

Clinical Validation of EndoPredict in Pre-Menopausal Women with Estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Primary Breast Cancer

Anastasia Constantinidou, MD, PhD^{1,2,3}; Yiola Marcou, MD²; Timothy Simmons, MStat⁴; Ryan Bernhisel, MStat⁴; Elisha Hughes, PhD⁴; Stephanie Meek, PhD⁴; Eleni Kakouri, MD²; Georgios Georgiou, MD⁵; Ioanna Zouvani, MD⁵; Gabriella Savvidou, BSc¹; Vanessa Kuhl, MS⁶; Jennifer Doedt, PhD⁶; Susanne Wagner, PhD⁴; Alexander Gutin, PhD⁴; Jerry S. Lanchbury, PhD⁴; Ralf Kronenwett, MD, PhD⁶; Emad A. Rakha, MD⁷

1. Medical School University of Cyprus, Nicosia, Cyprus 2. Bank of Cyprus Oncology Centre (BoCOC), Nicosia, Cyprus 3. Cyprus Cancer Research Institute, Nicosia, Cyprus
4. Myriad Genetics, Inc., Salt Lake City, UT 5. Department of Histopathology, Nicosia General Hospital, Nicosia, Cyprus 6. Myriad International GmbH, Cologne, Germany 7. University of Nottingham, Nottingham, United Kingdom

BACKGROUND

- The EndoPredict 12-gene prognostic assay is validated to predict distant recurrence-free survival (DRFS) and response to chemotherapy mainly in post-menopausal women with ER+, HER2- breast cancer.
- This study evaluated the performance of EndoPredict in pre-menopausal women.

METHODS

- ER+, HER2- primary breast tumor (pN0-1, <pT3) samples from women who were pre-menopausal at the time of diagnosis and were systemically treated with adjuvant endocrine therapy alone were obtained from University of Nottingham (NHU) and BoCOC.
- Samples were tested retrospectively with EndoPredict to produce a 12-gene molecular score (EP) which was algorithmically combined with pathologic tumor size and nodal status to produce the clinicomolecular EPclin score.
- Associations of EP and EPclin with 10-year DRFS were evaluated in terms of hazard ratios (HRs) from Cox proportional hazards models stratified by cohort.
- 10-year DRFS was estimated for EPclin and EP high-risk and low-risk women by Kaplan-Meier analysis.

RESULTS

- Out of 411 eligible cases, 385 had a valid EPclin score and were included in the analysis (Table 1).
- Over the observation period (median 9.7 years, interquartile range 6.6-13.9 years), 35 women had a distant recurrence within 10 years.
- Both the EP and EPclin scores were associated with increased risk of distant recurrence [HR 1.3, 95% confidence interval (CI) 1.2-1.5; p<0.001 and HR 3.6, 95% CI 2.3-5.7; p<0.001, respectively].
- In multivariate cox proportional hazard analysis only EPclin remained significantly associated with distant recurrence (Table 2).
- In multivariate cox proportional hazard analysis of EP score and clinical factors, EP, tumor size, nodal status, and tumor grade were all significantly associated with distant recurrence.
- At 10 years post-diagnosis, EPclin low-risk women (EPclin <3.3) who received endocrine therapy alone had a DRFS of 97% (95% CI 93-99%) while EPclin high-risk women (≥3.3) had a DRFS of only 76% (95% CI 67-82%) (Figure 1).
- When analyzed based on EP risk category, similar results were observed; EP low-risk (EP <5) DRFS 100%, EP high-risk (EP ≥5) 85% (95% CI 78-88%).

Figure 1. 10-year DRFS by EPclin Risk Category

The lines show DRFS and the shaded areas show the 95% confidence intervals.

