Identifying Biomarkers to Select Patients with Early Breast Cancer Suitable for Extended Adjuvant Endocrine Therapy

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Keywords

Multigene assay · Biomarker · Late recurrence · Breast cancer · Prediction · Risk stratification

Summary

Postmenopausal women with early oestrogen receptor-positive breast cancer who have received 5 years of endocrine therapy are at increased risk of developing a recurrence. An important clinical question is how to identify women who are at highest (or lowest) risk of a recurrence. The use of prognostic biomarkers allows individualised breast cancer therapy but correct identification of patients who will benefit most from extended endocrine therapy is essential. Several multigene assays have been developed to determine the likelihood of overall recurrence but so far none exist specifically for the prediction of late recurrence. Recent results from large clinical trials have shown that biomarker assays that include clinical information in their tests might be useful to predict and risk stratify patients for late recurrence. However, further research is needed to specifically offer multigene assays for the identification of late recurrence and thus justify routine use of these tests in the clinical setting.

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Introduction

Breast cancer is the most common cancer in women worldwide [1] and postmenopausal women with hormone receptor-positive breast cancer are treated with aromatase inhibitors (AIs) for

5 years. AIs have been shown to be highly effective in reducing the risk of distant recurrence in postmenopausal women with early hormone receptor-positive breast cancer [2–4]. However, despite this significant benefit, relapses after 5 years of endocrine therapy still occur in more than 50% of women. Therefore, the benefit of extending the duration of endocrine therapy either with an AI for an additional 5–10 years or tamoxifen for a further 10 years have been evaluated in large clinical trials [5–9]. These trials have shown an absolute benefit in risk reduction for recurrence of 2.5–4% and around 3% absolute reduction for mortality with extended endocrine therapy. The use of extended endocrine therapy, however, should be weighed against the potential risk of serious side effects. There is a great need to identify those women who are at increased risk of late relapse and who will benefit most from extended endocrine therapy. As important is to identify those women who are at a very low risk of late recurrence and who will do well without further interventions and, hence, can be spared the burden of toxicities from endocrine therapies.

Clinicopathological parameters such as tumour size, nodal status, and stage are routinely used to estimate the risk of breast cancer recurrence, particularly within the first 5 years after diagnosis. Nodal status has been shown to be a powerful prognostic marker for late recurrence [10, 11], whereas tumour size and in particular grade play a lesser role for the prediction of late relapses [10]. Immunohistochemical markers (oestrogen receptor (ER), progesterone receptor, HER2, and Ki67) have been widely investigated for prognostic purposes and use in treatment decisions. Although they are highly prognostic in the first 5 years after diagnosis, the prognostic strength of these markers diminishes for the prediction of late recurrence and should not be used as stand-alone for these purposes [10].

Biomarker assays have become important tools for determining the prognosis and management of patients with ER-positive breast cancer (table 1). These markers combine expression profiles of a panel of cancer-related genes and have mostly been developed and

Table 1. Prognostic signatures for the prediction of late distant recurrence

Test	Information included	Development population	Reference
Oncotype RS	21 genes (oestrogen, proliferation genes)	Pre- and postmenopausal, node negative, tamoxifen or placebo	[12, 13]
PAM50 ROR	50 genes, proliferation score, tumour size included	Pre- and postmenopausal, some chemotherapy, and pre- and postmenopausal, oestrogen receptor positive, tamoxifen	[18, 19]
BCI	H/I and 5 proliferation genes (molecular grade index) (BUB1B, CENPA, NEK2, RACGAP1, RRM2)	Postmenopausal, node negative, oestrogen receptor positive, tamoxifen Pre- and postmenopausal, node negative, oestrogen receptor positive, chemotherapy, tamoxifen	[24, 25]
EPclin	12 genes (proliferation, differentiation, oestrogen), nodal status and tumour size included	Postmenopausal, oestrogen receptor positive, HER2 negative, tamoxifen	[27]

RS = Recurrence Score, PAM50 ROR = Prosigna PAM50 risk of recurrence, BCI = Breast Cancer Index, EPclin = EndoPredict.

validated in ER-positive, HER2-negative, and node-negative patients. They all provide prognostic information for recurrence-free survival independent of traditional clinical markers such as nodal status, tumour size, and stage. None of these biomarker assays have been developed to specifically predict late (distant) recurrences, but nevertheless some of them have been investigated in this context and are reviewed here in more detail.

