Who needs adjuvant systemic treatment? Predicting prognosis in node-negative breast cancer; from bench to bedside
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Introduction & Outline Thesis
Who needs adjuvant systematic treatment

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J.M. Bueno-de-Mesquita
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Prognostic factors and clinical guidelines for adjuvant systemic treatment selection in lymph node-negative breast cancer patients

Breast cancer - general features
In the Netherlands, breast cancer is the most common malignancy in women. Currently, the breast cancer incidence is 13,000 and annually over 3,000 women die this disease.\(^1\) The lifetime risk to develop breast cancer is even one in nine.\(^2\)

The primary treatment of localised breast cancer is either complete tumour excision followed by radiation therapy (breast conserving therapy) or mastectomy with or without radiotherapy.\(^3\) Adjuvant systemic treatment (chemotherapy, endocrine therapy and/or trastuzumab) is used to control micrometastatic disease and leads to improved survival. The addition of systemic adjuvant therapies to the primary treatment of localised oestrogen receptor positive breast cancer has been shown to reduce the 15-year breast cancer specific mortality rate by approximately 50% in middle aged women.\(^4\) Prognostic factors are used to identify those patients at relatively high risk of developing distant metastases, as those patients benefit most from adjuvant systemic treatment. However, systemic treatment has a wide range of acute and long-term toxicities. The Oxford Overviews of systemic treatments demonstrate that a significant proportion of patients who have not received adjuvant systemic therapy are long-term survivors; and also that a proportion of patients will develop metastatic disease despite undergoing adjuvant systemic therapy.\(^4\) Using these clinicopathological guidelines it has been estimated that up to 33 patients may have to be treated with adjuvant systemic treatment to save one life.\(^5\) Therefore, an accurate selection of patients who will benefit from adjuvant systemic treatment is essential.

Prognostic factors
Strong adverse prognostic factors in breast cancer are tumour size and the presence of lymph node metastases.\(^6\) In all clinical treatment guidelines, the presence of lymph node metastases is considered a strong indication for undergoing adjuvant systemic therapy. For lymph node-negative breast cancer patients, other clinicopathological factors are used to guide adjuvant systemic therapy.

The main clinically used prognostic factors in lymph node-negative breast cancer are age, tumour diameter and histological grade.\(^6\) Clinicopathological risk (‘clinical risk’) assessment is based on these factors and is used to guide decisions on adjuvant systemic treatment. Choice of adjuvant systemic therapy is also dependent on the oestrogen receptor, progesterone receptor and HER2 status.

A large number of potential prognostic factors have been investigated to predict disease outcome. Even the strongest prognostic factors (e.g. lymph node status, tumour diameter and histological grade) are moderately precise in classifying breast tumours according to their clinical behaviour.
Clinical guidelines for adjuvant systemic treatment

Various clinical and pathological factors have been carefully evaluated as prognostic indicators of clinical course. Most of these variables have been combined into prediction models, such as the Nottingham Prognostic Index (NPI)\textsuperscript{7-10} and Adjuvant Online (www.adjuvantonline.com)\textsuperscript{11,12}, or included in algorithms used for the development of guidelines for treatment decision-making, such as the Sankt-Gallen guidelines\textsuperscript{13-15} and the Dutch CBO-guidelines\textsuperscript{16-18}. Using these predictions models or guidelines a patients’ prognosis can be estimated. Most of these guidelines subdivide patients in intermediate/high or low risk based on what their estimated long term overall survival is. A poor prognosis or intermediate/high clinical risk is defined as a relatively high likelihood that a patient will develop distant metastasis and eventually die of breast cancer. Depending on what guideline is used, a 10-year overall risk of dying of breast cancer of more than 10\% is considered a intermediate/high risk. In general, a intermediate/high clinical risk is viewed to be an indication for adjuvant systemic treatment.

Despite providing valuable information about the risk of recurrence, such prognostic tools have only limited ability to predict individual patient outcomes.\textsuperscript{3} Patients with the same clinicopathological parameters or breast cancer phenotype can have markedly different clinical courses and are associated with different survival rates. In addition, these prognostic tools are derived from the analysis of patient cohorts, which offer no information about treatment effects on outcome. Additional tools for determining an individual patient’s need and potential benefit from systemic therapy will be of great clinical benefit.

