BREAST CANCER

Predicting late recurrence in ER-positive breast cancer

Jack Cuzick

Identification of factors predicting recurrence of breast cancer is a long-standing goal, ranging from classical clinicopathological factors through to immunohistochemical assays of receptor levels and, more recently, the expression levels of several genes. A new paper explores new expression markers, especially for late recurrence of oestrogen receptor-positive breast cancer.

Refers to Rueda, O. M. et al. Dynamics of breast-cancer relapse reveal late-recurring ER-positive genomic subgroups. *Nature*. https://doi.org/10.1038/s41586-019-1007-8 (2019)

Breast cancer has been the subject of many studies aimed at the identification of prognostic markers and predictors of response to treatment (**TABLE 1**). Some of this work is several decades old, and the early discoveries of the importance of regional lymph node involvement and tumour size remain the most powerful pair of prognostic markers[4]. These markers have been combined with tumour grade, patient age, and treatment type to create the Clinical Treatment Score (CTS), which has prognostic value both for early[1] and late[2] recurrence of patients with oestrogen receptor (ER)-positive breast cancers. Immunohistochemical assays of ER and progesterone receptor (PR) protein level expression have also proven to be strong predictive biomarkers for response to endocrine treatment[9]. Furthermore, the levels of human epidermal growth factor receptor 2 (HER2) positivity inform on the likelihood of response to the anti-HER2 antibody trastuzumab and related agents, which have dramatically improved the outcomes of this traditionally poor prognostic patient subgroup. Pathological grade (or highly positive immunostaining for the proliferation marker Ki-67) is also a strong predictor of response to chemotherapy. Accordingly, these four immunohistochemical markers (ER, PR, HER2 and Ki-67) have been combined into the IHC4 score, which has shown comparable prognostic value to molecular markers in the first five years of follow up after diagnosis[1,2].

In the past decades, a range of RNA-based gene expression scores have also been developed and validated in breast cancer[3], and have been shown to have additional

prognostic value beyond that provided by CTS, especially during the first 5 years after diagnosis. However, only a few of these scores — notably the PAM50-based Prosigna risk of recurrence (ROR) score, the EndoPredict assay (EPclin), and the Breast Cancer Index (BCI) — have been useful in predicting late recurrence after five years of follow-up monitoring in patients with ER-positive breast cancer, which provides important information for deciding the duration of endocrine treatment[3].

The recurrence rate for ER-positive tumours is virtually constant for up to 20 years after diagnosis[4]. The reasons for this phenomenon are unclear, but probably involve the re-emergence of metastatic cancer clones that remain hidden both from detection and treatment in the early years (0–5 years) after diagnosis. By contrast, ER-negative tumours have a different temporal profile for recurrence, with a much higher recurrence rate in the first five years after diagnosis, followed by a lower recurrence rate subsequently[5].

The development of improved markers of late recurrence is a priority for women with ER-positive breast cancer. These late recurrences are almost certainly, at least partially, related to somatic changes in residual tumour cells after adjuvant therapy. Indeed, mutations in the *ESR1* gene seem to affect response to treatment with aromatase inhibitors and, at least in the metastatic setting, seem to be induced by aromatase inhibitor treatment[6]. Blood-based liquid biopsies performed during follow-up monitoring might be a solution for detecting such genetic changes, but our current ability to measure small amounts of cell-free tumour DNA or circulating tumour cells in patients without prior metastases is very limited.

The present study by Rueda and colleagues[7] focuses on factors that are apparent in the primary tumour specimen and builds upon work using current RNA-expression-based prognostic models. The investigators adopted a Markov model approach that is more complex than current prognostic models and that estimates the risk of breast cancer relapse and mortality over time, by estimating the transition rates through four distinct stages: localized diagnosis in the breast, locoregional recurrence, distant recurrence, and, finally, death from the disease[7]. By applying their model to 1,980 patients with breast cancer who had available molecular data, the investigators identified different relapse patterns across different molecular subgroups, including immunohistochemical subtypes, PAM50 subtypes, and eleven IntClust subtypes (which were based on patterns of gene expression and copy number variation). The value of this more complicated model is unclear, as most patients do not have an identifiable progression through all of these stages and, notably, most distant recurrences

