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Prognostic factors in breast cancer: one fits all?

Mook, S.

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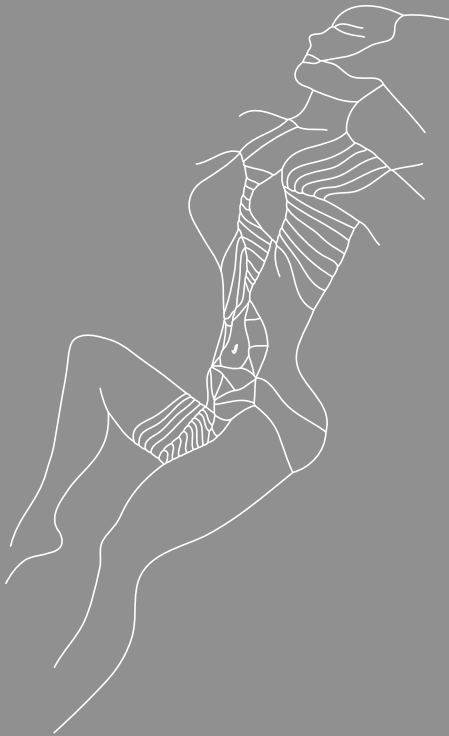
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Chapter 11

Summary



Breast cancer is the most frequently diagnosed malignancy in women worldwide. In the Netherlands in 2008, 13,005 women were diagnosed with invasive breast cancer and 3,327 patients died of the disease. Both the introduction of breast cancer screening and the improvement and more extensive use of adjuvant systemic therapy (AST) have led to a still ongoing decrease in breast cancer mortality. Nowadays, the majority of breast cancer patients is treated with adjuvant systemic therapy. Although these treatments have demonstrated to improve survival, not all patients will benefit from AST. Besides, chemotherapy can cause serious acute and long term side effects. Given that a substantial proportion of patients will be cured by locoregional therapy alone chemotherapy could be more harmful than helpful in a subgroup of patients. Traditional clinicopathological characteristics are currently used to estimate prognosis and identify those patients who are likely to be cured by locoregional therapy alone; however, these factors are only moderately accurate. This lack of accurate identification of patients with a low risk of developing distant metastases results in overtreatment with unnecessary exposure to treatment toxicity. On the other hand, inaccurate selection of patients can also induce undertreatment and consequently jeopardize survival. To tailor treatment to the individual patient, thereby avoiding both over- and undertreatment, new prognostic markers are urgently needed. This dissertation focuses on the utility of a new prognostic test (the 70-gene signature or MammaPrint™; chapter 2-7), an already extensively used prognostic tool (Adjuvant!; chapter 8) and a potentially new prognostic factor (method of detection; chapter 9). In addition, we evaluated whether these prognostic markers are applicable in all breast cancer subgroups (one fits all?).

In **Chapter 1** we provide a general introduction to breast cancer treatment, traditional prognostic markers and gene expression profiling. Furthermore, the rationale and outline of this thesis is described.

The first part of this thesis focuses on the feasibility and clinical utility of a relatively new prognostic marker, the 70-gene signature. In **Chapter 2**, we provide an overview of the development and initial validation of the 70-gene signature. The 70-gene signature have been identified in a retrospective series of 78 patients under the age of 55 years who were diagnosed with lymph node negative, invasive breast cancer of less than 5.1 cm in diameter (pT1-2). Among the 78 patients 44 remained free of distant metastases for at least 5 years (good prognosis), whereas 34 patients developed distant metastases within 5 years of diagnosis (poor prognosis). Using supervised analyses, 70 genes that were differentially expressed between the two prognostic groups and most accurately classified tumors in either the good- or the poor-prognosis group were selected. The first validation study was performed on a consecutive series of 151 lymph node negative and 144 lymph node positive breast cancer patients. This study showed that the signature could accurately distinguish a good-prognosis group (of 115 patients) from a poor-prognosis group (of 180 patients). Furthermore, the prognostic value of the signature was independent of traditional

