with survival; rates of local recurrence (LR) and regional recurrence (RR) have also been investigated in relation to LVI.

Results: See Table 1.

Table 1

LN	LVI	n	% in group	% 10 yr Survival
neg	Neg	3156	52	88.3
	Pos	550	9	76.9
1−3 pos	Neg	1540	26	75.2
	Pos	751	13	43.1
		5997		

Rate of LR was 3% at 10 years for LVI+ and 1% for LVI− (NS). The rate of RR in LN−/LVI+ patients was 3% at 10 years.

Conclusions: These figures verify in a multicentre International large data set that LVI+/LN− have the same survival as LN 1−3 positive cases; In LN+ cases LVI+ has no additional effect on prognosis.

LVI has a clear effect on prognosis of LN− cases whereas the effect of sentinel node micro metastases on survival is unconfirmed and LVI is more commonly found. Furthermore LVI+ does not give significantly higher rates of LR nor RR.

These findings suggest LVI could replace SLNB, being more accurate, easier and cheaper.

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Presence of bone marrow micrometastasis predicts metastatic pattern and disease-free interval in breast cancer patients – results from the Collaborative Group Bone Marrow Micrometastasis

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Background: To establish the prognosis and metastatic pattern in breast cancer patients in relation to bone marrow micrometastasis (BMM), that are readily detectable at the time of first diagnosis of cancer, a large series of patients was analyzed.

Methods: Individual patient data of 9 studies, involving 4,686 patients with breast cancer, were combined to analyze 10-year survival, specifically distant disease-free survival and the site of distant metastasis. We constructed Kaplan–Meier curves and computed incidence rate ratios with 95% confidence intervals. Survival estimates were adjusted for study center. The difference in median disease-free survival interval between BMM positive and BMM negative patients was tested with the Wilcoxon rank sum test.

Results: BMM were detected in 1,432 (30.6%) patients. Median follow-up was 62 months. Overall, distant metastasis occurred in 952 (20.3%) patients. Compared to patients without BMM, patients with BMM experienced twice as often distant metastasis (32.3% vs. 15.1%, $P < 0.001$) and had significantly shorter distant disease-free survival (log rank: $P < 0.001$; IRR 2.36, CI: 2.07−2.69, P(Wald) < 0.001). Among patients with distant metastasis during follow-up, the localization of distant metastasis was visceral (48.4%), bone (30.5%) and multiple sites (21.1%), the latter being defined as simultaneous occurrence of bone and visceral metastasis. The proportion of metastasis at multiple sites was significantly higher in patients with BMM than in patients without BMM (25.8% vs. 16.7%, respectively; $P = 0.003$). For each localization of distant metastasis, the disease-free interval was significantly shorter in patients with BMM than in patients without BMM: the respective medians of distant disease-free intervals were 23 vs. 29 months for visceral metastasis ($P = 0.030$), 24 vs. 33 months for bone metastasis ($P = 0.001$), and 14 vs. 22 months for metastasis at multiple sites ($P = 0.004$). Post-relapse survival was not different between patients with BMM and patients without BMM.

Conclusions: The results provide conclusive evidence that presence of BMM predicts a poor-prognosis pattern of distant metastasis, characterized by earlier distant relapse and first distant metastasis at multiple sites. BMM at the time of first diagnosis of primary breast cancer may be used as surrogate marker of distant metastasis and implemented in treatment strategies.

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Impact of histological grade on prognosis in very young breast cancer patients: pooled analysis of four EORTC trials

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Background: Young age at time of diagnosis of breast cancer is associated with unfavorable prognosis. Current guidelines recommend the administration of adjuvant chemotherapy to patients aged 35 years or less regardless of any tumor characteristics. However, since breast cancer at a very young age is a relative rare event, evidence concerning prognostic factors within this subgroup is lacking. Therefore, the individual patient data of four early stage breast cancer EORTC trials were pooled to study prognostic factors on long term outcome in young breast cancer patients.

Material and Methods: The total dataset consisted of 9938 early breast cancer patients of which 12% was younger than 41 years. Tumor material from 549 patients aged less than 41 years at time of diagnosis was available for renewed pathological analysis. The median follow-up was 7 years.

Results: In multivariate analyses, histological grade remained the only independent prognostic factor for overall survival (Grade III versus I: hazard ratio (HR) 3.92; 95% confidence interval (CI) 1.38 to 11.16). In the subgroup of young node-negative patients who did not receive adjuvant chemotherapy, histological grade was even stronger related to a favourable prognosis (Grade III versus I: HR 8.92; 95% CI 1.17 to 68.20). This association was independent of tumor size, type of surgery and hormone receptor status. Survival rates were excellent for young node negative patients with grade I tumors: 97% at 7 year follow-up compared to 72% for grade III tumors.

Conclusion: Histological grade is a strong independent prognostic factor in young breast cancer patients. These findings support the fact that histological grade is an excellent diagnostic tool to assess disease outcome and to plan systemic treatment strategy in young breast cancer patients.

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Long-term prognostic impact of risk classifications in node-negative breast cancer – comparison between Adjuvant!, St. Gallen, and a novel risk algorithm used in the prospectively randomized Node-Negative-Breast-Cancer-3 trial (NNBC-3)

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Background: defining risk categories in node-negative breast cancer is of great importance. We developed a novel risk classification which is currently evaluated prospectively in the Node-Negative-Breast-Cancer-3 trial (NNBC-3) trial using well-established clinico-pathological criteria. We compared its prognostic utility with the web-based tool Adjuvant! and the St. Gallen risk classification 2007.

Methods: we retrospectively analyzed 410 node-negative breast cancer patients with a median follow-up of 10 years which did not receive adjuvant systemic therapy. Patients with either (I) age <35 years, (II) G III, (III) HER-2 positivity, (IV) vascular invasion, (V) progesterone receptor negativity, (VI) G II tumors >2 cm, or (VII) G I tumors >5 cm were defined as high-risk. All patients were also characterized using Adjuvant! and the established St. Gallen 2007 risk category. We analysed disease-free survival (DFS) and overall survival (OS) for each of these risk classifications.

Results: Adjuvant! and the St. Gallen guideline classified 17% and 18%, respectively, of the patients as low-risk. Use of the novel NNBC-3 algorithm enlarged the low-risk group to 37%. Only the NNBC-3 algorithm retained its prognostic significance for DFS in multivariate analysis ($p = 0.006$; HR 2.02; 95% CI 1.22−3.35). Both Adjuvant! ($p = 0.027$; HR 3.81; 95% CI 1.16−12.47) and the NNBC-3 risk classification ($p = 0.049$; HR 1.95; 95% CI 1.00−3.81) predicted OS in multivariate analysis independently.

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.