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**ONCOPOOL, a comparison with SEER**

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ONCOPOOL pooled data from 12 European Breast Units, from 16,944 cases of operable (⩽5 cm) invasive breast cancers aged ⩽70, diagnosed consecutively on each unit in 1990−99 inclusive, with first line operative treatment.

It is of interest to compare the data with another large data set; SEER has long been quoted as the standard for comparisons of tumour factors and outcomes. SEER is USA based.

The data examined is from the 2 large data sets on women with primary breast cancers, with only cases obeying the same inclusion factors as for ONCOPOOL used for the SEER data.

**Comparisons will be of:** Numbers entered, Age at entry, Tumour size, lymph node status (sampling or clearance required), size .v. LN status, grade (and method used), ER and PgR status, grade .v. size, grade .v. ER status (pos, neg), formulae for relation of LN negativity and size to grade, Overall (OS) and Breast Cancer Specific Survival (BCS) for all cases at intervals to 180 months.

The data from each set will be applied to indices combining prognostic factors to estimate survivals (Nottingham Prognostic Index and FIN-PROG Index) and polynomial curves for each data set relating survival to index levels produced.

**Combined** data (extra data will be added from FINN PROG and Uppsala). Using the indices the combined data will be entered to estimate the effects of adjuvant therapies (eg) Cox analysis will be applied entering the prognostic index values and survival for treatment with hormone; also polynomial curves will be produced of survival against index value to allow comparisons of treatments (eg) no adjuvant therapy against endocrine only in ER+ cases.

The percentage risk reductions obtained will be compared with those shown by the EBCTCG Meta Analysis. Work at present shows a differential proportional effect in relation to prognosis, which the Meta Analysis is unable to demonstrate.

Effects in other situations can similarly be examined: effects of screening; radiotherapy after Breast Conserving Surgery by Van Nuys prognostic index.

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**Factors predicting disease free survival following neoadjuvant chemotherapy for breast cancer**

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**Background:** For primary operable breast cancers, different prognostic models, as the Nottingham Prognostic Index, have been developed and proven to work well. However, this model has limitations for patients who undergo neo-adjuvant chemotherapy (NACT) as not all clinicopathological features are readily available without complete surgery. We investigated which factors are prognostic in the prediction of disease free survival (DFS) among patients with large size and locally advanced breast cancer receiving NACT.

**Material and Methods:** A group of 161 consecutive patients diagnosed with primary breast cancer between January 2000 and December 2005 at the University Hospitals Leuven, receiving NACT was analysed. Patients diagnosed with distant metastases, receiving neo-adjuvant hormonal treatment, switching over to neo-adjuvant hormonal therapy or refusing operation were not included in this set. DFS was defined as any breast cancer related event.

**Results:** 43 patients (26.7%) experienced an event at a median follow-up of 4.83 yrs. Univariate Cox regression revealed positive estrogen receptor (ER), positive progesterone receptor (PR) and pathological complete response (pCR, including residual in situ lesion) following NACT as significant ($p < 0.05$) predictors for DFS. Due to the high correlation between ER and PR a combined variable (EPR) equal to 1 if both receptors are positive and zero otherwise was used in the multivariate model. The multivariate model showed that EPR (hazard ratio=0.127, 95% CI 0.050–0.325, $p < 0.0001$) and pCR (hazard ratio=0.187, 95% CI 0.066–0.526, $p = 0.0015$) are independent prognostic variables for DFS. The prognostic index (PI) is found as: EPR+pCR and is therefore 0 for patients with negative ER or PR without pCR, 1 for patients with positive PR/ER or pCR and 2 for patients with positive PR/ER and pCR. Table 1 illustrates the expected number of events together with DFS predicted by the model ($S_{COX}$) and the survival as estimated by the Kaplan-Meier method ($S_{KM}$).

**Conclusions:** This preliminary study revealed that both steroid receptors and pCR were independent prognostic factors for assessing DFS following NACT chemotherapy in our series.

Table: Classification in risk groups by the multivariate Cox model

| PI | n+ | # events | Event rate* | $S_{KM}$(5-year) | $S_{COX}$(5-year) |
|---|---|---|---|---|---|
| 0 | 65 | 33 | 0.14 | 0.52 | 0.51 |
| 1 | 87 | 9 | 0.02 | 0.89 | 0.90 |
| 2 | 5 | 0 | 0.00 | 1.00 | 0.99 |

+4 patients had no value for the estrogen/progesterone receptor.
*Expected percentage of events per year of follow-up.

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**Metastatic lymph node ratio: independent prognostic factor for disease free survival in node positive breast cancer**

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**Background:** The presence of axillary lymph node (ALN) metastasis is considered the most important prognostic factor for breast cancer survival. However, the role of the total number of excised ALNs has received less emphasis. This study investigated whether ratio between metastatic and total excised ALNs would prove to be independent prognostic factor for disease-free survival (DFS).

