Predicting residual risk of recurrence after neoadjuvant chemotherapy - a retrospective analysis of EndoPredict® in the GeparTrio trial

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Background

Patients with breast cancer who do not achieve a pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) have a poor prognosis and might be candidates for post-neoadjuvant clinical trials investigating novel agents. The CPS-EG score [1] is a combination of clinical and pathological parameters and is currently used as criterion for selecting patients with highest risk of recurrence after NACT [2].

Here, we examined whether the gene expression test EndoPredict (EP) investigated on surgical specimen after NACT provides independent prognostic information for predicting the likelihood of recurrence in breast cancer patients with estrogen-receptor-positive, HER2-negative (ER+/HER2-) disease.

Materials and Methods

The molecular EP score was determined by qRT-PCR in 76 available surgical specimen classified as ER+/HER2- from breast cancer patients with residual disease after NACT participating in the neoadjuvant GeparTrio trial. The pre-specified clinical/molecular hybrid score EPclin was determined using ypT and ypN after NACT as clinical variables. Patients were classified as having low or high risk according to pre-defined cut-off values (EP ≤5 vs >5; EPclin ≤3.3 vs >3.3) [3].

CPS-EG score was calculated based on stage before and after NACT and pre-treatment grade and ER status. Dichotomized groups for CPS-EG score were defined as CPS-EG <3 vs ≥3.

Primary endpoint was disease free survival (DFS). Overall survival (OS) was analysed as secondary endpoint. Associations were assessed with uni- and multivariate Cox proportional hazard models.

Results

Baseline and surgical tumor characteristics of the 76 evaluated ER+/HER2- breast cancer patients are shown in **Table 1**.

EP high-risk patients after NACT had a significantly increased risk for relapse compared to the low-risk group (**Figure 1A**). Bivariate Cox regression analysis showed that the EP-score provides independent prognostic information for DFS when both EP and CPS-EG score were included in the model as either continuous or dichotomized variables (**Table 2**).

The risk of relapse was also greater for EPclin high compared to low (**Figure 1B**). Bivariate Cox regression analysis including the EPclin and CPS-EG score showed that EPclin only provides independent prognostic information for DFS when used as a continuous variable, but not as a dichotomized variable (**Table 2**).

Results were similar for overall survival as shown in **Figure 2AB** and **Table 2**.

Table 1. Baseline and surgical tumor characteristics

Parameters	N	%
Tumor size at baseline (mm), median (range)	60 (15.0, 180.0)	
Tumor stage at baseline		
T1	1	1.3
T2	29	38.2
T3	23	30.2
T4a-c	14	18.4
T4d	9	11.4
Nodal stage at baseline		
node negative	15	19.7
LN1-3	54	71.1
LN 4-9	5	6.6
LN 10+	1	1.3
missing	1	1.3
Grading at baseline		
Grade 1/2	56	73.7
Grade 3	20	26.3
Histological type at baseline		
ductal invasive	52	68.4
lobular invasive	18	23.7
other	6	7.9
ER		
negative	0	0.0
positive	76	100.0
PR		
negative	21	27.6
positive	55	72.4
HER2		
negative	60	78.9
missing	16	21.1
Post-surgery tumor stage		
ypT1	15	19.7
ypT2	24	31.6
ypT3	25	32.9
ypT4a-c	12	15.8
Post-surgery nodal stage		
ypN0	16	21.1
ypN1	23	30.3
ypN2	20	26.3
ypN3	16	21.1
missing	1	1.3
EP, median (range)	5.06 (1.40, 13.60)	
EP		
low	38	50.0
high	38	50.0
EPclin, median (range)	4.15 (2.49, 7.20)	
EPclin		
low	13	17.1
high	62	81.6
missing	1	1.3

Table 2. Bivariate analysis of EP/EPclin and CPS-EG score on DFS and OS

	continuous variables		dichotomized variables	
	HR (95% CI)	p-value	HR (95% CI)	p-value
DFS				
EP	1.15 (1.03-1.29)	0.014	1.74 (1.17-2.58)	0.006
CPS-EG	1.51 (1.07-2.13)	0.019	3.28 (1.24-8.71)	0.017
EPclin	1.63 (1.14-2.31)	0.007	1.85 (0.88-3.88)	0.104
CPS-EG	1.26 (0.85-1.86)	0.260	2.54 (0.96-6.72)	0.061
OS				
EP	1.24 (1.07-1.44)	0.006	2.10 (1.16-3.80)	0.014
CPS-EG	1.55 (1.00-2.40)	0.051	4.35 (1.05-18.09)	0.043
EPclin	2.04 (1.25-3.33)	0.004	1.11 (0.52-2.37)	0.790
CPS-EG	1.18 (0.72-1.95)	0.516	3.04 (0.80-11.52)	0.101

References

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Conclusions

Our study shows that EP investigated on surgical specimen of ER-positive, HER2-negative patients after neoadjuvant chemotherapy is an independent predictor of recurrence in patients not achieving a pCR. EPclin provided independent prognostic information and performed better than the CPS-EG score. EP and EPclin high risk patients have an increased risk of recurrence, despite receiving standard (neo-) adjuvant chemo-endocrine therapy. The identification of molecular luminal high-risk patients could help to identify high risk patients as candidates for novel drug-based approaches in addition to endocrine therapy to overcome resistance in post-neoadjuvant trials.

Figure 1. Disease free survival for EP (A) and EPclin (B) low and high risk patients

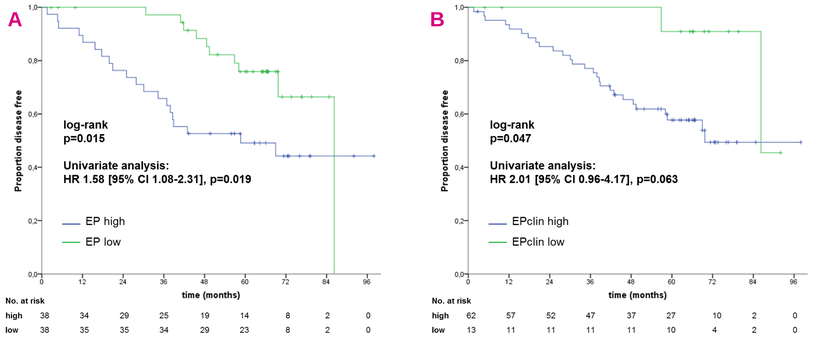
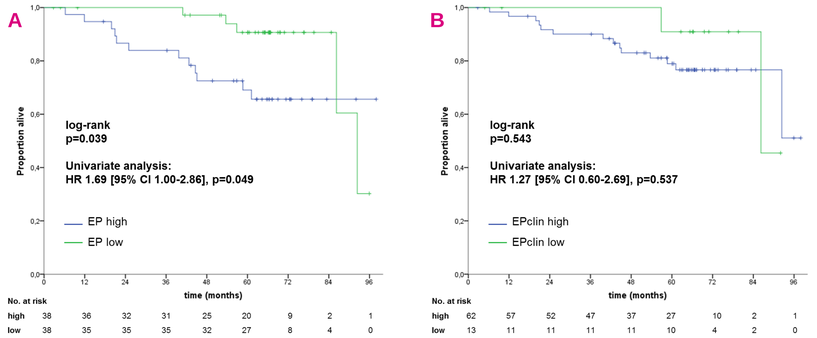


Figure 2. Overall survival for EP (A) and EPclin (B) low and high risk patients



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