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When to HER2 test? A cost perspective

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Background: Metastatic breast cancer patients with HER2 overexpression should be identified and given the option to be treated with trastuzumab. One approach, defined as prospective testing, establishes whether breast tumours overexpress HER2 at time of tumour diagnosis. Whereas retrospective testing examines retrieved archival tissue for HER2 overexpression, once patients are diagnosed with metastatic disease.

The objective was to assess the difference in the cost burden for the Yorkshire cancer network with a population of 2.5 million and for an average cancer network with a population of 1.4 million to perform HER2 testing using the prospective or retrospective approach.

Material and Methods: We developed a simulation model to look at the total cost attributed to both prospective and retrospective testing. The number of patients in the prospective arm equalled the number of breast cancer patients presenting in the network. For the retrospective testing this number equalled the number of patients diagnosed with metastatic disease eligible for further treatment. The cost of the testing kit is included. The retrospective strategy included the cost of retrieving patients' samples, the cost of an additional consultation to inform the patient of their HER2 status and eligibility for treatment with Herceptin. We also looked at the total cost of each strategy excluding the consultation costs.

Results: For the Yorkshire cancer network (Table 1), despite an increased number of patients requiring prospective testing, the overall cost of testing was shown to be less compared to retrospective testing by £11,928 per annum. This result was driven by the time expended to find and retrieve the samples of patients diagnosed with metastases, as well as the need for additional consultations. If there were no additional consultations prospective analysis would be more costly, however this additional cost would be negligible. Note the analysis did not take into account the potential benefits of not delaying treatment for patients progressing to metastatic breast cancer, which would make the prospective testing strategy even more attractive.

Table 1. Yorkshire cancer network

	Prospective	Retrospective	Variation
Number of patients	1420	710	+710
Total testing cost	£35,500	£17,750	+£17,750
Total cost of each strategy	£56,800	£68,728	−£11,928
Total cost excluding consultations	£56,800	£53,250	+£3550

Conclusions: We conclude that earlier prospective testing will be, as a whole, less costly than later retrospective testing. According to these findings, all patients should be HER2 tested at diagnosis of breast cancer rather than waiting for metastases to appear.

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HER-2 as an independent prognostic factor in node negative cases

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Many studies have claimed individual prognostic significance for HER-2 but are often too small, too short follow-up (FU) and lack multivariate (MVA) analysis.

A previous study from NCH (Lovekin et al 1991) failed to show overall independent significance, HER-2 over-expression being in any case associated with poor prognostic factors. The use of adjuvant therapies has also been a confounding factor since HER-2 may relate to therapeutic response.

Patients and; Methods n=674 LN negative cases. Median FU 20 years (14–30). No adjuvant therapies. DAKO antibody used with semiquantitative scoring.

Results: In LN negative cases c-erbB2 showed independent significance for survival in multivariate analysis with Size, Stage, Grade, LVI and the Nottingham Prognostic Index (NPI). Survivals in LN negative cases in the NPI Good and Moderate groups were significantly worse for c-erbB2 over-expression.

References

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HER-2/neu gene copy quantified by real-time PCR and serum HER-2/neu by Elisa assay: comparison with fluorescence in situ hybridization and immunohistochemistry

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Background: HER2 transmembranous receptor expression is commonly evaluated at the timepoint of surgery on the biopsy material by Immuno Histo Chemistry (IHC) with a good correlation to FISH testing (considered the 'gold standard'). HER2 overexpression is not only a prognostic factor in breast cancer but also a predictive factor of anti HER2 targeted therapy. HER2 extra-cellular domain (ECD) can be shedded into the blood and therefore measured during the whole timeperiod of the disease. A high level of ECD appears to be correlated to HER2 expression and may be interesting in the follow-up of treated patients. ECD level and quantification of HER-2 gene amplification by real time PCR is a new approach not yet compared together with FISH and IHC.

HERMES study is a multicentric French pharmacoeconomic study evaluating impact of trastuzumab treatment in metastatic HER2 overexpressed breast cancer and evaluating different method of early prediction of clinical response to this treatment. All patients included on this study had initial IHC, FISH, ECD and HER2 gene amplification by real time PCR. We compare the results of these different techniques.

Methods: The population (n=60) is represented by the patients included in HERMES study.

Amplification of HER-2 gene was analysed in situ by FISH. FISH was performed with the *Ventana Benchmark ISH system*. In situ protein overexpression was determined by IHC. IHC was performed on paraffin embedded samples with *Ventana Nexes* automates and the A485 antibody (*Dako, Glostrup, Denmark*). Immunostaining was scored according to the Herceptest scoring system. Amplification after DNA extraction tissue sample from embedded paraffin block was performed by real time PCR on *Light Cycler®* engine with LC-HER/neu quantification kit (*ref 3113922 Roche*). IHC and FISH are centralized and carried out by 2 pathologists from paraffin embedded tissue sample.