**Materials and Methods:** Data from 628 consecutive patients with pT1−3, pN1−3, nonmetastatic breast cancer were studied retrospectively. Patients were subdivided into three groups according to metastatic lymph node ratio (MLNR) value (<0.20, 0.20–0.80, 0.80–1.00). The MLNR was analyzed for their prognostic value in comparison with absolute number of metastatic lymph nodes. Cumulative DFS was determined using the Kaplan-Meier method, with univariate comparisons between groups through the log-lank test. The Cox proportional hazards model was used for multivariate analysis.

**Results:** On univariate analysis, parameters influencing the DFS were tumor size, estrogen receptor status and progesterone receptor status. In addition, both the absolute number of metastatic lymph nodes and the MLNR were associated significantly with DFS. On multivariate analysis, the MLNR still remained as independent prognostic factor for DFS. The absolute number of metastatic lymph nodes lost significance when the MLNR was taken into account.

**Conclusions:** Our study demonstrates that the MLNR is a more significant prognostic factor for recurrence than absolute number of metastatic lymph nodes in T1-T3, N1-N3, nonmetastatic breast cancer patients.

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**The influence of young age on disease free survival in stage I breast cancer**

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**Background:** Patient with invasive breast carcinoma who are ages 35 years or younger at the time of diagnosis have worse prognosis compared with older patients. The aim of this study is to assess the impact of young age on disease free survival (DFS) in stage I breast cancer.

**Material and Methods:** Between January 1995 and December 2005, 315 patients with stage I breast cancer were included. The median follow up was 62.6 months (range 1.2–157.2). The patients were divided into three groups, based on age at the time of diagnosis: age ⩽35 years (group A), 36−45 years (group B), >45 years (group C). The analyzed factors were tumor size, estrogen receptor status, c-erbB-2 status, operation method, adjuvant chemotherapy and adjuvant hormonal therapy. Relapse means locoregional recurrence and distant metastasis.

**Results:** The mean age is 48 years old (range 25−77). Age distribution showed that group A is 36 cases (11.4%), group B is 90 cases (28.6%), group C is 189 cases (60.0%). The 26 (8.3%) patients out of 315 were recurred. Fifteen patients have distant metastasis and nine patients have locoregional recurrence. In univariate analysis for DFS, the age is only significant factor. The 5-year DFS rate was 82.4% for group A, 95.6% for group B and 92.3% for group C ($p = 0.002$). The 10-year DFS showed 67.9% for group A, 95.6% for group B and 89.4% for group C. In multivariate analysis, the odds ratio of group A is 2.77 times higher than counter part groups ($p = 0.020$). The analysis of clinicopathologic factor according to groups, group A have more ER negativity and more chemotherapy than group C. The important finding on this analysis is that clinicopathologic

factors of group B are similar to group A; more ER negativity and more chemotherapy but their prognosis is better than group A.

**Conclusions:** Although this study is retrospective, the age of 35 is important prognostic factor in stage I breast cancer.

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**Prognostic importance of metastasis to level III lymph node with less than 10 metastasized lymph nodes in the N3 breast cancer**

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**Background:** The American Joint Committee on Cancer (AJCC) TNM System is the most common system used to describe the stages of breast cancer. According to this system, metastasis to level III (infraclavicular or subclavicular) axillary lymph nodes belongs to N3. However, its prognostic value still remains controversial. The aim of current study is to investigate the clinicopathologic features and prognosis of level III lymph node metastasis with less than 10 metastasized nodes.

**Materials and Methods:** Four hundred and fifty five breast cancer patients (N2 or N3 stages on final histology) underwent operations from January 1990 to December 2007 at our institution were included in this study. The patients were categorized into 3 groups by the number of metastatic lymph nodes and level of invasion: *N2 group* (level I or II patients with 4−9 metastatic nodes), *level III group* (metastasis to level III with less than 10 metastatic nodes) and *N3 group* (10 or more metastatic nodes). Clinicopathologic features of level III group were analyzed and survival rate of the level III group was compared with those of N2 and N3 groups.

**Results:** The mean age of patients at diagnosis was 46.0 years (ranging from 20 to 78) and the mean follow-up was 63.1 months. Five-year disease free survival (5-yr DFS) rates for level III metastatic patients and non-level III metastatic patients were 51.2% and 70.2%, respectively ($p < 0.001$). Five-year overall survival rates (5-yr OS) for the same patient groups were 70.2% and 83.2%, respectively ($p < 0.001$). Level III invasion was significantly related to larger tumor size ($p = 0.018$), 10 or more metastasized lymph nodes ($p < 0.001$ and relative risk=10.06) and positive Her-2 status ($p = 0.005$). Nevertheless, the only independent risk factor involved in level III invasion was 10 or more metastatic lymph nodes ($p < 0.001$ and relative risk=10.06). 5-yr DFS for N2, level III and N3 groups were 73.9%, 60.2% and 48.1%, respectively ($p < 0.001$) and 5-yr OS for the same groups were 86.2%, 76.0% and 60.7%, respectively ($p < 0.001$). There was significant difference between level III and N3 group for OS ($p = 0.023$). However, there was no survival difference between N2 and level III group.

