European Journal of Cancer (2013) 49, 3773–3779

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Prospective cost-effectiveness analysis of genomic profiling in breast cancer

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Available online 27 August 2013

KEYWORDS
Breast cancer
Gene expression profiling
Adjuvant systemic treatment
Real world cost-effectiveness

Abstract ***Background:*** The cost-effectiveness of the 70-gene signature (70-GS) (MammaPrint®) has earlier been estimated using retrospective validation data. Based on the prospective 5-year survival data of the microarRAy-prognoSTics-in-breast-cancER (RASTER) study, the aim here was to evaluate the cost-effectiveness reflecting the actual use in clinical practice, including reality-based compliance rates.

Methods: Costs and outcomes (quality-adjusted-life-years (QALYs)) were calculated in node-negative (N−) patients included in the RASTER study ($n = 427$). Sensitivity and specificity of the 70-gene and Adjuvant! Online (AO) were based on 5-year distant-disease-free survival (DDFS). Subgroup analyses were performed for two groups for whom benefit of the 70-gene had earlier been reported: (1) ductal, oestrogen receptor-positive (ER+), tumour diameter 10–30 mm, grade II, age 40–70; (2) ductal, oestrogen receptor-positive, tumour diameter 5–30 mm, grade II/III and age 40–70.

Results: Based on 5-year survival data, the cost-effectiveness of the 70-gene signature versus AO was prospectively confirmed. The total health care costs per patient were €26,786 for

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http://dx.doi.org/10.1016/j.ejca.2013.08.001

the 70-gene and €29,187 for AO. The quality adjusted life years yielded 12.49 and 11.88, respectively. The subgroups retrieved slightly higher life gains and higher costs, but all resulted finally in a favourable position for the 70-gene signature.

Conclusions: The use of the 70-gene signature, as judged appropriate by doctors and patients and supported by a low risk 70-gene signature as an oncological safe choice, was also found to be cost-effective.

1. Introduction

As growing expenditures for cancer care are today's reality, the question of sustainability, how to afford high quality and equitable cancer care, is increasingly urgent [1]. Governments and insurance agencies, especially in Europe, increasingly involve aspects of cost-effectiveness in policy decisions on the adoption of new medical technologies. Health economics and cost-effectiveness analyses (CEAs) specifically, can contribute to decisions on the achievement of affordable health care as it facilitates careful and explicit balancing of the clinical benefits and financial impact of cancer treatments. Personalised medicine offers improvement of cancer care by allowing clinicians to tailor treatments based on patients' molecular and epidemiologic profiles. Because of the unique nature of personalised medicine these efficient and effective technologies pose particular challenges for health systems, clinicians and patients.

An example of personalised medicine is gene expression profiling, in this case the 70-gene signature (70-GS) (MammaPrint®, Agendia Inc., Amsterdam, the Netherlands), a promising prognostic test to guide adjuvant treatment decisions in patients with early breast cancer [2,3]. It outperforms current guidelines, which offer most patients adjuvant chemotherapy (CT), while 60–70% have a good survival with loco-regional treatment alone [4]. This is likely to cause an important proportion of over-treatment [5]. Since adjuvant chemotherapy has severe side effects, and is very costly, a careful selection of patients is important. In order to choose the optimal prognostic test, a trade-off between survival, quality of life adjusted survival and costs is inevitable.

Recently, the 5 year survival data of the prospective feasibility 'microarRAy-prognoSTics-in-breast-cancER' (RASTER) study became available. The data provided important information on the excellent survival of patients with a low risk 70-gene signature result, for whom the omission of chemotherapy was judged appropriate by doctors and patients despite poor clinical pathological risk factors [6,7]. Earlier, an early stage Technology Assessment was performed, of which an early model-based cost-effectiveness analysis (CEA) was part of the research [8,9]. However, the input data of the CEA were retrieved from retrospective validation series, because there were no survival data available yet at that time [3,10,11]. To fill in the data gaps for this analysis, several scenario analyses regarding the potential diffusion of the 70-gene signature were performed, taking the dynamics of the use of the 70-gene signature in daily clinical practice into account [12]. At that time, we had to settle the model with these scenarios, resulting in a range of possible incremental cost-effectiveness ratios (ICERs) over time.

