The impact of EndoPredict®on decision making with increasing oncological work experience: can overtreatment be avoided?

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Abstract

Background Estimating distant recurrence risk in women with estrogen receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer is still challenging. EndoPredict® is a gene expression-based test predicting the likelihood of recurrent disease. We analyzed the difference in oncological decision making with and without the knowledge of gene expression tests.

Patients and methods This is a retrospective analysis including patients diagnosed with hormone-receptor positive, Her2 negative breast cancer between 2011 and 2015 at the Municipal Breast Cancer Centre Cologne, Germany. All patients received an evaluation by EndoPredict®. An oncological tumor board (TB) with knowledge of these results served as a baseline (control group). This baseline was compared to the treatment decision (adjuvant chemotherapy yes vs. no) made by oncologists with different experience levels (less than 5 years, between 5 and 15 years, and more than 15 years) who were not provided the EndoPredict® scores. All clinicians had access to clinical as well to histopathological data.

Results There was no significant difference between control group and the oncologists with different experience levels concerning a chemotherapy indication. A trend could be shown in the subgroup of nodal negative patients between the treatment recommendation and physicians with more than 15 years of experience ($p = 0.088$). A further trend could be demonstrated in the subgroup of patients with a low Ki67 index ($\leq 14\%$) ($p = 0.063$) between physician with 5–10 years of clinical experience and official treatment recommendation.

Conclusion It seems that inexperienced physicians may profit from the use of EndoPredict® to avoid an overtreatment. In nodal negative patients and patients with a low Ki67 index, undertreatment can be avoided with the use of EndoPredict® (borderline significance). Further prospective studies with larger study cohorts are needed to further validate this tool.

Keywords Endopredict® · Gene expression test · Prediction · Prognosis

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Background

Estimating distant recurrence risk in women with estrogen receptor positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer is still challenging. In patients with Her2-negative tumors, standard adjuvant chemotherapy is based on anthracyclines and taxane combinations [1]. Guidelines recommend conventional regimens that include 4 × EC/AC (epirubicin, cyclophosphamide or doxorubicin, and cyclophosphamide), followed by 12 × paclitaxel (weekly) [1]. Previously published long-term data showed the efficacy of this regime [1, 2]. Several tools have been developed to aid in decisions regarding adjuvant therapy. These include specialist guidelines, such as the St. Gallen consensus [3, 4]. Perou et al. were the first who described intrinsic subtypes in the molecular pathology of breast cancer with the help of gene expression analysis. The different intrinsic subtypes were associated with a different prognosis [5, 6] and hence correlated with different overall and disease-free survivals [6, 7].

Based on these results, gene expression test has been developed to estimate the risk for recurrent disease [6]. In patients with hormone receptor positive, HER2 negative patients with 0–3 lymph nodes gene expression tests are usually used to allow a treatment decision [1]. Commonly used gene expression tests include EndoPredict®, Prosigna, MammaPrint®, and Oncotype DX. EndoPredict® (Sividon Diagnostics GmbH, Cologne, Germany) is a gene expression-based test predicting the likelihood of recurrent disease. This gene-expression-based test measures the expression of eight cancer-related genes of interest (*BIRC5*, *UBE2C*, *DHCR7*, *RBBP8*, *IL6ST*, *AZGP1*, *MGP*, and *STC2*) and three reference genes (*CALM2*, *OAZ1*, and *RPL37A*). A molecular risk score (EP score) can be calculated with these data [8]. Patients can be stratified into a low- or high-risk group based on predefined cut-off values [8–10].

EndoPredict® has been proven to be highly prognostic for disease recurrence in endocrine-treated patients with ER+, HER2-negative disease [11, 12]. We analyzed the difference in oncological decision making with and without the knowledge of gene expression tests. Of special interest was the reduction of chemotherapy indications due to the use of gene expression tests and incidence of potential overtreatment due to lack of clinical experience.