**Conclusion:** The prognosis of breast cancer patients with level III lymph node metastasis having less than 10 metastatic nodes is similar to the prognosis of N2 group, and is better than the prognosis of N3 patients with 10 or more metastasized nodes. In conclusion, the number of metastatic axillary lymph nodes is a more important predictor of mortality than the level of invasion in N3 breast cancer.

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**Is 70-gene prognostic signature in breast cancer for Korean different from European?**

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**Background:** A 70-gene prognosis signature was previously shown to have prognostic value in patients with node-negative breast cancer in Europe. But there is no study about a 70-gene prognosis signature in Asian. We therefore investigated whether the 70-gene prognosis-signature can identify patients with node negative who have an excellent disease outcome or not.

**Material and Methods:** Between March, 2008 and September, 2009, 47 patients with breast cancer (clinical T1−2N0M0) were selected from four hospitals in Korea. Fresh tumor samples were analyzed with customized microarray for the 70-gene tumor expression signature.

Concordance between risk predicted by the 70-gene prognosis signature and risk predicted by commonly used clinicopathologic guidelines (St. Gallen guidelines, NIH guideline, Adjuvant! Online) was evaluated. Also we analyzed clinicopathologic features of patients compared with previous validation study.

**Results:** Of 47 eligible patients, 12 patients were excluded because of sampling failure (n = 10) and lymph node metastasis on permanent pathologic finding (n = 2). Prognosis signatures were assessed in 35 patients. There were no significant differences in clinicopathologic features of patients compared with previous studies. The 70-gene prognosis signature identified 5 (14.3%) patients with good prognosis and 30 (85.7%) patients with poor prognosis. Tumors with a poor prognosis-signature were more often classified as HER-2 positive tumor, high histologic grade and large tumor size.

The St. Gallen guidelines identified patients 29 (82.9%) with poor prognosis, which was concordant with those findings obtained with the prognosis signature in 28 (80%) patients. NIH guidelines identified 30 (85.7%) patients with poor prognosis with the signature and concordance in 29 (82.9%) patients. Adjuvant! Online guidelines identified 14 (40%) patients with good prognosis than did the signature alone and concordance with the signature occurred in 22 (62.9%) patients. Concordance rate between risks predicted by the prognosis signature and commonly used clinicopathologic guidelines was about 60−80%.

**Conclusions:** Our results are different from previous validation studies in Europe with about 40% good prognosis and about 60% poor prognosis. This difference should be studied whether the disparity of gene between Asian and European has influence to that or not.

Our results were the first data of gene prognosis signature in Asian breast cancer patients, but the small number of the cases, no data of follow-up and no assessment of predictive value of the prognosis signature are the limitations of the current study. Further investigation is required to overcome these limitations and to assess whether use of the 70-gene prognosis signature can predict prognosis of patients in Asian as well as European.

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**Predictive value of bone marrow micrometastasis detected by nested RT-PCR for cytokeratin 19 in breast cancer patients**

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**Background:** In breast cancer patients, systemic relapse may occur during the early phase. Some studies have shown a correlation between the presence of micrometastasis in bone marrow and the clinical outcome of patients. We previously reported prognostic value of cytokeratin 19 in early recurrence. The purpose of this study was to reestablish the meaning of cytokeratin 19 mRNA in bone marrow aspirates and their possible correlation with distant disease free survival in long term follow up.

**Materials and Methods:** Between June 2001 and December 2003, bone marrow samples were obtained from 248 breast cancer patients at the time of surgery. These patients had undergone breast operation and bone marrow aspiration from the iliac spine and were treated and subjected to follow-up studies similarly to other breast cancer patients, regardless of the results of the bone marrow reverse transcriptase polymerase reaction (RT-PCR) study. We separated the mononuclear fraction from the samples and carried out nested RT-PCR for the detection of cytokeratin 19 mRNA using two different pairs of primers. The clinical and pathological data and the results of the bone marrow cytokeratin 19 nested RT-PCR was reviewed and analyzed together with clinical results on distant metastasis free survival and overall survival.

**Results:** The median follow up time was 66 months. The median age of patients was 46 years old. Sixty-six (26.6%) of the 248 samples were cytokeratin-19 positive. According to staging, twenty cases (25.6%) were positive among 78 patients with stage I, 33 cases (28.4%) in 116 patients with stage II and 13 cases (28.9%) in 45 patients with stage III. However, no statistical significance was found between bone marrow micrometastasis and tumor size, lymph node metastasis and stage. Sixteen patients (24.3%) in the 66 cytokeratin 19 positive group showed systemic relapse. Twenty three patients (12.5%) in the 182 cytokeratin 19 negative group showed systemic relapse. Cytokeratin 19 positive group have shorter distant disease free survival rate than cytokeratin 19 negative group ($p = 0.015$). However, there was no statistically significant difference in overall survival ($p = 0.079$).

**Conclusions:** The nested RT-PCR of keratin 19 for micrometastasis of breast cancer showed high sensitivity for micrometastasis of bone marrow. Detection of occult micrometastasis in bone marrow using nested RT-PCR assay for cytokeratin 19 could be useful predictive factor for the systemic breast cancer relapse.