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Risk estimations and treatment decisions in early stage breast cancer: Agreement among oncologists and the impact of the 70-gene signature

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Abstract ***Background:*** Clinical decision-making in patients with early stage breast cancer requires adequate risk estimation by medical oncologists. This survey evaluates the agreement among oncologists on risk estimations and adjuvant systemic treatment (AST) decisions and the impact of adding the 70-gene signature to known clinico-pathological factors.
Methods: Twelve medical oncologists assessed 37 breast cancer cases (cT1–3N0M0) and estimated their risk of recurrence (high or low) and gave a recommendation for AST. Cases were

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presented in two written questionnaires sent 4 weeks apart. Only the second questionnaire included the 70-gene signature result.

Results: The level of agreement among oncologists in risk estimation ($\kappa = 0.57$) and AST recommendation ($\kappa = 0.57$) was 'moderate' in the first questionnaire. Adding the 70-gene signature result significantly increased the agreement in risk estimation to 'substantial' ($\kappa = 0.61$), while agreement in AST recommendations remained 'moderate' ($\kappa = 0.56$). Overall, the proportion of high risk was reduced with 7.4% (range: 6.9–22.9%; $p < 0.001$) and the proportion of chemotherapy that was recommended was reduced with 12.2% (range: 5.4–29.5%; $p < 0.001$).

Conclusion: Oncologists' risk estimations and AST recommendations vary greatly. Even though the number of participating oncologists is low, our results underline the need for a better standardisation tool in clinical decision-making, in which integration of the 70-gene signature may be helpful in certain subgroups to provide patients with individualised, but standardised treatment.

1. Introduction

Clinico-pathological guidelines are used to guide adjuvant systemic treatment (AST) decisions in early stage breast cancer patients. These guidelines combine clinico-pathological factors such as age, tumour size, grade, hormone-receptor status and nodal status to estimate the risk of recurrence and provide an AST advice. Commonly used clinico-pathological guidelines are Adjuvant! Online (AOL), the Sankt Gallen expert panel recommendations and the Nottingham Prognostic Index (NPI) [1,2]. In the Netherlands, the Dutch Institute of Healthcare Improvement (CBO) guidelines are used most often [3]. Nevertheless, correctly estimating whether an individual patient has a high risk of recurrence and is likely to benefit from AST remains challenging [4]. Most of the guidelines consider only a small proportion of patients at a low risk of recurrence. This may result in a substantial number of patients being treated with AST while they are unlikely to derive significant benefit [5]. Each guideline mentioned above defines a partly non-overlapping group of patients at a low or high risk, which indicates that predictive accuracy for the individual patient is not high [1,6–8]. Also, online tools such as AOL that provide a survival probability instead of a low/high risk estimation can be used with different cut offs. Therefore, a variation in risk estimations made by oncologists who are guided by different guidelines is expected. The extent of this variation remains unclear.

To refine risk estimations and provide a more tailored AST recommendation for the individual patient, gene expression prognosis classifiers have been developed [9]. One of these gene expression classifiers is the 70-gene signature (MammaPrint™, Agendia Inc., Amsterdam, The Netherlands) [10]. The first prospective study, in which the 70-gene signature was used in addition to clinical guidelines, was conducted in the Netherlands between 2004 and 2006. This microarRAy prognoSTics in breast cancER (RASTER) study showed discordance in risk estimation between the 70-gene signature and clinico-pathological guidelines in one third of the patients [11]. In daily clinical practice, medical oncologists are using the 70-gene signature the same way as it was used in the RASTER study, i.e. in addition to clinico-pathological guidelines [1,11]. However, the impact of the 70-gene signature on risk estimations and AST decisions in daily clinical practice is unknown. The aim of this survey was to determine the agreement among oncologists' risk estimations and AST recommendations based on clinico-pathological factors as are used in clinical guidelines, and to assess the impact of the 70-gene signature.

2. Methods

Two written questionnaires were developed (C.A.D., S.C.L., H.C.v.d.H., M.K.S.) and reviewed by an independent oncologist (G.S.S.). Thirty-seven cases of breast cancer patients were presented to 29 medical oncologists specialised in breast cancer in Europe. The oncologists were chosen because of their area of expertise and the country they work in. We included oncologists from all over Europe to not only demonstrate the situation among oncologists in one country, but for an entire continent. The oncologists were asked to indicate their use of clinical guidelines and to give their risk estimation (high/low) and recommendation of AST (none, endocrine therapy, chemotherapy, trastuzumab or a combination) for each case. Several weeks later, the same cases were presented in a randomly changed order in a second questionnaire. In this second questionnaire, the 70-gene signature result was provided along with clinical characteristics.

2.1. Cases

To provide a reflection of true clinical practice, 37 cases of breast cancer patients were selected from the