## Emmanuel van der Schueren Award Lecture

# E1. Molecular strategies improve therapeutic decisions

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Breast cancer starts as local disease and may metastasise to the lymph nodes and distant organs. Currently, at primary diagnosis, prognostic markers are used to assess the likelihood that the transition to systemic disease has occurred. The prevailing model of metastasis reflects this view, suggesting that metastatic capacity is a late acquired event in tumourigenesis. Others have proposed that breast cancer is intrinsically a systemic disease. New molecular technologies, such as DNA microarrays, support the notion that metastatic capacity might be a breast tumour's inherent feature. These data have important implications for prognosis prediction, our understanding of metastasis, and may provide the new prognostic markers that are urgently needed to identify patients with breast cancer who are at the highest risk for developing metastases.

Improving our understanding of the molecular mechanisms of the metastatic process might also improve clinical management of the disease. According to the widely held model of metastasis, rare subpopulations of cells within the primary tumour acquire advantageous genetic alterations over time, which enable these cells to metastasise and form new solid tumours at distant sites. Many studies have challenged this 'genetic-selection' model of metastasis in the past, but only recent data obtained by gene expression profiling of human breast carcinomas have received broader attention. DNA microarray studies reported that primary breast tumours that developed metastases could be distinguished by their gene expression profile from those that remained localised. The data imply that the metastatic capacity of 'poor-prognosis' breast tumours might be acquired by mutations at much earlier stages of tumourigenesis than previously assumed (Fig. 1).

The gene expression profiling studies of primary breast tumours performed by different laboratories have resulted in the identification of many apparently different prognostic profiles/gene sets, which show little overlap in gene identity (Fig. 2, example NKI 70 gene profile). A comparison of the different prognostic profiles shows that, even though different gene sets and algorithms are being used with breast cancer patients, there is a significant agreement in outcome predictions for individual patients. These profiles are probably tracking a common set of biological phenotypes, but specific profiles have their advantages in different clinical settings.

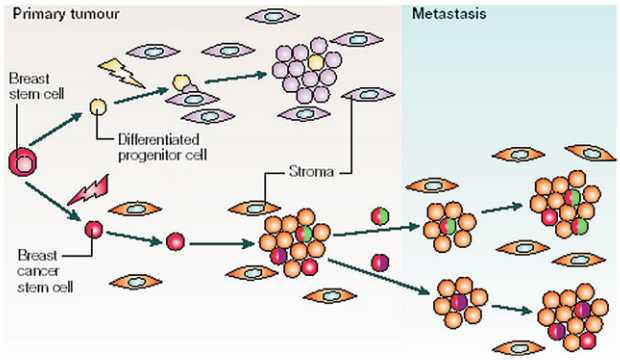


Fig. 1. An integrative model of breast cancer metastasis. Oncogenic mutations occurring in a breast stem cell (red) can cause the transformation to a breast cancer stem cell, generating 'poor-prognosis' tumours (orange). Mutations occurring in differentiated progenitor cells (yellow) might form a non-metastatic 'good-prognosis' breast carcinoma (pink). In the metastatic poor-prognosis tumours, under the influence of stromal fibroblasts, only the population of breast cancer cells has the ability to metastastise. There might be variant cancer stem cells that differ in their tissue selectivity for metastasis, expressing an additional tissue-specific profile (for example: green, bone; purple, lung). At the site of metastasis, the disseminated cancer stem cells would again induce a similar stromal response as in the primary breast tumour. Source: Weigelt B, Peterse JL, van 't Veer LJ. *Nature Reviews Cancer* 2005, **5**, 591–602.

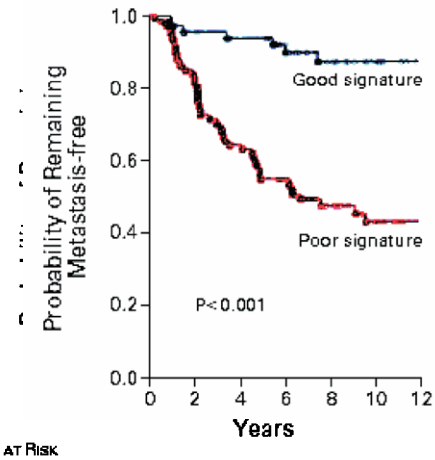


Fig. 2. Kaplan–Meier analysis of the probability that lymph-node-negative patients would remain free of distant metastases. Source: van de Vijver M, He Y, van 't Veer LJ, *et al. N Engl J Med* 2002, **347**, 1999–2009.

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Nowadays, consensus guidelines on the management of breast cancer select up to 95% of lymph-node-negative breast cancer patients for adjuvant systemic therapy (e.g. National Institutes of Health [NIH] and St Gallen consensus criteria). As 70–80% of these patients would have remained disease-free without this adjuvant treatment, these patients are being 'over-treated'. The 'poor-prognosis' signatures provide a novel strategy accurately to select patients who would benefit from adjuvant systemic therapy and can greatly reduce the number of patients who receive unnecessary treatment.

Recent results show that the molecular program established in a primary breast carcinoma is highly preserved in its distant metastasis. These findings further strengthen the idea that metastatic capability in breast cancer is an inherent feature, and is not based on clonal selections. Importantly, these results further imply that neo-adjuvant treatment given to patients based on response expression profiles of their primary breast tumour might indeed prevent the outgrowth of micro-metastases.

Currently, the European Organisation for Research and Treatment of Cancer (EORTC) breast group is performing a randomised trial of 6000 patients to compare the efficacy of selection of breast cancer patients for adjuvant chemotherapy based on either clinical criteria or the 70-gene microarray prognosis profile, Mammaprint (Microarray In Node negative Disease may Avoid ChemoTherapy [MINDACT] trial within the EU-TRANSBIG program, EORTC 10041 BIG 3-04 Inter-group study). Two aims of the study are to confirm that the microarray test will save up to 30% of patients from undergoing unnecessary chemotherapy and to identify 5% of patients who are nowadays 'undertreated'. In addition, in this trial therapy response profile can be tested to predict the efficacy of hormonal therapy and chemotherapy.

Management of breast cancer tailored to individual patients by molecular strategies is of benefit to the patients.