Patients and methods

This is a retrospective, hospital-based analysis including 79 patients diagnosed with hormone receptor positive (HR+), HER2 negative (Her2-) breast cancer between 2011 and 2015 who were treated at the Municipal Breast Cancer Centre in Cologne, Germany. All 79 patients received an evaluation by EndoPredict® test. EndoPredict® test was done in G2 tumors, luminal A tumors in combination with other risk factors (e.g., young age and nodal positive status) and patients request.

Tumor board (TB)

The control group of this trial was represented by a tumor board decision with knowledge of EndoPredict® test results. The board consisted of gynecological oncologists, internal medicine oncologists, radiologists, radiation therapists, pathologists as well as psycho-oncologists and breast care nurses. A decision for or against an adjuvant chemotherapy was anonymous for all 79 cases. The experience level within this tumor board varied across all tested subgroups. In case of low-risk EndoPredict® scores, chemotherapy was not recommended, whereas high-risk EndoPredict® scores led to a recommendation for adjuvant chemotherapy. The cut-off value for or against chemotherapy was 5. The low-risk group was defined as an EP score between 0 and 5, whereas the high-risk group was defined as an EP score > 5 and < 15 [13]. The recommendation of the tumor board depended on the EndoPredict® results. There were no deviations.

Test groups

The baseline was compared to treatment decisions (adjuvant chemotherapy "yes" vs "no") made by gynecological oncologists with different experience levels (EL) (less than 5 years, between 5 and 15 years, and more than 15 years) who were not provided the EndoPredict® scores. All clinicians had access to clinical and histopathological data. This resulted in three test groups including physicians with low experience, medium experience and high experience. A single test person was tested in each category requiring each of them to evaluate all 79 cases. Patient cases were evaluated anonymously. The aim was to obtain a recommendation, i.e., chemotherapy "yes" vs. "no". Results were then compared to the tumor board baseline. A subgroup analysis followed evaluating these differences according to tumor size, nodal status, Ki67 index, menopausal status, and tumor histology.

Statistics

Statistical analysis was performed using the VassarStats® (Vassar College, Poughkeepsie, NY, USA) statistics program. *T* test and Chi-square test were used to evaluate significances when appropriate.

Results

In total, 79 patients have been included into this analysis. Median age was 58 (range 31–74). Main characteristics of the patients are illustrated in Table 1.

According to this analysis, 40.5% of the patients were pre- and 59.5% were postmenopausal, respectively. Most patients (93.7%, $n = 74$) were between 40 and 70 years, whereas 2.5% were < 40 years and 3.8% were older than 70 years. In this analysis, T-stage was stratified into two groups, ≤ pT2 representing 58.2% of the study cohort versus > pT2 representing 41.8% of the study cohort. The majority of patients (64.6%) were nodal negative, whereas 35.4% of patients had axillary lymph node metastases (Table 2).

The Ki67 index was ≤ 14% in 57.0% of all patients, compared to 32.9% in the intermediate Ki67 index subgroup. When analyzing the histological subtype of patients, we found that 82.3% of all cases showed a "no specified type", 13.9% an "invasive lobular", and 3.8% a "mixed type", respectively.

According to the official recommendation of the interdisciplinary tumor board 48.1% of the patients had an indication for an adjuvant chemotherapy according to a high-risk result in the EndoPredict® testing. Based on the test results, physicians with > 15 years and physicians with 5–10 years of clinical experience recommended in 39.1% of all cases an adjuvant chemotherapy ($p = 0.268$). Physicians with < 5 years of clinical experience recommended in 50.6% of all cases an adjuvant chemotherapy ($p = 0.752$).

Subgroup analysis, according to experiences of evaluating physician, showed no statistical significant results. A trend could be seen in the subgroup of nodal negative patients between the treatment recommendation and physicians with more than 15 years of experience ($p = 0.088$) (see Fig. 1).

