EndoPredict®

Breast Cancer Prognostic Test

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CLINICAL SUMMARY

Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone

Sestak I. et al.: Breast Cancer Res Treat. 2019; 176:377-386

Introduction

- Almost all women with ER-positive (ER+), HER2-negative (HER2-) breast cancer will receive at least 5 years of endocrine therapy (ET) but the question of who will benefit from adjuvant chemotherapy (C) is still challenging.
- Myriad Genetics EndoPredict Breast Cancer Prognostic Test (EPclin) is a validated prognostic test to guide decisions on the use of chemotherapy plus endocrine therapy versus endocrine therapy alone for patients with ER+, HER2- breast cancer.
- Despite the prognostic ability of EPclin, it has not yet been shown whether it can predict chemotherapy benefit.

Study design

- Since archived samples from previous randomised trials of ET +/- C in patients with ER+, HER2- breast cancer have been depleted and a prospective trial withholding chemotherapy from high-risk patients would be unethical, the investigators used an alternative study design: A non-randomised, retrospective, comparative analysis, to evaluate the ability of EPclin to predict adjuvant chemotherapy benefit for patients with ER+, HER2- disease.

Methods

- Retrospective, comparative analysis of n= 3746 pre- and post-menopausal women with ER+, HER2- breast cancer treated with ET alone or ET + C using data from five large clinical trials:
- **1° endpoint:** *distant recurrence-free interval (DRFI).*
- **1° objective:** to generate risk curves estimating 10-year distant recurrence (DR) as a continuous function of EPclin score separately for patients who received adjuvant ET + C and those who received ET only.

Study	GEICAM/ 9906	GEICAM 2003/02	ABCSG 6	ABCSG 8	TransATAC
N=	500	616	378	1324	928
5 years ET +/- C	ET + C	ET + C	ET	ET	ET

Results

- 2630 women (70.2%) who received ET alone were all postmenopausal, significantly older, had significantly smaller tumours, significantly more node-negative disease, and significantly fewer poorly differentiated tumours (all $P < 0.05$) compared to 1116 pre- and post- (49%, 51%) menopausal women who received ET + C.
- **EPclin was highly prognostic ($P < 0.0001$) in women who received ET alone (HR 2.79), and in those who received ET + C (HR 2.27). This was true for early (0–5 years) and late (5–10 years) late recurrence.**
- Women receiving ET alone had larger 10-year DR risks with increasing EPclin scores compared to ET + C. E.g. EPclin score 5, the 10-year DR risk for ET alone 46% vs. ET + C 26% (absolute risk difference 20%) (Fig. 1; Tab. 1).
- In contrast, no differences in 10-year DR risks were observed for low EPclin scores.
- A sensitivity analysis **excluding** premenopausal women showed very similar results (10-year DR risk for EPclin score 5: ET 46% vs. ET + C 28%).

- **A statistical interaction test between EPclin and treatment (ET vs. ET + C) was significant (P=0.022) indicating that EPclin is predictive of chemotherapy benefit.**

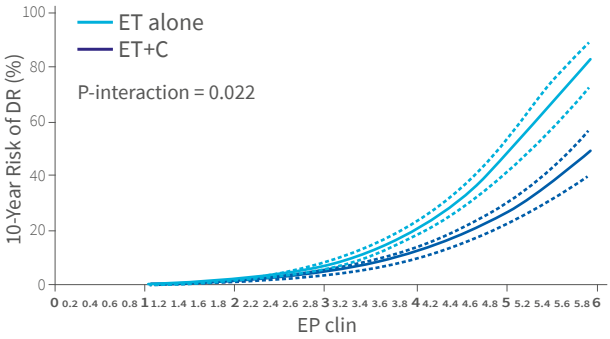

Fig. 1: Likelihood of distant recurrence (DR) as a continuous function of EPclin for ET alone (sky blue) and ET + C (blue), (95% CI).

EPclin Score	ET alone	ET+C	Absolute risk difference between ET alone and ET+C
1	1.0% (0.6–1.4)	1.1% (0.5–1.7)	-0.1%
2	2.8% (2.1–3.5)	2.5% (1.5–3.5)	0.3%
3	7.6% (6.4–8.8)	5.7% (4.1–7.2)	1.9%
4	19.8% (17.6–22.0)	12.4% (10.1–14.6)	7.4%
5	46.1% (40.2–51.4)	25.8% (22.0–29.5)	20.3%
6	82.2% (72.1–88.6)	49.2% (40.5–56.7)	33.0%

Tab. 1: 10-year risk (%) with 95% confidence intervals and absolute risk differences for distant recurrence for endocrine-treated patients alone (ET alone) and endocrine plus chemotherapy-treated patients (ET + C) according to EPclin score.

Conclusions

- **EPclin was highly prognostic in women receiving ET alone and in those who received ET + C.**
- Women with high EPclin scores benefitted from chemotherapy compared to those with the same EPclin score but receiving endocrine therapy alone, irrespective of node-positivity of the disease.
- Although the approach was an indirect comparison of EPclin in ET vs ET+C, the analysis demonstrated that **a high EPclin score can predict chemotherapy benefit in women with ER+, HER2- disease.**

Strengths

- A large group of 3746 pre- and postmenopausal women with ER+, HER2- breast cancer from five large randomised clinical trials with long-term follow-up.
- Well characterized tissue samples.
- Patients were treated with modern chemotherapy regimens such as FEC/FAC with or without paclitaxel. it.

Limitations

- Investigators were unable to compare the predictive value of EPclin in a prospective, randomised trial design.
  - Authors believe that this retrospective approach is an effective way to evaluate the clinical usefulness of EPclin, as data from large prospective, randomized trials are not available due to ethical, time and resource considerations.

Bottom line

EndoPredict has shown in 4 different prospective-retrospective clinical validation studies its excellent prognostic ability for early and late distant recurrence resulting in level-of-evidence of 1. Therefore, EndoPredict was used to identify patients at such a low risk of recurrence that they could forgo chemotherapy.

In this study including 3746 patients from five different clinical trials, it was demonstrated that EndoPredict is not only prognostic but also predictive of benefit from current chemotherapy regimens. It was confirmed that EPclin low risk patients did not have a better outcome after addition of adjuvant chemotherapy compared to ET alone. Moreover, the results showed that patients with an EPclin high score had an absolute benefit from chemotherapy.

This supports the use of EndoPredict as a tool to identify those patients for whom endocrine therapy alone is sufficient and those who could benefit from adjuvant chemotherapy.

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