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Prognostic factors in invasive breast carcinoma: Do new molecular techniques/profiling add significantly to traditional histological factors?

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Summary Greater awareness and use of screening has led to an increase in the proportion of 'early' breast cancers. Conventional prognostic factors such as tumour size and nodal status are of limited use with these tumours, because most of them are node negative and small. There is a need for factors that are not only prognostic, but also predict response to therapy, in the selection of appropriate therapy for these low-risk patients, especially to avoid the administration of toxic therapies to patients who are unlikely to gain significant benefit. This has led to the emergence of newer molecular prognostic factors, gene-expression signatures being the latest. Although not many of these newer prognostic factors have proved clinical utility, recent studies report remarkable results with the use of gene-expression signatures as prognostic and predictive factors. These results, though promising, have been compared only with simple parameters such as tumour grade and with broad practice guidelines. Additional studies documenting superiority of gene signatures over existing prognostic algorithms such as the Nottingham prognostic index and Adjuvant! Online are necessary before their widespread routine use. Currently, gene signatures are best used as a part of randomized clinical trials such as MINDACT and TAILORx. In this review, we discuss the biological basis, scientific evidence and clinical application of conventional and molecular prognostic factors, including gene-expression signatures.

Introduction

A 60-year-old post-menopausal woman walks into a breast oncologist's clinic with the histopathology report of her recent breast conservation surgery. She has a 2 cm, low-grade, node-negative, hormone-sensitive breast cancer, which has low risk of

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recurrence based on currently used prognostic factors. Before deciding on whether to take chemotherapy, she wants to know whether there are additional tests that could predict more precisely her risk of recurrence.

Conventional histopathological prognostic factors broadly group patients into low-risk, intermediate-risk and high-risk categories, and such grouping helps in treatment planning.[1] However, in many circumstances, especially in low-risk or intermediate-risk groups, conventional information is insufficient to make accurate treatment decisions, as illustrated above. These clinical situations highlight the need for additional prognostic factors (or tools) that will further classify/regroup patients more accurately to aid in making treatment decisions.

The quest for better prognostic factors has occupied breast cancer researchers for the last two decades and has led to a recent increase in prognostic tools. Most of these newer tools are based on molecular pathology/biology techniques such as HER-2 expression, markers of angiogenesis and invasion, and the more recent gene-expression signatures and molecular portraits. Readers should note that all prognostic factors are predictive factors for recurrence, and some of these additionally serve as predictive factors for therapy [e.g. oestrogen receptor (ER), HER-2]. In this review, we discuss the conventional prognostic markers and newer molecular prognostic markers, and examine whether these tools help us in making more informed therapeutic decisions.

Conventional prognostic factors

TNM stage, certain routine histopathological features such as grade, lymphovascular invasion and hormone receptor status are conventional prognostic factors that have been validated extensively over many years. For a detailed discussion of the methodologies, limitations and variability of analysis, readers are directed to the consensus statement of the College of American Pathologists.[2] This statement classifies prognostic parameters into three categories based on their importance and usefulness in clinical management. Category I (factors of proven importance) includes nodal status, tumour size, histological grade and type, and hormone receptor status. Category II includes factors that have been extensively studied biologically and clinically, but the importance of which remains to be statistically validated. This category includes HER-2, proliferation markers, lymphatic and vascular channel invasion and p53. Category III includes factors that have not been sufficiently studied to demonstrate their prognostic value. This includes DNA ploidy analysis, microvessel density (MVD), epidermal growth factor receptors, transforming growth factor-β, bcl-2, pS2 and cathepsin D.

Nodal status: Axillary nodal status is the strongest prognostic factor in breast cancer. Surveillance, Epidemiology, and End Results (SEER) study data from more than 24,000 patients showed that the 5-year overall survivals (OS) for node-negative patients, one to three positive axillary lymph nodes, and more than four involved nodes was 92%, 81% and 57%, respectively.[3] Recent studies have documented the practical utility and specificity of sentinel node biopsy, and algorithms based on patient age and other tumour parameters of use in predicting the likelihood of additional nodal disease have been described[4] and validated.[5] Evidence for the prognostic value of lymph node micrometastasis detected by cytokeratin-based immunohistochemistry or reverse-transcriptase PCR (RT-PCR) in otherwise node-negative patients is conflicting, with some studies claiming such value while other studies refuting it. One reason for the confusing data is the different adjuvant therapies (or lack thereof) that the patients have received; this makes comparisons difficult, if not impossible.

Tumour size: This is the next most important prognostic factor. The same SEER dataset had more than 13,000 node-negative patients, and the 5-year OS in those with node-negative tumours of less than 1, 1–3 or 3–5 cm was 99%, 89% and 86%, respectively.[3]

Tumour type: The importance of tumour type is significantly diminished due to the fact that approximately 90% of tumours are classified as infiltrating ductal carcinoma (no special type) in most series. The incidence of infiltrating lobular carcinoma, the second most common type, is less than 5%. Uncommon types such as pure tubular, papillary and medullary, which have better survival with low short-term recurrence rates, constitute the remainder.

Tumour grade: One of the more widely used systems for tumour grade assessment is the Elston and Ellis modification[6] of the Scarff–Bloom–Richardson score, based on architectural differentiation, nuclear pleomorphism and mitotic index. Tumour grade correlates not only with disease-free survival, but also with post-relapse survival. Although many studies on both sides of the Atlantic have confirmed the prognostic significance of tumour grade, inter-observer variability, mainly due to lack of strict adherence to the defined criteria, remains an important concern that limits its use as a strong prognostic factor.