A further trend could be demonstrated in the subgroup of patients with a low Ki67 index (≤ 14%) ($p = 0.063$) between physician with 5–10 years of clinical experience and official treatment recommendation (see Fig. 2).

Discussion

In this retrospective analysis, we evaluated the impact of EndoPredict® on treatment decisions and potential overtreatment dependent from clinical experience. As reported in the previous works we find that the use of gene expression assays generally reduces the recommendation for adjuvant chemotherapy [14, 15].

Table 1 Patients' characteristics

	Number of patients	%		Number of patients	%
Cohort			Hormone-receptor status		
Gender (f)	79	100.0	Median ER IRS	12 (2–12)	–
Median age (range)	58 (31–74)	–	Receptor		
Premenopausal	32	40.5	Median PR IRS	9 (0–12)	–
Histology			HER2-expression		
NST	65	82.3			
Invasive lobular	11	13.9	0	43	54.4
Mixed type	3	3.8	1+	33	41.8
Lymph node status pN0	51	64.6	2+	3	3.8
Lymphangiosis L0	51	65.4	Side		
Resection R0	71	92.2	Left	46	58.2
			Right	30	38.0
Ki67 (%)			Bilateral	3	3.8
≤ 14	45	57.0	Stage		
> 14	26	32.9	pT1a	0	0.0
≥ 25	8	10.1	pT1b	6	7.6
			pT1c	40	50.6
Grading			pT2	32	40.5
G1	4	5.1	pT3	0	0.0
G2	72	91.1	NA	1	1.3
G3	2	2.5			
NA	1	1.3			

Table 2 Comparison of therapy decisions between control group and different levels of clinical experience

|		Tumorboard		> 15 years of experience			5–15 years of experience			< 5 years of expericnce		
		Yes		Yes		p-value	Yes		p-value	Yes		p-value
		Number of patients	%	Number of patients	%		Number of patients	%		Number of patients	%	
Age												
Total (n=79)	%	38	48.1	31	39.2	0.268	31	39.2	0.268	40	50.6	0.752
< 40 years (n=2)	2.5	2	100.0	1	50.0	N/A	2	100.0	N/A	2	100.0	N/A
40–70 years (n=74)	93.7	35	47.3	29	39.2	0.32	28	37.8	0.245	36	48.6	0.863
> 70 years (n=3)	3.8	1	33.3	1	33.3	N/A	1	33.3	N/A	2	66.7	N/A
Size												
≤ pT2 (n=46)	58.2	20	43.5	14	30.4	0.195	19	41.3	0.842	26	56.5	0.21
> pT2 (n=33)	41.8	17	51.5	16	48.5	0.807	11	33.3	0.135	13	39.4	0.322
Nodal status												
pN0 (n=51)	64.6	20	39.2	12	23.5	**0.088**	14	27.5	0.207	20	39.2	1
pN1 (n=28)	35.4	18	64.3	19	67.9	0.777	17	60.7	0.777	20	71.4	0.566
Ki 67												
≤ 14% (n=45)	57.0	17	37.8	12	26.7	0.26	9	20.0	**0.063**	14	31.1	0.507
> 14% (n=26)	32.9	16	61.5	13	50.0	0.403	14	53.8	0.572	19	73.1	0.374
≥ 25% (n=8)	10.1	5	62.5	6	75.0	0.59	8	100.0	0.055	7	87.5	0.249
Menopause												
Pre (n=32)	40.5	18	56.3	15	46.9	0.454	13	40.6	0.212	15	46.9	0.454
Post (n=47)	59.5	20	42.6	16	34.0	0.396	18	38.3	0.671	25	53.2	0.301
Histology												
NST (n=65)	82.3	33	50.8	26	40.0	0.218	26	40.0	0.218	32	49.2	0.863
Invasive lobular (n=11)	13.9	4	36.4	4	36.4	1	5	45.5	0.663	7	63.6	0.20
Mixed type (n=3)	3.8	1	33.3	1	33.3	N/A	0	0.0	N/A	1	33.3	N/A

