Prediction of Distant Recurrence Using EndoPredict Among Women with ER-positive, HER2-negative Breast Cancer with a Maximum Follow-up of 16 Years

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BACKGROUND

- Treatment decisions for women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer are made at two time points, at diagnosis and 5 years post-diagnosis for adjuvant chemotherapy and extended endocrine therapy, respectively.
- EndoPredict has been previously validated as a prognostic test in women with ER-positive, HER2-negative disease who received endocrine therapy only as part of the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-6 (tamoxifen-only arm) and -8 trials, as well as the monotherapy arms of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial.[1-6]
- Here, we further evaluate the prognostic value of EndoPredict in the combined ABCSG-6 and -8 cohort with longer-term follow-up and compare 10-year distant recurrence (DR) and 5-15 years late recurrence according to nodal status.

METHODS

- This analysis included 1702 patients with ER-positive, HER2-negative disease who received endocrine therapy only (n=1166 N0; n=453 N1-3; n=83 N≥4; Table 1).
- All women were post-menopausal and received 5 years of adjuvant endocrine therapy alone (no chemotherapy).
- Prognostic value of EPclin score and EPclin risk category (high, low) on the risk of distant recurrence adjusted for patient and disease characteristics was evaluated using multivariable Cox proportional hazard models.
- Kaplan-Meier estimates were used to evaluate DR according to EPclin class and were compared using log rank test.
- Analyses were performed for the overall cohort, by nodal status, and for patients who were DR-free at year 5 (late recurrence).

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RESULTS

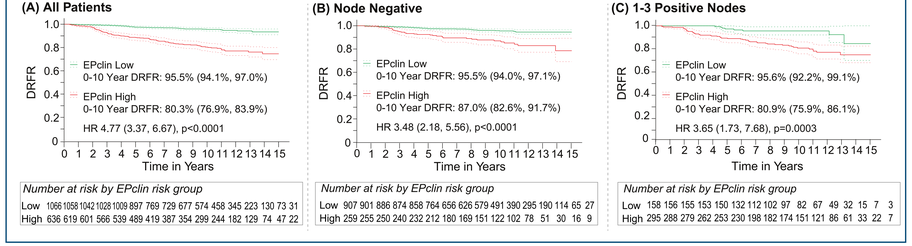
- Median follow-up was 9.6 years (range 0-16.6), an increase of 4.2 years over previous reports.

Table 1. Multivariable Cox model with EPclin score for distant recurrence in newly diagnosed patients according to nodal status.

		All Patients (N=1702)		Node Negative (N=1166)		1-3 Positive Nodes (N=453)	
Characteristic		**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
EPclin*		2.55 (2.11, 3.08)	<0.0001	1.68 (1.18, 2.37)	0.0043	2.68 (1.77, 4.08)	<0.0001
Tumor Grade	Grade 1	*reference*		*reference*		*reference*	
	Grade 2	1.16 (0.71, 1.90)	0.1944	1.20 (0.62, 2.32)	0.3684	1.75 (0.62, 4.97)	0.0076
	Grade 3	0.64 (0.27, 1.50)		2.33 (0.76, 7.09)		NE	
Age		1.02 (1.00, 1.04)	0.0361	1.02 (0.99, 1.06)	0.1820	1.01 (0.98, 1.04)	0.5424
Ki67		1.01 (0.99, 1.02)	0.4666	1.01 (0.98, 1.04)	0.4038	1.01 (0.98, 1.03)	0.4656
ER	10-50%	*reference*		*reference*		*reference*	
	51-80%	1.00 (0.58, 1.74)	0.8934	1.01 (0.44, 2.35)	0.9358	0.52 (0.22, 1.23)	0.1788
	81-100%	0.92 (0.54, 1.56)		0.92 (0.41, 2.03)		0.43 (0.19, 0.99)	
PR	0-9%	*reference*		*reference*		*reference*	
	10-50%	0.94 (0.59, 1.51)	0.5964	1.12 (0.56, 2.23)	0.1359	0.78 (0.33, 1.80)	0.9382
	51-80%	0.74 (0.47, 1.17)		0.53 (0.25, 1.11)		0.85 (0.41, 1.72)	
	81-100%	0.91 (0.58, 1.44)		1.11 (0.55, 2.22)		0.85 (0.40, 1.81)	
Treatment	Tamoxifen + Anastrazole	*reference*	0.2762	*reference*	0.5369	*reference*	0.8351
	TAM only	1.22 (0.85, 1.74)		1.18 (0.69, 2.03)		1.06 (0.61, 1.84)	

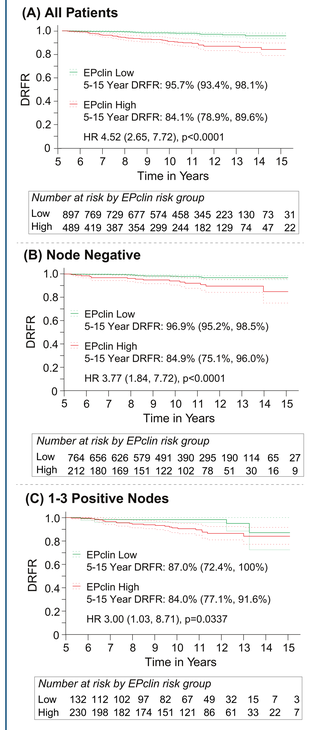
*Hazard Ratio (HR) per unit score after adjusting for age, tumor grade, Ki67, ER, PR, and treatment. Nodal status and tumor size are not included because these variables are included in the EPclin score. ER, estrogen receptor; PR, progesterone receptor

Figure 1. Kaplan-Meier curves of estimated DRFR for patients with newly diagnosed disease.