clinicopathological criteria (adjusted hazard ratio (HR) for distant metastases as a first event was 4.6; 95% confidence interval (CI) 2.3–9.2; $p < 0.001$). These results were confirmed by a second and independent validation study in 302 lymph node negative patients who did not receive AST and were diagnosed in 5 European hospitals. Furthermore, the so-called RASTER (Microarray Prognostics in Breast Cancer) study, showed the feasibility of using the signature for adjuvant treatment decision-making in 16 community based hospitals in the Netherlands. In a European pilot study, which is also described in detail in **chapter 3**, the logistics for the prospective MINDACT (Microarray In Node-negative and 1-3 positive lymph node disease may Avoid ChemoTherapy) study were tested and optimized. This study showed that it is feasible to collect good quality fresh frozen tissue in different European hospitals and that frozen samples can be shipped to a central microarray facility on a real-time basis. The success rate of the 70-gene signature was 77% (46/60) when a tumor sample could be obtained. The main reason for exclusion from profiling was a non-representative sample of the tumor; 18% (11/60) of the samples contained $< 50\%$ tumor cells. Based on these results and the experience gained in this pilot study standard operating procedures, which are currently used in the MINDACT trial, were developed. The prospective MINDACT trial is discussed in more detail in the **appendix** of this thesis. This international randomized trial will evaluate whether patients who are considered high risk according to the currently available prognostic tool Adjuvant! but classified as low risk by the 70-gene signature can be spared chemotherapy without jeopardizing disease outcome. Recruitment of the trial is anticipated to be completed mid 2011.

Up to now, the 70-gene signature has been developed and validated in a selected group of patients: predominantly premenopausal patients with lymph node negative disease. In order to assess the potential improvement of prognostication by using the 70-gene signature thereby broaden its application, we assessed the prognostic value of the 70-gene signature in several clinically relevant breast cancer subgroups. In **Chapter 4** we report on the prognostic value and clinical utility of the signature in 148 postmenopausal patients who were aged between 55 and 70 years and diagnosed with lymph node negative breast cancer. Patients classified as good prognosis by the signature had a 5-year breast cancer-specific survival (BCSS) of 99% (Standard error (SE) 1%), compared with 80% (SE 3%) in patients with a poor prognosis signature respectively ($p = 0.036$). Furthermore, the 70-gene prognosis-signature was a significant and independent predictor of BCSS, especially during the first 5 years of follow-up with an adjusted HR of 14.4 (95% CI 1.7-122.2; $p = 0.01$). The benefit of chemotherapy in postmenopausal patients seems to be most pronounced in the first 5 years after diagnosis, therefore results of this study indicated a more accurate allocation of AST using the signature. In **Chapter 5** we describe the validation of the 70-gene signature in an independent retrospective series of breast cancer patients with 1-3 positive lymph nodes. The aim of this study was to identify patients with 1-3 positive nodes who are likely to remain free of distant metastases. Among the 241 patients, 99 (41%) were classified

as good prognosis by the 70-gene signature, whereas 142 (59%) patients were classified as poor prognosis. The 10-year distant metastasis-free (DMFS) and BCSS probabilities were 91% (SE 4%) and 96% (SE 2%) for patients with a low risk 70-gene signature, respectively and 76% (SE 4%) and 76% (SE 4%), respectively for patients with a high risk signature. The signature was associated with disease outcome independent of traditional prognostic factors, with an adjusted HR of 7.17 (95% CI 1.81-28.43; $p = 0.005$). In contrast to the 70-gene signature, Adjuvant! Classified only 32 patients (13%) as clinical low risk and 209 patients (87%) as clinical high risk, resulting in discordant risk assessments in 32% (72 patients). Remarkably, among the patients who were classified as high risk by Adjuvant! the signature could identify 72 patients (34%) who had a low risk signature and indeed a good disease outcome (10-year BCSS of 94% (SE 3%)). Furthermore, the signature was associated with disease outcome in patients who did not receive adjuvant chemotherapy. The results of this study showed that the 70-gene signature could identify patients with an excellent disease outcome, even among patients with lymph node positive disease who might be safely spared chemotherapy. Based on these results the MINDACT trial has extended its eligibility criteria to include patients with up to 3 positive nodes.

The aim of the study described in **chapter 6** was to evaluate the accuracy of the 70-gene signature in patients with tumors less than 2.1 cm (pT1). With the introduction of mammographic screening the proportion of small breast tumors has increased tremendously. In a pooled database of 964 patients the signature accurately distinguished patients with a good outcome from those with a poor outcome; this prognostic value was independent of clinicopathological characteristics with an adjusted HR of 3.25 (95% CI 1.92-5.51; $p < 0.001$) for BCSS at 10 years. The results of this study emphasize that a considerable proportion of small tumors metastasize, supporting the idea that metastatic capacity is an early inheritance that can be identified by the 70-gene signature (28% distant relapse rate at 10 years in tumors classified as poor prognosis by the signature). Therefore, the 70-gene signature can be useful to optimize and individualize treatment decision-making in patients with pT1 tumors.