In the current study, we were able to calculate the cost-effectiveness reflecting the actual use in clinical practice, including reality based compliance rates [6], using the newly available 5-year outcome data from the RASTER study. In addition, the cost-effectiveness was calculated for two specific subgroups of patients for whom the benefit of the 70-gene signature was described in earlier papers [3,10,11]: (1) ductal carcinoma, 10–30 mm, grade II, oestrogen receptor (ER)+, lymph node (N)−, age 40–70 and (2) ductal carcinoma, 5–30 mm, grade II+III, ER+, N− and age 40–70.

2. Materials and methods

2.1. Clinical risk classifications

In the RASTER study, decisions for adjuvant systemic treatment were based on the Dutch Institute of Healthcare Improvement (CBO) guidelines of 2004 [13], the 70-gene signature result and doctors' and patients' preferences. To study how the addition of the 70-gene signature to a risk prediction tool used today influences clinical practice we used the clinical–pathological Adjuvant! Online (AO) software (www.adjuvantonline.com, version 8.0), to calculate 10-year survival probabilities based on the patient's age, tumour size, tumour grade, oestrogen receptor status and nodal status [14,15]. The AO was used because it is worldwide one of the most commonly used tools for risk profiling in breast cancer.

2.2. Model description

A Markov model was constructed with four mutually exclusive health states: disease free survival, relapse (including local and regional recurrences, secondary primary and contralateral breast cancer), distant metastasis and death. The study adopted a health care perspective. The model simulated the course of events for two prog-

nostic tests: 70-gene signature, and AO. Patients were evaluated as AO low risk, if their 10-year survival probability was estimated by AO as 90% or higher. For the 70-gene signature, patients classified as having a poor prognosis had an odds ratio (OR) of 15 (95% confidence interval (CI) 4–56, $p < 0.0001$) to develop a distant metastasis within 5 years compared with patients who had good prognosis [3].

In the model, for each prognostic test, patients were classified as having a true low, true high, false low, or false high risk of developing metastasis based on the sensitivity and specificity. Patients with a 'low risk' were deemed to have a good prognosis considered by the 70-gene signature or AO and, therefore, could be spared adjuvant systemic treatment with its associated adverse effects, whereas patients with a 'high risk' were judged to have a poor prognosis and should be considered for adjuvant systemic treatment. Based on the 5-year follow-up data of the RASTER-study, the extrapolated long-term (20 years) consequences for survival, quality of life and costs were calculated. For further details on the model assumptions see Retèl et al. [8].

2.3. Probabilities

The sensitivity and specificity of each prognostic test were calculated based on the RASTER population as described by Bueno-de-Mesquita et al. [6]. From this database, a total of 427 treated and untreated, node negative tumour samples were selected and classified by the 70-gene signature and the clinical pathological guideline as low or high risk of developing distant metastasis. We calculated the sensitivity and specificity of the two strategies for distant disease free survival (DDFS) at 5 years (see Table 1). All statistical analyses were performed with SPSS 17.0 for Windows (SPSS Inc., Chicago, IL). The remaining transition probabilities were based on Lidgren et al. [16].

2.4. Costs and health effects

Quality of life was modelled by assigning utilities to the different health states [17]. Lidgren et al. calculated utility weights of the EuroQol (EQ5D) norm values for the general population. For patients who received adjuvant treatment, the utilities were calculated as long as they received any form of treatment; in the first year for chemotherapy (CT) and over 5 years for endocrine therapy (ET). The costs of the health states DFS, relapse and distant metastasis (health states costs and onetime costs of patients dying of breast cancer) were based on Lidgren et al. (2008), except the costs of chemotherapy and hormonal therapy [16]. The costs of the 70-gene signature are €2,675, and were provided by Agendia Inc., Amsterdam; full costs include transport, additional specimen processing at the local hospital and Value Added Tax (VAT). There were no costs accounted for AO. Costs were expressed in 2005 Euros, to be able to compare the calculation with the original article [8]. For more details on the estimates of costs and utilities see Retèl et al. [8]. Future costs and effects were discounted to their present value by rates of 4% and 1.5% per year respectively, which are commonly used in Europe [18].