Biomarker Assays

Oncotype DX Recurrence Score

The 21-gene-based Oncotype DX Recurrence Score (Oncotype RS) is a well-established multigene assay that was developed to assess the risk of recurrence (ROR) in women with hormone receptor-positive, node-negative breast cancer treated with tamoxifen (table 1) [12]. The signature generates a continuous Oncotype RS, with a higher Oncotype RS corresponding to an increased ROR. The Oncotype RS furthermore classifies women into low (< 18), intermediate (18–30), and high (> 30) risk groups for recurrence. The Oncotype RS has been validated in a number of clinical trials and results confirm the prognostic value of the Oncotype RS for (distant) recurrence in the first 5 years after diagnosis [12–14]. The Oncotype RS was validated in the transATAC study [15] and was shown to have prognostic value for distant recurrence independent of clinicopathological parameters.

The prognostic value of the Oncotype RS for late distant recurrence was furthermore evaluated in the transATAC trial [10]. The Oncotype RS was compared to clinical factors and other molecular scores. The Oncotype RS added significant prognostic value in the first 5 years after breast cancer diagnosis, but failed to be substantially predictive of late distant recurrence in the overall population when adjusted for clinicopathological parameters. In women with node-negative and HER2-negative disease, the Oncotype RS was

somewhat more prognostic for late metastasis [10], but failed to provide any substantial prognostic value for women with node-positive disease. When compared to other molecular assays, the Oncotype RS was least prognostic for the prediction of late distant recurrence (fig. 1). These results strongly suggest that the Oncotype RS is not a solid candidate for the prediction of late distant recurrence in women with ER-positive disease. However, more recently, the Oncotype RS was evaluated in patients from the NSABP B-28 and B-14 trials for the prediction of late distant recurrence within low and high *ESR1* levels [16]. The study found that Oncotype RS is strongly prognostic for late distant recurrence in women with a high *ESR1* level (cut-off 9.1) and that extended tamoxifen therapy is warranted in those with high expression of *ESR1* and intermediate/high risk patients. In contrast to this study, an exploratory analysis of the individual Oncotype RS genes in the transATAC cohort revealed that for oestrogen-related genes the prediction of distant recurrence was substantially different between early versus late follow-up period [17]. These differential findings need to be confirmed and a clearer understanding gained of whether a certain *ESR1* level is needed for the use of Oncotype RS in the context of predicting late distant recurrence.

Prosigna PAM50 Risk of Recurrence

The Prosigna PAM50 risk of recurrence (PAM50 ROR) score is based on a 50-gene test, which was developed in women with node-negative or node-positive disease to identify intrinsic breast cancer subtypes (table 1) [18, 19]. The PAM50 ROR is derived from an expression profile of 50 genes and includes tumour size in its signature. The PAM50 ROR can be used as a continuous score but also classifies women into 3 risk groups to determine 5-year ROR.

In the transATAC trial, the PAM50 ROR was evaluated for the added prognostic information for distant recurrence beyond that of clinicopathological parameters in the first 5 years but also over-

all 10 years of follow-up [20]. The PAM50 ROR score was highly prognostic for overall distant recurrences above and beyond clinical parameters. These results were confirmed in the ABCSG-8 trial [21] in which the PAM50 ROR score added significant prognostic value beyond that of clinical parameters for distant recurrence in the overall population and all subgroups. More recently, the PAM50 ROR score was additionally investigated for the prediction of late distant recurrence in the transATAC trial [10]. The PAM50 ROR score was the strongest prognostic test in all patient subgroups when compared to the Oncotype RS, and furthermore reclassified more women into the low- or high-risk group. This were the first results to show that the PAM50 ROR score added significant prognostic information for late distant recurrence and can be used in this context. These findings were furthermore confirmed by the ABCSG study group, which showed that the PAM50 ROR score and ROR-based risk groups can differentiate patients with respect to their risk of late distant recurrence beyond that which can be achieved by clinicopathological parameters alone [22].