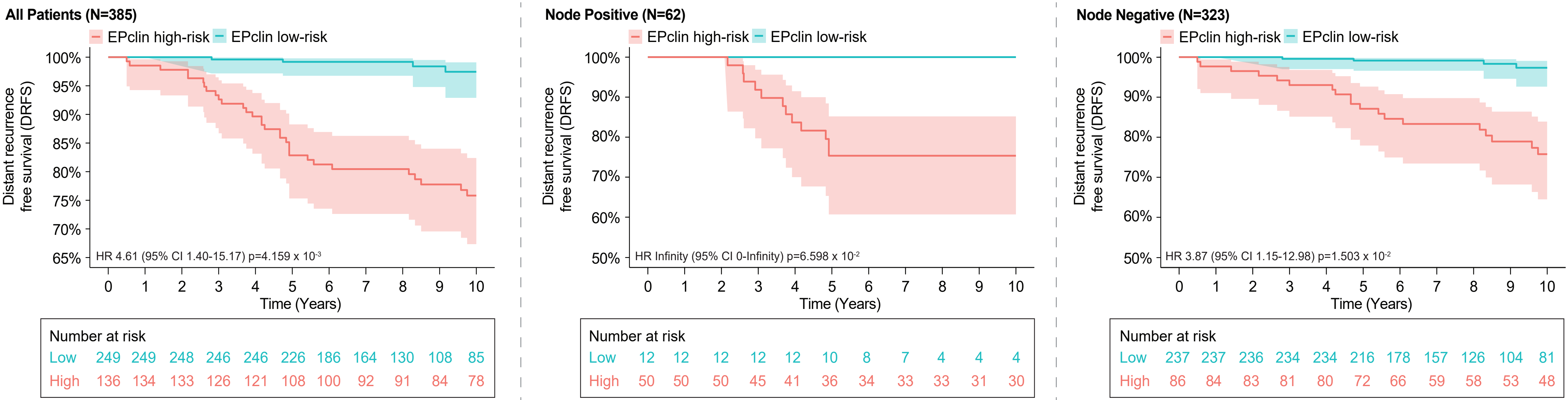


Table 1. Patient Characteristics

Variable		BoCOC (N=276)	NHU (N=109)	Total (N=385)
Median follow-up time (years)		8.4	17.7	9.7
Age at diagnosis (years), mean (SD)		46.8 (4.5)	45.7 (4.9)	46.5 (4.7)
Tumor size (cm), mean (SD)		1.3 (0.7)	2.2 (0.9)	1.6 (0.8)
Tumor grade, n (%)	I	76 (27.8%)	9 (8.3%)	85 (22.3%)
	II	187 (68.5%)	52 (47.7%)	239 (62.6%)
	III	10 (3.7%)	48 (44.0%)	58 (15.2%)
Nodal status, n (%)	Positive (1-3 nodes)	16 (5.8%)	46 (42.2%)	62 (16.1%)
	Negative (0 nodes)	260 (94.2%)	63 (57.8%)	323 (83.9%)
Ki-67 expression, mean (SD)		11.0 (10.6)	24.2 (22.4)	14.7 (16.0)
ER expression (%), mean (SD)		81.9 (17.0)	87.2 (17.3)	83.4 (17.2)
PgR expression (%), mean (SD)		80.9 (25.4)	72.0 (39.9)	78.5 (30.3)
Ovarian Function Suppresion (yes/no), n (%)		177 (64.1%)	37 (33.9%)	214 (55.6%)

Table 2. Multivariate Cox Proportional Hazards for EPclin

Variable	Reference	Level	HR	95% CI	LR* p-value
EPclin (continuous)	—	—	2.91	1.70-4.97	8.25 x 10 ⁻⁰⁵
Age at diagnosis (continuous)	—	—	0.96	0.90-1.02	0.18
Tumor grade (categorical)	I	II	8.98 x 10 ⁷	0-Inf	0.06
		III	1.01 x 10 ⁸	0-Inf	
		Missing**	0.72	0-Inf	
Ki-67 (categorical)	≤5	6-29%	2.51	0.57-10.97	0.41
		≥30%	1.61	0.33-7.97	
		Missing***	3.88	0.33-46.14	
ER expression (%) (continuous)	—	—	0.99	0.97-1.02	0.59
PgR expression (%) (continuous)	—	—	1.00	0.99-1.01	0.69

*Likelihood ratio **Missing n=3 ***Missing n=16

CONCLUSION

- In this study with a median follow-up time of 9.7 years, the EP and EPclin scores were highly associated with DRFS in pre-menopausal women who received adjuvant endocrine therapy alone.
- Based on these data, pre-menopausal women with EPclin low-risk breast cancer with up to three positive lymph nodes may safely forgo adjuvant chemotherapy in addition to endocrine therapy.