2.5. Uncertainty analysis

We programmed the model in Microsoft Excel (Microsoft, Redmond, WA). Incremental cost-effectiveness ratios (ICERS) were calculated by dividing the

Table 1
Input test accuracy using the 5-year prospective outcome of the 70-gene signature (70-GS) and Adjuvant! Online (AOL).

Strategy		Event	%		No event	%	Total	%
Total RASTER population (n = 427)								
70-GS	True high	23	5	False high	185	43	208	49
	False low	10	2	True low	209	49	219	51
AOL	True high	26	6	False high	269	63	295	69
	False low	7	2	True low	125	29	132	31
Subgroup (I) (n = 111); Ductal, 10–30 mm, grade II, ER+, N−, age 40–70								
70-GS	True high	4	4	False high	32	29	36	32
	False low	5	5	True low	70	63	75	68
AOL	True high	6	5	False high	83	75	89	80
	False low	3	3	True low	19	17	22	20
Subgroup II) (n = 187); Ductal, 5–30 mm, grade II+III, ER+, N−, age 40–70								
70-GS	True high	7	4	False high	79	42	86	46
	False low	7	4	True low	94	50	101	54
AOL	True high	10	5	False high	132	71	142	76
	False low	4	2	True low	41	22	45	24

70-GS: 70-gene signature.
AOL: Adjuvant! Online.
ER+: Oestrogen Receptor positive.
N−: Node negative.

incremental costs by incremental quality adjusted life years (QALYs). Uncertainty in the input parameters was handled probabilistically; by assigning distributions to parameters [19]. Parameter values were drawn at random from the assigned distributions, using Monte Carlo simulation with 1000 iterations. The results of the simulation are illustrated in a Cost-Effectiveness (CE) plane, each quadrant indicates whether a strategy is more or less expensive and more or less effective. To show decision uncertainty, cost-effectiveness acceptability curves (CEACs) are presented. CEACs show the probability that a pathway has the highest net monetary benefit, and thus is deemed cost-effective, given different cost per QALY ratios. Whether a strategy is deemed efficient depends on how much the society is willing to pay for a gain in effect, which is referred to as the ceiling ratio [20]. In the United States (US) this threshold is $50,000–100,000/QALY, while Europe handles a threshold of around €30,000 per QALY [21,22].

2.6. Subgroups

We performed two subgroup analyses. The first subgroup contained patients with ductal carcinoma, 10–30 mm, grade II, ER+, N− and age 40–70. This is currently the group for whom a 70-gene signature is recommended according to expert opinion. The second subgroup contained patients with ductal carcinoma, 5–30 mm, grade II+III, ER+, N− and age 40–70 years. This is the group for whom a 70-gene signature can be considered according to expert opinion (see Table 1).

2.7. Sensitivity analyses

First, the current price level of chemotherapy or hormonal therapy can change in time, due to the fact that they run out of patents, or other chemotherapies become available. As an example, very recently, the patents of all Aromatase Inhibitors (AIs) have run out, and prices have dropped significantly (total costs of hormonal treatment became €206 instead of €822). We therefore also calculated the cost-effectiveness using the present off-patent costs for AIs, however, this did not change the results (data not shown). Second, the discount rates were changed to 3% for costs and effects, as this had no impact on the results, we did not show these data

3. Results

The total health care costs per patient were: €26,786 for the 70-gene signature and €29,187 for AO (see Table 2). The 70-gene signature yielded more quality adjusted life years (12.49) compared to the AO (11.88). This means that the 70-gene signature is more effective and less costly than AO (see Fig. 1). The probability of cost-effectiveness of the 70-gene signature is nearly 100%.

For both subgroups, it was found that the 70-gene signature amounted to higher health gains and savings compared to using AO than in the total population (see Table 2). But these were slight changes; the overall result was that the 70-gene signature retrieved a 'cost-neutral' situation, as it was for all analysis less costly and more effective.

Additionally, all sensitivity analyses had no impact on the results.

4. Discussion

This is the first study to report the cost-effectiveness of the use of the 70-gene signature in daily clinical practice based on prospective data. Test accuracy data from 5 year survival data confirmed the cost-effectiveness of the 70-gene signature. The cost-effectiveness was even better in the subgroups of patients for whom the 70-gene signature originally was developed and is currently recommended.