A combined analysis of the transATAC and ABCSG studies evaluated and confirmed the use of the PAM50 ROR score for the prediction of late distant recurrences [23]. 2,137 postmenopausal women who were recurrence free within the first 5 years after diagnosis were evaluated. When adjusted for clinicopathological parameters, the PAM50 ROR score provided independent significant prognostic information for late distant recurrence in all patients, and was more predictive in node-negative and node-negative/HER2-negative patients than clinical factors alone [23]. The results of this analysis indicated that the PAM50 ROR score is able to identify women who are at sufficiently low risk of late distant recurrence, even if they have node-positive disease, and therefore might be spared additional endocrine therapy, overtreatment, and potential toxicities. Further research is needed to determine which genes of the PAM50 gene panel are the strongest predictors for late distant recurrence. This is being currently evaluated in the transATAC study where the aim is to determine the prognostic information of all individual 50 genes and as clusters of fully correlated

genes to determine the optimal combination of those genes for late distant recurrence. This new combination of genes might lead to a specific predictor of late recurrence for women with ER-positive, HER2-negative breast cancer.

Breast Cancer Index

The Breast Cancer Index (BCI) is a gene expression module based on 2 components: the HOXB13/IL17BR (H/I) and the proliferation module Molecular Grade Index (MGI) and was developed in tamoxifen-treated women with lymph node-negative disease. The BCI has been shown to be a good predictor for early distant recurrence in this cohort [24, 25]. In addition, the BCI categorised the majority of women as low risk for distant recurrence in years 0–5 but also showed prognostic value for late recurrence.

The BCI was further evaluated in the transATAC cohort for the prediction of distant recurrence in the early and specifically late follow-up period [26]. The results showed that the BCI as a continuous score was an independent strong predictor for late distant recurrence in women with node-negative and HER2-negative/node-negative disease and furthermore identified women at sufficiently low risk of late distant recurrence in whom additional endocrine therapy is not warranted. An exploratory analysis was performed to investigate whether both components of the BCI score can predict late distant recurrence. Only the H/I ratio significantly predicted late recurrence, whereas both components added prognostic value in the first 5 years after diagnosis when adjusted for clinical parameters [26]. Other results [10] also demonstrated that proliferation-related factors, such as Ki67 or clinical tumour grade, are not prognostic for late distant recurrence. This is in contrast to the proliferation-related genes in the Oncotype RS, where similar recurrence risk and prognostic abilities were found for early and late time periods [17]. The BCI identifies women with node-negative disease at increased risk of late distant recurrence and might be used in the clinical setting to identify women who might benefit from further endocrine therapy. However, this signature has not been evaluated in this context for women with node-positive disease.

Endopredict

The Endopredict (EP) was developed for women with hormone receptor-positive, HER2-negative disease and includes information of 8 cancer-related and 4 normalisation genes [27]. The signature has been validated in a cohort of women from 2 large clinical trials (ABCSG-6/8), who were treated with adjuvant endocrine therapy only. The EPclin, which combines the EP with nodal status and tumour size, has furthermore been shown to have strong prognostic abilities for the prediction of distant recurrence above and beyond clinicopathological parameters [28]. Both signatures are available as continuous scores or as low and high risk groups as defined by pre-specified cut-off points. The EP and EPclin were recently validated in the transATAC cohort [29] in which both scores added significant prognostic information for distant recurrence, independent of clinical parameters, and performed better than the Oncotype RS. The value of the EPclin was further evaluated for the prediction of late distant recurrences in the same study and it was shown to be a strong predictor for late recurrences, irrespective of nodal status. This finding was confirmed in the ABCSG study [30] in which the EPclin was clearly associated with the prediction of late metastasis and identified a subgroup of patients who have a very good prognosis after 5 years of endocrine therapy. As with the other signatures, evaluation of the individual genes to determine which contribute to the prediction of late distant recurrence is important.