are not preceded by a detectable locoregional recurrence. Nevertheless, improved characterization of the tumour at diagnosis using molecular signatures is likely to extend the prognostic accuracy beyond that of the currently available signatures. Across the 11 IntClust subtypes, the authors found that four of these subtypes were associated with late recurrence in patients with ER-positive HER2-negative tumours (IntClust1, IntClust2, IntClust6, and IntClust9, which comprised 26% of such tumours). However, whether or not patient stratification by discrete subtypes is the best way to utilize molecular data is unclear, and a discussion of the key genes that characterize these subtypes would have been useful. Even when patients were stratified according to the five PAM50 subtypes (normal, luminal A, luminal B, basal, and HER2), the difference in relapse between luminal A and luminal B cancers is not dichotomous, but rather a continuous variation based largely on the cell cycle progression component of the score, or similar variation of an immunohistochemical Ki-67 measurement. Several other expression-based algorithms for recurrence have been published[3] and it would have been useful to indicate what advantages the current classification has over these.

Rueda et al.[7] focus on prognostic markers for recurrence, but current breast cancer classifications also provide insight into the most appropriate treatment for different tumours, which will become an even more pressing need beyond predicting prognosis as new treatments are developed. Looking at changes in molecular profiles before and after presurgical systemic treatment is also likely to provide useful guidance[8].

Although validation of the findings from the study by Rueda et al.[7] in a separate cohort is needed, work in this important area of molecular classification of tumours is likely to continue to provide additional insights into prognosis and, especially, the most effective treatment for individual tumours.

Jack Cuzick

Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine,

Queen Mary University of London, London, UK.

Email: j.cuzick@qmul.ac.uk

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Competing interests

The author declares that he is a consultant for Myriad Genetics, who market the EndoPredict assay (EPclin).

Pullquotes

The present study by Rueda and colleagues … builds upon work using current RNA-expression-based prognostic models

molecular classification of tumours is likely to continue to provide additional insights into prognosis

Table 1 | **Clinicopathological and molecular biomarkers in breast cancer.**

Marker	**Uses**
Clinicopathological markers	
Nodal involvement	Strongest overall prognostic factor for follow-up monitoring, both before and after the first 5 years following diagnosis
Tumour size	Important prognostic factor for follow-up monitoring, both before and after the first 5 years following diagnosis
Tumour grade	Useful in first 5 years following diagnosis; predicts response to cytotoxic chemotherapy
CTS/CTS5	Model that integrates clinical factors for distant recurrence; CTS5 is specific for distant recurrence after 5 years following diagnosis
Immunohistochemistry and/or FISH markers	
ER/PR	Useful in the first 5 years following diagnosis; predicts response to endocrine therapy
HER2	Predicts response to trastuzumab and related compounds

Ki-67	Similar to grade; useful in first 5 years following diagnosis; predicts response to cytotoxic chemotherapy
IHC4	Model that integrates ER, PR, HER2, and Ki-67 levels
RNA expression or gene copy number markers	
Oncotype DX recurrence score	The first widely used molecular test; uses 21 genes; developed for ER-positive node-negative patients
Mammoprint	Uses 70 genes and creates high-risk and low-risk groups
PAM50-based Prosigna risk of recurrence score	For ER-positive early-stage breast cancer; uses 598 genes and clinical data
EndoPredict (EpClin)	For ER-positive HER2-negative early-stage breast cancer; uses 12 genes and clinical data; useful for follow-up monitoring, both before and after the first 5 years following diagnosis
Breast Cancer Index (BCI)	For ER-positive HER2-negative early-stage breast cancer; useful for follow-up monitoring, both before and after the first 5 years following diagnosis
IntClust	Identifies 11 new subtypes with different recurrence characteristics

CTS, Clinical Treatment Score; ER, oestrogen receptor; PR, progesterone receptor.