The specific subgroups we applied in this study, were patient groups for whom the 70-gene signature has benefit in clinical practice, as was proven in earlier papers [3,10,11]. As soon as the final data from the recently finished randomised controlled trial 'Microarray In Node-negative Disease may Avoid ChemoTherapy' (MINDACT-trial) will be available, this patient group could be even larger, including additional subgroups [23].

In this analysis the 70-gene signature was compared to AO in this study. However, one should take into account that the 70-gene signature has been validated on historic data to refine risk estimation based on current (Dutch) guidelines [6]. Furthermore, the AO risk predictions are based on 10-year outcomes, while here 5-year outcomes are reported [6,7]. Therefore, the results need to be re-evaluated at 10-year follow-up. For the current analysis, DDFS was used. In the survival analysis of the publication of Drukker et al., both distant recurrence-free interval and the DDFS were calculated [7]. Second primaries other than breast did not change survival, however they are important for costs and quality of life.

In the current study we used the outcome measure cost/QALY. Theoretically, the best survival for the entire group of breast cancer patients will be obtained by offering adjuvant systemic treatment to all patients, as long as prognostic tests are not 100% accurate [7,8]. However, the real discussion is how many unnecessary deaths we are generally accepting to spare unnecessary toxicity of adjuvant chemotherapy and consequent deterioration in the quality of life, as our colleagues explain in the accompanying clinical article [7].

To conclude, based on 5-year survival data, the cost-effectiveness of the 70-gene signature was confirmed.

Table 2
Results of cost-effectiveness of the 70-gene signature (70-GS) versus Adjuvant! Online (AOL) using the 5-year prospective outcome.

Strategy	QALYs	Costs (€)	ΔQALYs	ΔCosts	ICER
Total RASTER population (n = 427)					
70-GS	12.49	€26,786			
AOL	11.88	€29,187			
70-GS versus AOL			0.62	−€2,401	DOMINANT[a]
Subgroup (I) (n = 111); Ductal, 10–30 mm, grade II, ER+, N−, age 40–70					
70-GS	12.85	€23,607			
AOL	11.42	€32,620			
70-GS versus AOL			1.43	−€9,013	DOMINANT[a]
Subgroup (II) (n = 178); Ductal, 5–30 mm, grade II+III, ER+, N−, age 40–70					
70-GS	12.47	€26,647			
AOL	11.61	€31,131			
70-GS versus AOL			0.86	−€4,484	DOMINANT[a]

70-GS: 70-gene signature.
AOL: Adjuvant! Online.
[a] DOMINANT: less costs, higher QALYs.

Moreover, the 70-gene signature proved to be even more cost-effective in both subgroups for which the 70-gene signature is currently recommended. The omission of chemotherapy as judged appropriate by doctors and patients and supported by a low risk 70-gene signature was both a cost-effective as well as an oncological safe choice.

Conflict of interest statement

W.H. van Harten is a non-remunerated, non-stake holding member of the supervisory board of Agendia Inc. MK received an unrestricted educational grant by Agendia Inc. All other authors declared no conflict of interest.

Contributors

VPR, MJ and WHvH were responsible for the study design and development of the protocol. WHvH ensured financing. JMBdM and SCL coordinated the clinical study. JMBdM, VPR, MK and CAD took part in data collection. VPR and MJ performed the economic analysis, HvT performed the clinical data analysis. VPR, MJ

