Conclusion: the novel NNBC-3 risk algorithm classifies considerably more patients to the low-risk group than Adjuvant! or the St. Gallen 2007 risk category and is the only risk classification predicting DFS as well as OS in multivariate analysis.

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Dutch population-based validation of the prognostic evaluation tool Adjuvant!

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Background: Adjuvant treatment recommendations for early stage breast cancer depend on the risk of disease recurrence and the expected benefit of adjuvant therapy. Adjuvant! is a web-based tool that calculates individualized 10-year survival probability and estimated benefit of adjuvant systemic therapy based on age, co-morbidity, tumour size, grade and oestrogen-receptor status. This model is constructed using 10-year observed overall survival for women diagnosed with breast cancer between 1988 and 1992 recorded in the US SEER registry (Surveillance, Epidemiology and End Results). In 2005, Adjuvant! was validated in 4,083 patients from British Columbia (Olivotto et al. JCO). In the Netherlands, Adjuvant! is used in addition to the national 'CBO' (The Dutch Institute for Healthcare Improvement) guidelines. The aim of our study is to validate the estimated disease outcome by Adjuvant! in a Dutch breast cancer population.

Methods: Clinicopathologic characteristics and treatment data were registered prospectively in the Eindhoven Cancer Registry. There are 16,881 patients in this registry with T1−T3, N1−N3, M0 primary breast cancer diagnosed between 1970 and 2004. For this analysis, we will use those patients for which there are the variables used by Adjuvant!, and we will explore whether systematic biases are introduced in cases with missing data. Patients were between 20 and 90 years of age at diagnosis and were treated with breast conserving therapy or mastectomy with definitive axillary staging. About 40% of the patients received adjuvant systemic therapy. Adjuvant! is used to calculate predicted 10-year breast cancer outcome for each patient, and compared to observed outcomes.

Results: The concordance between predicted and observed survival for the overall cohort and for subgroups of age and years of diagnosis will be presented at the meeting. In addition, a multivariate analysis will be performed to evaluate whether the prognostic features used by Adjuvant! (such as histologic grade) are prognostic in this patient population.

Future prospects: In addition to this Dutch population-based validation of Adjuvant!, we will also validate the tool in two hospital-based patient cohorts from the Netherlands (~10,000 cases). Finally, when Adjuvant! performs reliably in the Dutch breast cancer population, the tool will be considered for the national guidelines for adjuvant treatment-decision. This is the first European large scale validation of Adjuvant!

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The 70-gene profile is a powerful predictor of disease outcome in breast cancer patients with 1−3 positive lymph nodes

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Introduction: The axillary lymph node status is considered to be one of the most powerful prognostic factors for operable breast cancer, with a decrease in survival as the number of positive nodes increases. However, approximately 30% of lymph node-positive patients will remain free of distant metastases without adjuvant chemotherapy. We have previously shown in two independent datasets that the '70-gene profile (MammaPrint®™)', which was developed in node-negative patients (van 't Veer *et al.* Nature 2002), is excellent in predicting disease outcome in patients with 1−3 positive nodes (NEJM 2002; SABCS 2007). We now combine the two datasets to allow further detailed analysis.

Methods: Three-hundred-forty-seven patients with T1, T2 or operable T3 breast cancer and 1−3 positive lymph nodes of 2 hospitals were selected. Patients were treated with breast conserving therapy or mastectomy with axillary lymph node dissection. Thirty-nine patients (11%) received no adjuvant systemic therapy, 118 (34%) chemotherapy only, 94 (27%) endocrine therapy only, and 84 patients (24%) received both. Median follow-up was 8.7 years. Distant metastases occurred in 75 patients. Samples were analyzed by gene expression profiling for the 70-gene profile.

Results: Among the 347 patients, 142 (41%) were assigned to the genomic low risk and 205 (59%) to the genomic high risk group. The 5- and 10-year overall survival (OS) probability was 99% (SE 1%) and 96% (SE 2%) for the genomic low risk group versus 86% (SE 3%) and 68% (4%) for the genomic high risk group, respectively. In a multivariate analysis adjusted for known prognostic factors, the 70-gene profile was a powerful significant predictor of OS and distant metastases as first event, with an estimated hazard ratio (HR) of 4.8 (95% CI 2.0−11.7; $p < 0.001$) and 3.0 (95% CI 1.4−6.7; $p = 0.006$), respectively. The profile maintained its prognostic value for OS (HR 3.9, $p = 0.02$) in a multivariate model including an interaction term between chemotherapy and the profile (interaction $p = 0.60$).

Conclusion: Our data show that the 70-gene profile is a strong predictor of overall survival and distant metastases as first event in patients with 1−3 positive lymph nodes. Furthermore, the profile can accurately identify a group of patients with an excellent survival who may be safely spared chemotherapy. Based on these data the inclusion criteria of the MINDACT trial will be enlarged to include patients with 1−3 positive nodes.

Friday, 18 April 2008 12:30–14:30

POSTER SESSION

Side effects of treatment

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Risk of febrile neutropenia as a function of age and disease stage in breast cancer patients receiving pegfilgrastim primary prophylaxis versus current practice neutropenia management – results from the NeuCuP analysis

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Background: Febrile neutropenia (FN) is a serious adverse event related to myelosuppressive chemotherapy (CT). Age and disease stage also determine overall FN risk. Granulocyte colony-stimulating factor (G-CSF) prophylaxis can reduce the incidence of FN and related complications, but its use in current practice (CP) can be inconsistent. Here, we compare predicted risk of FN for patients in different age groups and stages of breast cancer depending on whether they received pegfilgrastim primary prophylaxis (PPP) or CP neutropenia management.

Methods: Studies involving breast cancer CT regimens with moderately–high (15−20%)/high (≥20%) risk of FN were identified by literature review. For this integrated analysis, individual patient data were available from 8 clinical trials and 3 observational studies involving these regimens and PPP (6 mg, all cycles) or CP (no G-CSF or pegfilgrastim/daily G-CSF in any cycle). The primary outcome measure was the overall incidence of FN. A mixed effects generalized linear model was fitted in which treatment arm (PPP vs CP), age and disease stage (I−III vs IV) influenced FN. The model was used to predict proportions of patients with FN depending on their age and disease stage.

Results: 2282 patients were analyzed: mean age (±SD, yrs) was 51.4±10.4 for PPP vs 52.0±9.9 for CP, 28% vs 28% had Stage IV disease, and 30% vs 37% had prior CT/radiotherapy. The most common regimens were docetaxel (Doc) (37% vs 50%), Doc / doxorubicin(A) / cyclophosphamide (31% vs 27%), and ADoc (27% vs 3%). In cycle 1, 75% of CP patients had no G-CSF. In the model ($N = 2210$), the odds for FN were significantly lower with PPP vs CP (OR: 0.124; 95% CI: 0.08, 0.194; $P < 0.0001$). The predicted proportions of patients with FN ranged from 3% vs 22% (PPP vs CP) for a young patient with early stage disease, to 8% vs 41% in an elderly patient with metastases (Table).

Conclusions: PPP was associated with significantly lower odds of FN than CP in breast cancer patients receiving CT with moderately-high/high FN risk. These data illustrate the likely clinical benefits of PPP over CP in patients of all ages and stages of disease.