Number of positive nodes did not affect management decision. Regional radiotherapy was given to the axilla from an anterior field, 50 Gy D_{max} in 25 daily fractions. Outcomes of recurrence and 'breast cancer specific survival' (BCSS) were assessed.

Results: 387 patients with 1−3 positive nodes who received ART were identified. The number with 1, 2 or 3 nodes involved was 222, 106 and 59 respectively. Median follow up was 129 months (5–247) There were 28 (7%) RR, with median time to recurrence of 50 months (12–175). Estimated RR free survival (SE) was 95.3% (0.011) at 5 years, 93.1% (0.014) at 10 years.

Univariate survival analysis demonstrated that 1 node positive status predicted a lower risk of RR compared to those with 2/3 nodes positive (HR 0.376, 95% CI 0.173–0.815, p = 0.013.) This remained significant on multivariate analysis, adjusting for tumour grade and tumour size (p = 0.02).

Estimated BCSS (SE) was 85.8% (0.018) at 5 years, 72.4% (0.024) at 10 years, with appearances of improved survival in the 1 node positive group; however, this was of borderline significance, p = 0.086.

Conclusion: RR is uncommon in 1−3 node positive patients treated with ART, but the risk is significantly lower in the 1 node positive sub-group. Less aggressive strategies of regional management should be considered and investigated for these patients.

304 Poster

Clinical Significance of Stem Cell Phenotype (CD44+/CD24−) Relating to Molecular Subtype of Breast Cancer − a Multi-institutional Retrospective Study

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Background: The breast is the first solid organ that has been discovered its cancer stem cells. $CD44^{+}CD24^{-/low}Lineage^{-}$ tumorigenic cells showed stem cell properties. However, the clinicopathologic significance of stem cell phenotype has not been clarified yet. To investigate the prognostic significance of stem cell phenotype ($CD44^{+}/CD24^{-}$) in breast cancer cells and its relation to molecular subtype, we performed a multi-institutional retrospective study.

Materials and Methods: From 8 institutions of South Korea, 1401 consecutive breast cancer cases were collected which were resected from 1997 to 2003. Median follow-up period is 73.1 month. Immunohistochemical (IHC) stainings of ER, PR, EGFR, CK5/6, CK14, c-kit, CD44 and CD24 were done on slides of 64 tissue microarray blocks. To identify the stem cell phenotype ($CD44^{+}/CD24^{-}$), double IHC staining for CD44 and CD24 was done. The status of HER2/neu amplification was investigated by dual-color silver-enhanced *in situ* hybridization (SISH). Clustering of CD44/CD24 expression pattern was done using k-means clustering (stem cell phenotype). In addition, clustering of stem cell phenotype and molecular subtype markers was done using k-modes clustering. Univariate and multivariate survival analyses were done using Kaplan-Meier method and cox regression test.

Results: Seven hundred forty five cases were analyzed which had all available IHC stain, SISH results and follow up data. CD44/CD24 expression pattern was classified into stem cell rich/poor phenotype using k-means clustering. The pattern of stem cell phenotype and molecular subtype markers was classified into five subtypes using k-modes clustering. Those were hormone receptor positive and stem cell rich subtype (19.5%), hormone receptor positive and stem cell poor subtype (41.3%), basal-like subtype (4.7%), null subtype (23.2%) and *HER2* positive subtype (11.3%). The hormone receptor positive and stem cell rich subtype shows best prognosis, followed by basal-like, hormone receptor positive and stem cell poor, null, and *HER2* positive subtypes (p < 0.001, log-lank test) and the significance remained after adjustment with TNM stage.

Conclusions: By clustering analysis, hormone receptor positive breast cancer is divided stem cell rich/poor phenotypes. The stem cell rich phenotype shows better prognosis than stem cell poor phenotype. The stem cell phenotype could be a prognostic marker in hormone receptor positive type. In addition, the stem cell rich phenotype is associated with basal-like and null subtypes and stem cell poor phenotype is associated with *HER2* positive subtype.

305 Poster

A Validated Web-based Nomogram for Predicting Positive Surgical Margins in Breast-conserving Therapy

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Background: Breast-conserving therapy (BCT) is considered standard treatment for early-stage breast cancer. One of the most important risk factors for local recurrence following BCT is the presence of positive surgical margins. We aimed to develop and validate a user-friendly prediction model (nomogram) based on preoperatively obtainable variables to predict for positive surgical margins in BCT.