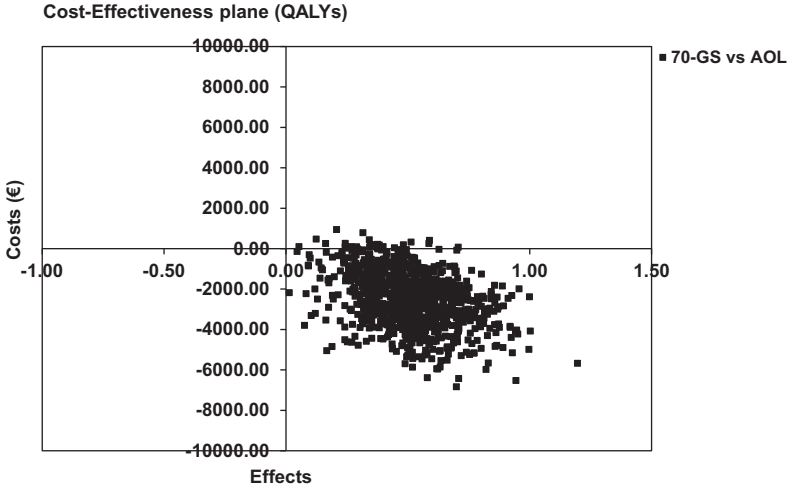

Fig. 1. Cost-effectiveness (CE) plane of the quality adjusted life years (QALYs) per costs of the 70-gene signature (70-GS) versus Adjuvant! Online (AOL). *The scatter plot shows the mean differences in costs and outcomes from the data using 1000 bootstrap replicates. Ninety-seven percent of the dots are in the South-East quadrant which indicates that the 70-gene signature is in most cases less expensive and more effective.*

and WHvH took part in data interpretation and manuscript writing. All authors were involved in reviewing the report.

Role of the Funding Source

This study was funded by the Dutch Health Care Insurance Board (DHCIB, CVZ), The Netherlands. The DHCIB had no role in the study design and the collection, analysis and interpretation of data and the writing of the article and the decision to submit it for publication.

Acknowledgements

We are indebted to the women who participated in this study; to the doctors, nurses and data managers from the participating hospitals in the Netherlands that enrolled patients in the RASTER study.

Appendix A. Principal and co-investigators of the RASTER study

The following clinicians entered patients and/or participated in the study The following clinicians entered patients and/or participated in the study (between the brackets, the number of accrued patients is mentioned): J. Meijer, J. Klinkenbijl, J. Douma, Alysis Care Group, Arnhem (31); J. Wijsman, D. van der Meer, P. de Wit, O. Loosveld, Amphia Hospital, Breda (4); S. Veltkamp, A. Baan, G. Timmers, K. van der Hoeven, Amstelland Hospital, Amstelveen (66); J. van der Bijl, A.M. Lenssen, I. Snijders, M. Nap, J. Wals, M. Pannebakker, Atrium Medical Center, Heerlen (13); L. Strobbe, F. van den Wildenberg, R. Berry, B. Dekker, E. Thunnissen, A. Uyterlinde, C. Mandigers, Canisius-Wilhelmina Hospital, Nijmegen (21); J.W. Arends, H. de Vries, A. Hemels-van der Lans, A. Imholz, Deventer Hospital, Deventer (40); I. Burgmans, C.I. Perre, T. van Dalen, J. van Gorp, D. ten Bokkel Huinink, P. Thunissen, Diakonessenhuis, Utrecht (4); J. Roussel, C. Bernhart, E. Weltevreden, S. Radema, Gelre Hospitals, Apeldoorn (21); R. Roumen, P. Reemst, A. Brands, K. Vercoelen, M. van Beek, W. Dercksen, G. Vreugdenhil, Maxima Medical Centre, Eindhoven/Veldhoven (114); T. van der Sluis, A. Stam, Lotus Sterk, Medisch Spectrum Twente, Enschede (6); M.J. Baas-Vrancken Peeters, H. Oldenburg, I. Eekhout, H. Hauer, J. Schornagel, Netherlands Cancer Institute, Amsterdam (172); H. van der Mijle, D. de Vries, I. Kruithof, S. Hovenga, Nij Smellinghe Hospital; Drachten (18); B. de Valk, M. de Boer, P.J. Borgstein, A. Walter, Onze Lieve Vrouwe Gasthuis, Amsterdam (16); C. van Krimpen, P.W. de Graaf, C. van de Pol, N. van Holsteijn, A. van Leeuwen, M.M.E.M. Bos, E. Maartense, Reinier de Graaf Group, Delft (124); A. Zeillemaker, G. van Leeuwen, J. Calame, W. Molendijk, G. Jonkers, F. Cluitmans, Rijnland Hospital, Leiderdorp (59); and F. Bellot, G. Heuff, A. Tanka, P. Hoekstra, K. van de Stadt, J. Schrama, Spaarne Hospital, Hoofddorp (103).

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