- Reanalysis with longer follow-up (15 years) confirms that EPclin is a significant predictor of DR after adjusting for clinical factors, regardless of nodal status (Table 1).
- Overall, 62.6% of patients had low risk EPclin scores, and 10-year distant reccurence-free rate (DRFR) was significantly improved relative to those with high risk scores (p<0.0001; Figure 1A).
  - Low-risk women had a 10-year DRFR of 95.5% (95% CI: 94.1%, 97.0%), while high-risk women had a significantly lower 10-year DRFR of 80.3% (76.9%, 83.9%; Figure 1A).
  - This significant difference holds true regardless of nodal status (Figure 1B-C).
- For patients who had not recurred by 5 years post-diagnosis (N=1386), EPclin was also highly prognostic 5-15 years post-diagnosis after adjusting for clinical variables, independent from nodal status (Table 2).
- Women with low EPclin had better long-term outcomes than EPclin high-risk patients (HR 4.52, 95% CI 2.65-7.72; p<0.0001).

Figure 2. Kaplan-Meier curves of estimated DRFR for patients who were distant recurrence free at 5 years.



Wide, overlapping confidence intervals after 12 years of follow-up are due to low numbers of evaluable patients at these later time points

- The low-risk group had a DRFR of 95.7% (93.4%, 98.1%) during years 5-15 post-diagnosis, while the high-risk group had a DRFR of 84.1% (78.9%, 89.6%) over this period (Figure 2A).
- These results were significant regardless of nodal status (Figures 2B-C).

Table 2. Multivariable Cox model with EPclin score for late recurrence in patients who were distant recurrence free after 5 years according to nodal status.

		All Patients (N=1386)		Node Negative (N=975)		1-3 Positive Nodes (N=362)	
Characteristic		**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
EPclin*		2.56 (1.88, 3.49)	<0.0001	2.01 (1.19, 3.39)	0.0101	3.43 (1.74, 6.76)	0.0005
Tumor Grade	Grade 1	*reference*		*reference*		*reference*	
	Grade 2	1.33 (0.61, 2.88)	0.1313	1.84 (0.62, 5.51)	0.5087	1.38 (0.31, 6.16)	0.0826
	Grade 3	0.38 (0.07, 2.04)		1.51 (0.16, 14.67)		NE	
Age		1.00 (0.96, 1.03)	0.8918	1.00 (0.95, 1.05)	0.9003	0.99 (0.94, 1.04)	0.7528
Ki67		1.01 (0.98, 1.03)	0.7192	1.01 (0.97, 1.05)	0.6049	1.01 (0.96, 1.05)	0.8082
ER	10-50%	*reference*		*reference*		*reference*	
	51-80%	1.61 (0.58, 4.46)	0.3955	1.96 (0.40, 9.57)	0.5258	0.46 (0.11, 1.91)	0.5842
	81-100%	1.86 (0.71, 4.84)		2.23 (0.49, 10.14)		0.50 (0.13, 1.97)	
PR	0-9%	*reference*		*reference*		*reference*	
	10-50%	0.92 (0.42, 2.03)	0.6230	0.57 (0.17, 1.85)	0.4505	1.46 (0.36, 5.81)	0.7023
	51-80%	0.78 (0.38, 1.62)		0.54 (0.19, 1.51)		1.80 (0.52, 6.18)	
	81-100%	1.23 (0.60, 2.52)		1.07 (0.39, 2.89)		2.10 (0.58, 7.66)	
Treatment	Tamoxifen + Anastrazole	*reference*	0.9280	*reference*	0.8997	*reference*	0.2279
	TAM only	0.98 (0.57, 1.66)		0.95 (0.44, 2.07)		0.60 (0.26, 1.37)	

*Hazard Ratio (HR) per unit score after adjusting for age, tumor grade, Ki67, ER, PR, and treatment. Nodal status and tumor size are not included because these variables are included in the EPclin score.

CONCLUSIONS

- Here we show that EPclin successfully predicts risk of early (0-10 years) and late (5-15 years) recurrence for patients with both node-negative and node-positive disease.
- This analysis of longer follow-up on previously published cohorts[1-4] confirms that EPclin can identify a large group of patients at low risk of distant recurrence after 10 years who may be adequately treated with only 5 years of adjuvant endocrine therapy.
- Replication of these results for the distant recurrence period (5-15 years) indicates that EPclin scores are also informative for selecting patients who may safely forgo extended endocrine therapy.

References: 1. Filipits et. al., *Clin. Cancer Res.,* 2011;17(18): 6012-20 2. Dubsky et. al., *Br. J. Cancer,* 2013;109(12): 2959-64 3. Dubsky et. al., *Ann. Oncol.,* 2013;24(3): 640-7 4. Fitzal et.al., *Br. J. Cancer,* 2015;112(8): 1405-10 5. Buus et.al., *J. Natl. Cancer Inst.*, 2016;108(11) 6. Sestak et.al., *JAMA Oncol.*, 2018;4(4):545-553