Fig. 1 Comparison of tumor board decision and decision of physicians with different levels of experience in nodal negative patients
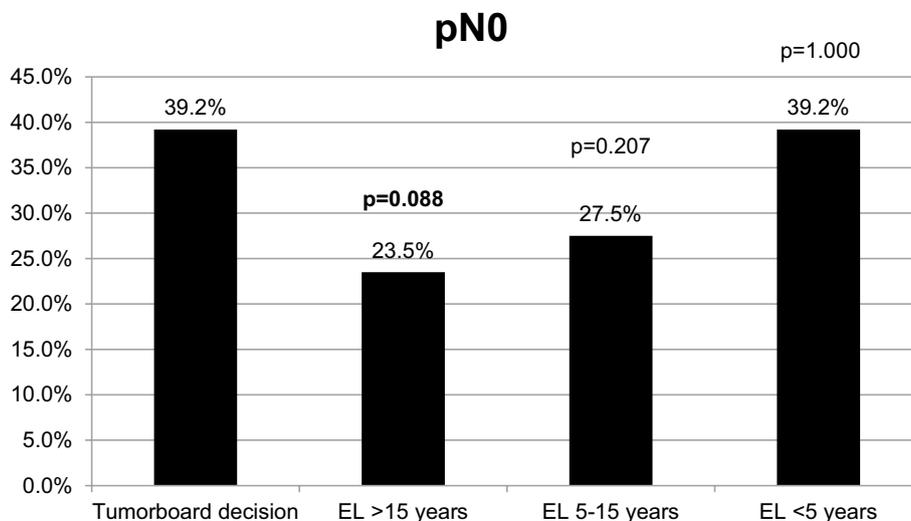
The EndoPredict® test is able to predict both late metastasis and local recurrence in hormone receptor-positive breast cancer [6, 16, 17]. Furthermore, Martin et al. showed that EndoPredict® was prognostic in premenopausal patients (HR 6.7, 95% CI 2.4–18.3; $p = 0.0002$)

and postmenopausal patients (HR 3.3, 95% CI 1.3–8.5; $p = 0.0109$) [18].

Although the results were not significant in the current analysis, we could show a decrease of chemotherapy indication for therapy independent from experience level of

Fig. 2 Comparison of TB decision and decision of physicians with different levels of experience in patients with Ki67 index < 14%

Ki67- Index ≤ 14 %
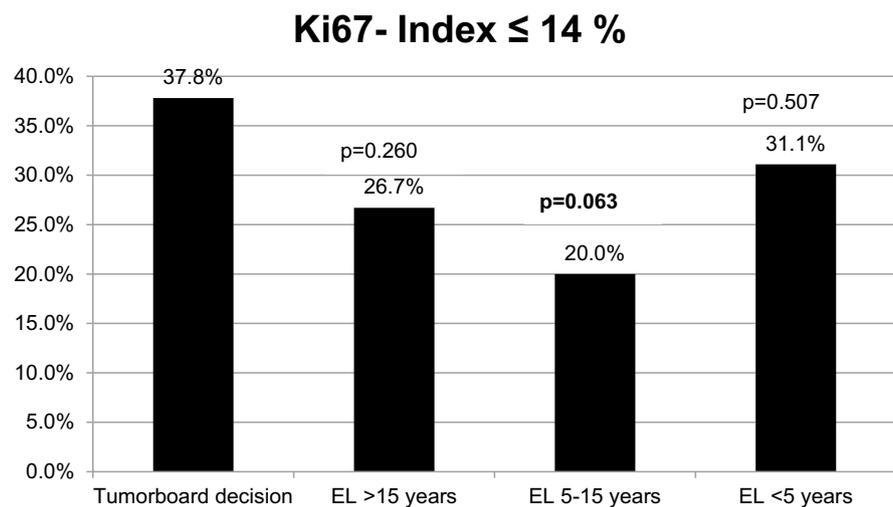
physician (p = n.s.). Especially , physicians with less clinical experience could profit from the use of EndoPredict®.