In **Chapter 7** we analyzed 541 patients from a retrospective pooled database who had received adjuvant systemic therapy and who were classified by the 70-gene signature. Among the 541 patients who received either endocrine therapy alone ($n=315$) or in combination with chemotherapy ($n=226$) the 70-gene signature classified 252 patients as low risk and 289 patients as high risk. Patients with a high risk 70-gene signature treated with chemotherapy followed by endocrine therapy had a significantly better 5-year distant disease-free survival (DDFS) compared with high risk patients who were treated with endocrine therapy alone (88% *versus* 76%, respectively; $p < 0.01$). Conversely, patients with a low risk 70-gene signature who were treated with chemotherapy followed by endocrine therapy had similar disease outcomes as low risk patients treated with endocrine therapy alone (5-year DDFS 99% *versus* 93%, respectively; $p = 0.62$). This suggests that patients classified as high risk by the signature do benefit from adjuvant chemotherapy in addition

to endocrine therapy. Moreover, the benefit of chemotherapy appears to be absent in patients with a low risk signature, which will further justify withholding chemotherapy in these patients.

In **Chapter 8** we describe a validation study of the computer tool Adjuvant! in 5,380 Dutch breast cancer patients. Adjuvant! is a web-based tool that predicts disease outcome and treatment benefit for the individual patient, based on clinicopathological characteristics such as age, co-morbidity, tumor size, tumor grade, lymph node status and estrogen receptor status. The program has been developed and validated on American and Canadian breast cancer patients. The aim of this study was first to assess the accuracy of predicted outcome by Adjuvant! in (subgroups of) Dutch breast cancer patients. In addition, we investigated its ability to discern patients having good outcomes from those having poor outcomes (discriminatory accuracy). Results showed that the model could accurately predict outcome on group level (differences between predicted and observed outcomes were within 2% for most clinically relevant subgroups) and could be applied to most patients, with the exception of patients younger than 40 years. Adjuvant! overestimated outcome in these patients by approximately 4.5% and predictions of Adjuvant! in patients less than 40 years should be treated with caution, especially in patients with an estrogen receptor positive tumor. The discriminatory accuracy of Adjuvant! was only moderate, suggesting that the model's predictions could be improved by adding additional prognostic information, such as provided by the 70-gene signature.

As we have shown in the previous chapter, models such as Adjuvant! can predict disease outcome but are still suboptimal. Therefore, we investigated whether method of detection has additional prognostic value that could improve the estimation of prognosis. This question is addressed in **chapter 9**, where we studied the accuracy of prediction by Adjuvant! in patients with a screen-detected carcinoma as well as assessed the independent prognostic value of screen-detection in a retrospective patient cohort of 2,592 breast cancer patients aged 50-69 years, with invasive breast cancer. Method of detection was classified as (1) screen-detected carcinomas, defined as carcinomas that were mammographically detected in the first or subsequent screening rounds (n = 958); (2) interval carcinomas, defined as symptomatic carcinomas that were diagnosed within 24 months of a negative screening (n = 417); and (3) nonscreening-related carcinomas, defined as symptomatic carcinomas in patients who were not participating in the screening program (n = 1,217). Adjuvant! predicted the outcome among patients with nonscreening-related carcinomas accurately (predicted survival was within 2% of the observed survival and/or not significantly different in all but one group), whereas Adjuvant! predictions underestimated overall survival and breast cancer-specific survival among patients with screen-detected and interval carcinomas. Prediction of breast cancer-specific survival was underestimated by Adjuvant! for patients with screen-detected carcinomas by -3.2%. Screen-detected carcinomas were

associated with a significant reduced mortality compared with nonscreening-related carcinomas. The prognostic value of screen-detection was independent of the well-known stage shift that is caused by screening (*i.e.* earlier stage at diagnosis), with an adjusted HR of 0.62 (95% CI 0.50-0.78; $p < 0.001$). In addition, the prognostic value of method of detection was similar across tumor size and lymph node status categories, again indicating its prognostic value beyond stage migration. As a consequence of these results, we propose that method of detection should be used in combination with traditional markers of tumor burden and aggressiveness to estimate prognosis for each patient, and to guide their decision to receive adjuvant systemic therapy.

In **chapter 10** the major results presented in this thesis are discussed and put in perspective of current clinical practice. In general, the 70-gene signature could improve the prediction of disease outcome in several subgroups. Most likely the combination of (new) clinicopathological factors and gene expression signatures could even further improve accurate estimation of prognosis.