To measure ECD, sera were collected within one day before initiation of treatment and performed by an enzyme-linked immunosorbent assay (*Human HER-2/neu Quantitative Elisa – Oncogene Science/Bayer ref OSDI-10*).

Results: Preliminary results show a statistically strong correlation between the 4 techniques evaluating HER2 expression (IHC, FISH, Elisa assay and HER2 realtimePCR). These results are under validation considering the overall population of the HERMES study.

Conclusions: Considering these results, HER2 status could be evaluated by different techniques presenting different advantages. In a daily practice, techniques on primary tumour (IHC, FISH or realtimePCR) could represent a 'standard'. The realtimePCR could be an alternative technique to FISH considering specificity results, simplicity of the technique, rapidity of the results and economical point of view (cheaper technique).

ECD explore not only the HER2 status at metastatic time but also could help for predicting the impact of antiHER2 therapies during the treatment.

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The number of resected axillary lymph nodes (ALN) influences the risk for axillary recurrences in node-positive, but not in node-negative patients

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Background: Based on broad evidence, the 'International Consensus Conference, Primary Therapy of Early Breast Cancer' St. Gallen 2003 established sentinel lymph node excision as sufficient surgical procedure in the axilla of node-negative breast cancer patients. However, there is little data available, whether the excision of a low number of ALN increases the risk for axillary recurrences, compared to systematic axillary dissection.

Material and Methods: By multivariate analysis of 3800 pts. treated for early breast cancer UICC stage I–III, we investigated the prognostic relevance of the number of resected ALN for axillary recurrences in patients with and without evidence of axillary lymph node metastases. Pts. with carcinoma in situ, distant metastases at time of presentation, primary systemic therapy, unknown hormone receptor status or histopathological grading were excluded. Data were contemporaneously collected and pts. were followed for a mean of 72 months.

Results: Axillary recurrences as sole manifestation site of recurrence occurred in 67 pts (1.7%). In node negative patients (n=2667), multivariate analysis, allowing for number of removed ALN, histopathological grading, tumor size and hormone receptor status, revealed only grading (P=0.04,

RR 2.7, 95% CI 7.1–1.1) and tumor size (P=0.03, RR 2.8, 95% CI 7.1–1.1), but not the number of removed ALN (P=0.42) as predictor for axillary recurrence. In contrast, in node positive pts. (n=1133), multivariate analysis demonstrated the number of removed ALN as independent significant predictor for axillary recurrences (P=0.002, RR 9.9, 95% CI 2.7–35.3), next to tumorous fixation of ALN (P=0.005, RR 3.6, 95% CI 1.5–8.3).

Discussion: There is no evidence that a low number of removed ALN increases the risk for axillary recurrences in node negative pts. However, evidence suggest that complete axillary dissection should be maintained in node positive pts.

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Prediction of which screen (mammographically) detected breast cancers (SDBC) require chemotherapy: Validation of new index

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Meta-analysis of symptomatic breast cancer trials advises chemotherapy to women less than 70 years of age at high risk of death (i.e. benefit of >1% survival benefit from treatment) but UK screen detected breast cancers (SDBC) (aged 50–65 years) have an overall 95.45% 5 year relative survival. NIH Guidelines (2001) recommend chemotherapy for all cancers >10 mm in size (i.e. 35% SDBC) whereas in 2001/2 only 22% SDBC in the UK received chemotherapy.

To determine which women will benefit from chemotherapy, we have analysed 4195 operable SDBC (aged 50–65 years) treated by NHSBSP surgeons from 1996–1997 and compared standard prognostic factors and the Nottingham Prognostic Index (NPI) with a novel screening index (SI) for the prediction of death from breast cancer. The SI is based on combined scores for grade (1:2:3), size (<1.5 mm = 1, 1.5–2.5 = 2, >2.5 = 3) and nodal status (negative = 1, <4 nodes = 2, >4 nodes = 3). All cases were followed up for a minimum of 5 years (to 31 March 2002) and are part of the British Association of Surgical Oncology Audit Project. Both the Nottingham Prognostic Index and the Manchester Screening Index significantly predicted survival (p<0.001).

	All Cases					
Manchester	1996–97		1996/97 Cases Only			CT use in
SI	N	%	Grade III	Node positive	5-year relative survival (±95% CIs)	2001/2
3	833	(20)	0%	0%	100%	1%
4	1111	(26)	0%	9%	98.5% (97.1–100.0)	6%
5	1090	(26)	20%	25%	96.3% (94.7–98)	22%
6	630	(15)	42%	55%	93.6% (91–96.1)	49%
7	363	(9)	49%	80%	81.1% (78.5–85.7)	63%
8	143	(3)	66%	100%	71.6% (63.4–79.8)	83%
9	26	(1)	100%	100%	57.1% (38–78.3)†	85%

Chi-Squared test for trend (†p<0.001). Index scores identified women at high risk of mortality (score 7–9).