A previously published work examining the impact of OncotypeDx® showed that inexperience led to a significant increase in recommendations for chemotherapy, with those made by the tumor board being least frequent (41.6% vs. < 5 years = 55.6%, 5–15 years = 50.4%, and > 15 years = 42.5%; $p < 0.05$) [19]. Missing significance in the current analysis can be explained by the limited number of patients in the study cohort.

Ettl et al. reported that the EPclin test resulted in a change in therapy recommendation in 41% of the cohort. In 38% of their cohort, chemotherapy could be avoided, in 20 patients (5%), chemotherapy had to be added [6]. In clinical routine, it seems that overtreatment of patients is the main problem that obviously can be avoided with the use of gene expression tests. Interestingly, in our study, undertreatment in nodal negative patients and patients with a low Ki67 index could also be avoided. Nodal negative patients as well as patients with a low Ki67 index seem to appear as low-risk patients, so that especially, experienced oncologists tend to avoid recommending chemotherapy. However, node-negative (N0) breast carcinomas are heterogeneous diseases with different potentials to metastasize [20].

Even patients with node-negative, estrogen receptor negative, grade 1 tumors may have a high relapse rate of almost 20% over 10 years [21]. In addition, it is reported that the relapse rate is higher in patients with grade 2/3 tumors [21]. Furthermore, it is known that the Ki67 index has a prognostic impact on disease-free survival in patients with hormone receptor-positive and HER2neu-negative tumors. Though, it has to be stressed that strict cut-off value was not suitable for distinguishing between high- and low-risk patients and their response to adjuvant chemotherapy in previously published studies [22, 23].

The small study cohort of 79 patients has to be considered as a limitation. Though trends could be shown statistically, indicating that an increased number of patients could lead to statistically significant results.

Conclusion

Inexperienced physicians may profit from the use of EndoPredict® to avoid overtreatment. In nodal negative patients and patients with a low Ki67 index, undertreatment can be avoided with the use of EndoPredict® (borderline significance). Further prospective studies with large study cohorts are needed to further validate this tool.

Compliance with ethical standards

References

1. Liedtke C, Jackisch C, Thill M et al (2018) AGO recommendations for the diagnosis and treatment of patients with early breast cancer: update 2018. Breast Care 13:196–208. https://doi.org/10.1159/000489329
2. Sparano JA, Zhao F, Martino S et al (2015) Long-term follow-up of the E1199 phase III trial evaluating the role of taxane and

schedule in operable breast cancer. J Clin Oncol 33:2353–2360. https://doi.org/10.1200/JCO.2015.60.9271

3. Goldhirsch A, Ingle JN, Gelber RD et al (2009) Thresholds for therapies: highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2009. Ann Oncol 20:1319–1329. https://doi.org/10.1093/annonc/mdp322

4. Mokbel K, Wazir U, Wazir A et al (2018) The impact of endopredict clinical score on chemotherapy recommendations in women with invasive ER+/HER2- breast cancer stratified as having moderate or poor prognosis by nottingham prognostic index. Anticancer Res 38:4747–4752. https://doi.org/10.21873/anticanres.12782

5. Perou CM, Sørlie T, Eisen MB et al (2000) Molecular portraits of human breast tumours. Nature 406:747–752. https://doi.org/10.1038/35021093

6. Ettl J, Klein E, Hapfelmeier A et al (2017) Decision impact and feasibility of different ASCO-recommended biomarkers in early breast cancer: Prospective comparison of molecular marker EndoPredict and protein marker uPA/PAI-1. PLoS ONE 12:e0183917. https://doi.org/10.1371/journal.pone.0183917

7. Sorlie T, Perou CM, Tibshirani R et al (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci 98:10869–10874. https://doi.org/10.1073/pnas.191367098

