncology
National Cancer Center Hospital, Tsukiji. Tokyo, Japan 104-0045
Email: aysaito@ncc.go.jp
Website: https://www.ncc.go.jp/en/ncch/index.html

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