According to the NPI and NIH Guidelines 18 and 40% of SDBC should receive chemotherapy. Our new SI identifies only 13% SDBC women with 5 year survival below 93.6% who would benefit from chemotherapy (scores 7–9). The better survival of mammographically detected breast cancer (aged 50–70 years) suggests that a proportion of the remaining 87% of women with SI scores 3–6 who have received chemotherapy, may have received unnecessary treatment.

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Survival in BRCA1-associated breast cancer: long-term follow-up and prognostic factors

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Introduction: Results of survival studies in BRCA1-associated breast cancer are inconsistent; while most studies suggest an identical or non-significantly worse survival, others find a significantly worse survival as compared to breast cancer patients with sporadic tumours. Reasons for the inconsistencies might include the different impact of the various gene mutations or comparison groups and/or varying control for other prognostic factors. We updated and extended our previous series of BRCA1-associated breast cancer to obtain stable and long-term survival estimates, perform subgroup analyses and assess the impact of the 'classical' prognostic and treatment factors.

Methods: We selected 230 consecutive patients with primary, invasive breast cancer diagnosed within families with a proven germline BRCA1-mutation. All patients were counseled at the Rotterdam Clinical Genetics Department, the year of breast cancer diagnosis was from 1980–2001. Tumor and treatment characteristics and follow-up were extracted from medical files. Endpoints of interest were the occurrence of contralateral breast cancer (CBC), local and distant disease-free (DDFS) and overall survival (OS). Cox Proportional Hazards modeling was used to investigate the joint impact of the classical prognostic as well as treatment factors.

Results: Mean age at diagnosis was 41 years (range 24–82 years); median follow-up 4.9 years (range 0.07–21.4 years). Tumor size was <2 cm in 51%, 65% was node-negative. Estrogen-receptor (ER) status was negative in 74% of the cases whereas 72% had a negative progesterone-receptor (PR) status. Forty-four percent received adjuvant chemotherapy, 7% hormonal therapy. Thirty-nine percent of patients opted for BPSO.

The yearly incidence of metachronous contralateral breast cancer (CBC) was 3.8%; the 5-, 10- and 15-year CBC incidence rate was 16%, 29% and 40%, respectively. Five, 10 and 15-year DDFS was 72%, 62% and 53%, respectively; for OS these rates were 76%, 64% and 61%, respectively. In our previous paper, 5 year-estimates were 49% for DDFS, 63% for OS and 19% for CBC incidence. In the multivariate analysis, independent prognostic factors for DDFS and OS were tumor stage, BPSO and the administration of adjuvant chemotherapy. Factors that significantly influenced contralateral breast cancer rate were age at first breast cancer diagnosis and BPSO.

Conclusions: OS and DDFS in this extended series of BRCA1-associated breast cancer patients appear to be improved as compared to our earlier estimates; the high risk of contralateral breast cancer was confirmed. In addition to tumor stage, the administration of chemotherapy and BPSO are independent prognostic factors. In line with findings of others, we found that BPSO significantly reduced the incidence of a 2nd primary BC in BRCA1-associated breast cancer.

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Hospital caseload and participation to research are determinants of breast cancer outcomes

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Background: Although caseload appears as a critical determinant of performance in many studies, the specificity of this relationship is unclear since volume is often correlated with other aspects of the organization of health services related to proficiency of care. The goal of this analysis was to evaluate the relative contribution of hospital caseload and participation to clinical research to survival in a large population-based cohort of women with breast cancer.

Methods: We selected women newly diagnosed with node-negative breast cancer between 1988 and 1994 among residents of five health regions in Quebec, Canada, and followed them to document adverse events or until December 31, 1999. Information at baseline and at follow-up was collected by chart review, queries to attending physicians, and linkage with several administrative databases. Data were collected on the patient, her disease, treatment received, characteristics of the physician and hospital of primary care, recurrences and deaths. Research activity was defined as collaboration to multicenter clinical trials other than those sponsored by the pharmaceutical industry. Data were analyzed by Kaplan-Meier actuarial method and Cox proportional hazards analysis using a 5% level of statistical significance.

Results: The study population included 1727 women with median follow-up of 6.8 years. For the whole cohort, 7-year survival (95% confidence interval) was 82% (80%,84%). As compared to women treated in large centers (≥100 cases per year) active in clinical research, hazard ratios (HR) of death from any cause were 1.15 (0.56,2.36) and 1.28 (0.90,1.82) among individuals treated in hospitals active in research with 25–49 and 50–99 cases per year. In hospitals not active in research, HR decreased from 1.93 (1.32,2.83) in centers with less than 25 cases, to 1.68 (1.18,2.38) and 1.57 (1.06,2.33) in those with 25–49 and 50 or more cases each year. Both volume and research activity were significant predictors of outcomes, but not independently.

Conclusions: Increasing hospital volume of cases and promoting participation to collaborative clinical trials represent effective strategies for improving survival of women with early stage breast cancer. Better outcomes in patients treated in larger centers are partly explained by these centers' participation to research.