Comparison of Biomarker Assays for Late Prediction

For a biomarker to be used in the context of prediction of late recurrence, they need to show independent prognostic value above and beyond clinicopathological parameters. They also need to be able to stratify patients into specific risk groups for whom it is acceptable to withhold further endocrine therapy (low risk) or extended treatment (high risk). So far, only 1 study has directly compared the prognostic ability of the above assays for the prediction of late distant recurrence [31]. A head-to-head comparison was performed to establish which test has the most prognostic ability to predict late distant recurrence in women with ER-positive and HER2-negative disease, independent of clinicopathological parameters (as expressed by the Clinical Treatment Score, which includes information on nodal status, tumour grade, tumour size, age, and treatment). For those with node-negative disease, the BCI, PAM50 ROR, and the EPclin provided strong independent prognostic value for late distant recurrence (fig. 1). These three signatures were also able to identify a large proportion of women with node-negative disease (~60% of women) who were at a very low risk of late distant recurrence (less than 5% at 10 years) where extended endocrine therapy is not indicated. Between 13–26% of women with node-negative were categorised into the high-risk group and for these women additional endocrine therapy is an option that potentially might lower the risk of distant recurrence. For women with node-positive disease, only the PAM50 ROR and the EPclin provided some, albeit little, additional prognostic information

above and beyond clinicopathological parameters, whereas the 2 purely molecular assays (BCI and Oncotype RS) did not provide any prognostic value for late distant recurrence. Nevertheless, the PAM50 ROR and Epclin identified around 15% of women with node-positive disease as low risk, and in these patients, despite having 1 or more positive nodes, extended endocrine therapy is not warranted. The analysis of this comparison also highlighted the importance of the combination of molecular biomarkers with clinical information. The 2 assays that include clinical information in their score (PAM50 ROR and EPclin) performed best and were able to provide prognostic value and clear risk stratification for women with node-negative and node-positive disease. This analysis further confirmed that the Oncotype RS did not provide any prognostic power for the prediction late distant recurrence, irrespective of nodal status of the disease.

Guidelines

Several guidelines have published their recommendation for these test for the prediction of (late) recurrences [32–35]. These guidelines put particular emphasis on studies involving the validation of the biomarker in prospective or prospective-retrospective trials, and some indicate a level of evidence [36] for their use in the clinical setting. Although all these test are commended for women with node-negative disease for the first 5 years after diagnosis, some guidelines do not recommend these multigene assays for women with node-positive disease or do not recommend using a test at all. None of the guidelines recommend multigene assays for the prediction of late (distant) recurrence; however, the EGTM [34] addresses the issue that further validation of these test is needed for predicting late recurrences following adjuvant endocrine therapy. Even though these test are not recommended for prediction of late recurrence, in this context, all tests, apart from the Oncotype RS, provide clinical utility and contribute clinically useful information beyond that already provided by clinicopathological information. This is further underlined by the fact that all tests show level IB evidence as established by Simon et al. [36].

Conclusion

Multigene assays are useful for the prediction of late recurrence and risk stratification but their ability to predict endocrine therapy efficacy has not been evaluated yet. An improved risk stratification has been accurately achieved by multigene assays and, therefore, these tests might help determine which patients may benefit from extended endocrine therapy or in which patients it can be omitted. Clinicopathological parameters, in particular nodal status and tumour size, are very well established predictors for late recurrence, but molecular multigene assays improve the prediction as some prognostic information is not captured in clinical parameters. In several retrospective validation trials [22, 26, 29, 31, 37], the PAM50 ROR, BCI, and EPclin have all shown to add significant

prognostic information for late recurrence in postmenopausal women with ER-positive breast cancer. However, it has become apparent that those assays that include clinical information outperform purely molecular assays for the prediction and risk stratification of late (distant) recurrence. Another important clinical question is the optimal duration of extended endocrine therapy and several trials have addressed this with differing results [38–40]. Patients deemed high risk by clinical parameters and multigene assays after 5 years of endocrine therapy, in particular those with node-positive disease, may very well benefit from extended endocrine therapy, but the benefit-risk ratio needs to be discussed on an individual basis. Overall, there is good evidence that the PAM50 ROR and the EPclin predict late recurrence and identify a good number of women as low risk who might not need extended endocrine therapy. For women who are deemed low risk by clinical parameters (less than 5% ROR), by Adjuvant Online!, Nottingham

Prognostic Index, PREDICT, or other risk tools, multigene assays may help identify those who are at increased risk of developing a late distant recurrence, i.e. high risk by multigene assay, and hence extended endocrine therapy is indicated. For women who are clinically high risk (over 10% ROR), PAM50 ROR and EPclin are useful for determining patients who are at high risk of developing a late distant recurrence. Finally, none of these tests have been developed particularly for the prediction of late distant recurrence. Ongoing work includes identifying individual genes from the PAM50 and EP gene panels to establish tests that are tailored towards predicting late distant recurrences.

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