Gene expression profiling in breast cancer

Thousands of genes coordinate the behaviour of a tumour and the course of the disease of the patient. Analysis of differential gene-expression patterns across thousands of genes in a single experiment (as opposed to hundreds to thousands of experiments measuring the expression of one gene at a time), and extrapolation of these data to answer clinically pertinent questions such as those relating to tumour metastatic potential, can help define the best therapeutic regimens for particular patient subgroups.

Gene expression profiling using microarray-based technology has provided researchers with an ideal opportunity to begin taking steps towards performing comprehensive molecular and genetic profiling of breast cancer; hereby learning more about the genotype of a breast cancer tumour and a patient’s individual disease outcome.

Currently, microarray technology is in a transition phase whereby scientific information is beginning to guide clinical practice decisions. Before microarrays qualify as a useful standard clinical tool, however, they must demonstrate reliability and reproducibility. The high-throughput nature of microarray experiments imposes numerous limitations, which apply to simple issues such as sample acquisition and data mining, to more controversial issues that relate to the methods of biostatistical analysis required to analyze the enormous quantities of data obtained. Methods for validating proposed gene-expression profiles and those for improving trial designs represent some of the recommendations that have been suggested.\textsuperscript{19}
Prognostic signatures could help us selecting poor prognosis patients for adjuvant systemic treatment. Several research groups have used gene expression profiling to define subgroups of tumours associated with good or poor outcome.\textsuperscript{20-34} For breast cancer in particular, several independent groups have conducted comprehensive gene expression profiling studies identifying prognosis signatures with the objective of improving on traditional prognostic markers.\textsuperscript{\textsuperscript{3;23;30;35-37}} In most studies validation in a sufficiently large independent patient series is suboptimal, and this constitutes one of the major limiting factors to transfer this technique from bench to bedside.\textsuperscript{38} Recently, the 70-gene prognosis signature was identified by performing gene expression profiling on 78 breast cancer tumours selected from the tissue bank of the Netherlands Cancer Institute.\textsuperscript{23} This prognosis signature appeared a more powerful prognostic factor for distant metastasis and death than current clinicopathological factors. Van de Vijver et al. validated this signature in a series of 151 lymph node-negative breast cancer patients (<53 years; 40% good vs. 60% poor prognosis signature).\textsuperscript{24} Buyse et al. performed a second international validation in 302 patients (<61 years; 37% good vs. 63% poor prognosis signature).\textsuperscript{32} In these two validation studies, the prognosis signature appeared a strong independent prognostic factor in node-negative breast cancer patients.

**Outline Thesis**

The aim of the research described in this thesis was to assess the clinical relevance and value, the feasibility of clinical implementation, and the potential clinical use and impact on adjuvant systemic treatment decisions of the microarray-based 70-gene prognosis signature as a diagnostic test in lymph node-negative breast cancer patients in anticipation of level ‘one’ evidence from large international randomized controlled clinical trials.

Chapter two of this thesis is a review discussing microarray-based gene expression profiling techniques for different cancer types, the accompanying limitations and its potential use in answering clinical questions. Chapter three provides the results of an independent representative validation of the 70-gene prognosis signature in more recently diagnosed (1996-1999) node-negative breast cancer patients and in patients of an earlier validation study with prolonged follow-up. In Chapter four and five, the feasibility of implementation of the 70-gene prognosis signature in node-negative breast cancer is addressed by presenting the results of the RASTER-study (MicroarRAY PrognoSTics in Breast CancER) and reflecting on these results.

The adherence to adjuvant systemic treatment guidelines, which are based on clinicopathological prognostic factors, was investigated in several Dutch Hospitals and these results are presented in Chapter six. The inter-observer variation of pathological examination of breast cancer is discussed in Chapter seven. Chapter eight discusses the clinical relevance and the potential use of the 70-gene prognosis signature as a diagnostic test in node-negative breast cancer in anticipation of the results of prospective randomised controlled trials with sufficient follow-up (e.g. MINDACT trial). A summary of the results presented in this thesis is given in chapter nine.
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References

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