8. Peláez-García A, Yébenes L, Berjón A et al (2017) Comparison of risk classification between EndoPredict and MammaPrint in ER-positive/HER2-negative primary invasive breast cancer. PLoS ONE 12:e0183452. https://doi.org/10.1371/journal.pone.0183452

9. Denkert C, Kronenwett R, Schlake W et al (2012) Decentral gene expression analysis for ER+/Her2− breast cancer: results of a proficiency testing program for the EndoPredict assay. Virchows Arch 460:251–259. https://doi.org/10.1007/s00428-012-1204-4

10. Kronenwett R, Bohmann K, Prinzler J et al (2012) Decentral gene expression analysis: analytical validation of the Endopredict genomic multianalyte breast cancer prognosis test. BMC Cancer 12:456. https://doi.org/10.1186/1471-2407-12-456

11. Buus R, Sestak I, Kronenwett R et al (2016) Comparison of EndoPredict and EPclin with oncotype dx recurrence score for prediction of risk of distant recurrence after endocrine therapy. J Natl Cancer Inst 108:149. https://doi.org/10.1093/jnci/djw149

12. Simon RM, Paik S, Hayes DF (2009) Use of archived specimens in evaluation of prognostic and predictive biomarkers. JNCI J Natl Cancer Inst 101:1446–1452. https://doi.org/10.1093/jnci/djp335

13. Filipits M, Rudas M, Jakesz R et al (2011) A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res 17:6012–6020. https://doi.org/10.1158/1078-0432.CCR-11-0926

14. Petkov VI, Miller DP, Howlader N et al (2016) Breast-cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. Breast Cancer 2:16017. https://doi.org/10.1038/npjbcancer.2016.17

15. Stemmer SM, Steiner M, Rizel S et al (2017) Clinical outcomes in patients with node-negative breast cancer treated based on the recurrence score results: evidence from a large prospectively designed registry. NPJ Breast Cancer 3:33. https://doi.org/10.1038/s41523-017-0034-6

16. Dubsky P, Brase JC, Jakesz R et al (2013) The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2− breast cancer patients. Br J Cancer 109:2959–2964. https://doi.org/10.1038/bjc.2013.671

17. Fitzal F, Filipits M, Rudas M et al (2015) The genomic expression test EndoPredict is a prognostic tool for identifying risk of local recurrence in postmenopausal endocrine receptor-positive, her2neu-negative breast cancer patients randomised within the prospective ABCSG 8 trial. Br J Cancer 112:1405–1410. https://doi.org/10.1038/bjc.2015.98

18. Martin M, Brase JC, Calvo L et al (2014) Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2− breast cancer patients: results from the GEICAM 9906 trial. Breast Cancer Res 16:R38. https://doi.org/10.1186/bcr3642

19. Eichler C, Fromme J, Thangarajah F et al (2019) Gene-expression profiling—a decision impact analysis: decision dependency on oncotype DX® as a function of oncological work experience in 117 Cases. Anticancer Res 39:297–303. https://doi.org/10.21873/anticanres.13111

20. Vénat-Bouvet L, Fermeaux V, Leobon S et al (2014) Adjuvant chemotherapy in node-negative breast cancer: UPA/PAI-1 determinations for 163 cases. Anticancer Res 34:1213–1217

21. Harbeck N, Thomssen C (2011) A new look at node-negative breast cancer. Oncologist 16:51–60. https://doi.org/10.1634/THEONCOLOGIST.2011-S1-51

22. Thangarajah F, Enninga I, Malter W et al (2017) A retrospective analysis of Ki-67 index and its prognostic significance in over 800 primary breast cancer cases. Anticancer Res 37:1957–1964

23. Viale G, Regan MM, Mastropasqua MG et al (2008) Predictive value of tumor Ki-67 expression in two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. J Natl Cancer Inst. https://doi.org/10.1093/jnci/djm289