Patients and Methods: Breast cancer patients who underwent BCT throughout the North-East region of the Netherlands between June 2008 and July 2009 were selected from the Netherlands Cancer Registry (n = 1185). Results from multivariate logistic regression analyses served as the basis for development of the nomogram. Nomogram calibration and discrimination were assessed graphically and by calculation of a concordance index, respectively. Performance of the nomogram was validated on an external independent dataset (n = 331) from the University Medical Center Groningen.

Results: The following clinicopathological variables were associated with positive surgical margin status in BCT and were included in the final model: microcalcifications on mammogram (OR: 1.37), absence of preoperative MRI (OR: 1.80), suspicion of multifocality (OR: 2.81), non-palpable tumor (OR: 1.51), positive preoperative N-stage (OR: 1.73), large tumor size (OR: 1.33), high density of the breast (OR: 1.22), lobular histological type (OR: 2.90), high histological grade (OR: 1.44), positive ER status (OR: 1.80), and presence of DCIS (OR: 3.11). Concordance indices were calculated of 0.70 (95% CI: 0.66–0.74) and 0.69 (95% CI: 0.63–0.76) for the modeling and the validation group, respectively. Calibration of the model was considered good in both groups. A nomogram was developed as a graphical representation of the model.

Conclusions: We developed and validated a nomogram to predict the probability of positive surgical margins in BCT using preoperatively obtainable clinicopathological variables. Moreover, a web-based version (*Breast Conservation!*) of the nomogram is accessible at http://www.breastconservation.com (login name: review; password: ArrBaw5X). Our nomogram could support clinicians in counseling patients regarding the likelihood of requiring further surgery, identify high risk patients who could benefit from more extensive surgery, and allow for the stratification of patients in clinical trials.

306 Poster

The Influence of Education Level On the Survival of Breast Cancer

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Background: The prognostic role of education level (EL) in breast cancer has been not consistent but still controversial. We tried to investigate the role of EL as a prognostic factor of breast cancer.

Materials and Methods: Data of 36,299 primary breast cancer patients diagnosed between 1987 and 2008 from the Korean Breast Cancer Registry was analyzed. EL was classified into the low EL group (<12 years; n = 13,178) and the high EL group (⩾12 years; n = 23,121) according to time spent in education.

Results: The high EL group had younger age, earlier tumor stage, more estrogen receptor positivity, less HER2 positivity, lower histologic grade, less lymphovascular invasion, and less body mass index compared to the low EL group. The high EL group received more lumpectomy and/or more adjuvant therapy than the low EL group regardless of tumor size, node positivity, tumor stage, and operation methods. Both overall survival rate and breast cancer specific survival rate of the high EL group were higher than those of the low EL group (log-rank test, both $P < 0.001$). The differences in survival rates between the high and low EL groups were more evident under clinicopathologically more favorable conditions.

EL was a statistically significant independent factor with adjustment for various clinicopathologic parameters.

Conclusions: EL was a strong independent prognostic factor of breast cancer and these results were more evident under clinicopathologically more favorable conditions. Earlier diagnosis and active treatments are suggested as the main causes of superior survival in the women with higher EL.

Table: Univariate and multivariate analyses of overall survival according to clinicopathologic characteristics

	Univariate analysis			Multivariate analysis								
Characteristic	Cox's proportional hazard model			Biological model[a]			Treatment model[b]			Combined model[c]		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Education level, high vs low	0.759	0.709-0.812	<0.001	0.776	0.684-0.880	<0.001	0.804	0.743-0.870	<0.001	0.837	0.727-0.964	0.014
Age, >35 vs ⩽35	0.652	0.593-0.718	<0.001	0.628	0.527-0.748	<0.001				0.578	0.479-0.698	<0.001
Tumor size, >2 cm vs ⩽2 cm	3.064	2.829-3.320	<0.001	1.895	1.648-2.178	<0.001				1.613	1.369-1.900	<0.001
Node positivity, yes vs no	3.762	3.484-4.061	<0.001	2.648	2.292-3.058	<0.001				2.247	1.892-2.668	<0.001
Metastasis, yes vs no	12.024	10.720-13.487	<0.001	5.221	3.994-6.825	<0.001				4.413	3.156-6.170	<0.001
Hormone receptor, positive vs negative	0.501	0.466-0.540	<0.001	0.477	0.421-0.540	<0.001				0.546	0.444-0.671	<0.001
HER2, positive vs negative	1.345	1.234-1.465	<0.001	1.046	0.931-1.176	0.446				1.014	0.892-1.153	0.833
Histologic grade, 3 vs 1, 2	2.257	2.082-2.445	<0.001	1.665	1.463-1.894	<0.001				1.608	1.394-1.855	<0.001
Lympho-vascular invasion, yes vs no	2.537	2.280-2.821	<0.001	1.492	1.307-1.704	<0.001				1.475	1.268-1.716	<0.001
Body mass index, >25 vs ⩽25	1.109	1.031-1.193	0.005	1.021	0.902-1.157	0.740				1.104	0.962-1.266	0.159
Operation, mastectomy vs lumpectomy	2.799	2.558-3.062	<0.001				4.608	4.104-5.173	<0.001	2.816	2.346-3.380	<0.001
Radiation therapy, yes vs no	0.926	0.861-0.997	0.040				2.178	1.990-2.384	<0.001	1.498	1.289-1.739	<0.001
Chemo-therapy, yes vs no	1.629	1.473-1.802	<0.001				1.276	1.138-1.431	<0.001	0.779	0.599-1.015	0.064
Hormonal therapy, yes vs no	0.593	0.551-0.639	<0.001				0.613	0.566-0.663	<0.001	0.865	0.707-1.058	0.157

HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2. [a]Cox's proportional hazard model adjusted with nine factors including age, tumor size, node positivity, metastasis, hormonal receptor, HER2, histologic grade, lymphovascular invasion, and BMI. [b]Cox's proportional hazard model adjusted with four factors including operation, radiation therapy, chemotherapy and hormonal therapy. [c]Cox's proportional hazard model adjusted with all thirteen factors described above.

307 Poster

Ki-67 as Predictive Biomarker for Systemic Chemotherapy in Breast Cancer

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Background: Biological markers that reliably predict clinical or pathological response to primary systemic therapy early during the course of chemotherapy may have considerable clinical potential. Aim of the study is to evaluate changes in Ki-67 (MIB-1) labeling index and apoptotic index (AI) before, during, and after neoadjuvant anthracycline chemotherapy in breast cancer.

Materials and Methods: Breast cancer tissue were collected from Grant Medical College and Sir J.J. Groups of Hospitals, Mumbai, India. Twenty-seven patients receiving neoadjuvant FEC (5-fluorouracil, epirubicin, and cyclophosphamide) chemotherapy for operable breast cancer underwent repeat core biopsy after 21 days of treatment.

Results: The objective clinical response rate was 56%. Eighty patients (31%) achieved pathological response by histopathological criteria; two patients had a near-complete pathological response. Increased day-21 AI was statistically significant predictor of pathological response ($p = 0.049$). A strong trend for predicting pathological response was seen with higher Ki-67 indices at day 21 and AI at surgery ($p = 0.06$ and 0.06 respectively).

Conclusion: The clinical utility of early changes in biological marker expression during chemotherapy remains unclear. Until further prospectively validated evidence confirming the reliability of predictive biomarkers is available, clinical decision-making should not be based upon individual biological biomarker profiles.

308 Poster

Triple-negative Breast Cancer − Which Classical Prognostic Factors Can Help in Identifying Patients with Early Relapse?

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Background: Triple-negative breast cancer (TNBC) belongs to a poor prognostic group with the highest risk of relapse during the first few years after radical surgery. We investigated the influence of classical prognostic factors and adjuvant CHT (A-CHT) on 2-year prognosis in early TNBC pts treated at the Institute for Oncology and Radiology of Serbia (IORS).

Patients and Methods: We identified a group of 165 stage 1/2 TNBC pts diagnosed during 2006–2008 treated with radical surgery ± postoperative radiotherapy and A-CHT as per protocol. TN status was defined as IHC ER0−3/PR0−3/HER2:0−1 or IHC HER2:2+/CISH−. We analyzed the following prognostic factors: patients' age, menopausal status, medullar histology, tumor size, tumor grade, nodal status, HR/HER2 phenotype (ER0/PR0/HER2:0 vs. non-ER0/PR0/HER2:0) and A-CHT (anthracyclines vs. non-anthracyclines). Disease free survival (DFS) and overall survival (OS) were the main end points. Fisher Exact test, Pearson Chi-squared test and Log-rank test were used for statistical analysis.

Results: Median age of analyzed group was 58 years (range 26−84) and median follow-up was 24 months (range 3−56). Disease relapse experienced 31/165 (18.8%) pts, and 21/165 (12.7%) pts died, all from BC. Women ⩽50 years more frequently undergone subcutaneous mastectomy with immediate reconstruction ($p < 0.0001$) and received more frequently anthracycline − containing CHT ($p < 0.0001$) compared to women >50 years. Medullar BCs were more frequently associated with grade 3 tumors than non-medullar BCs ($p < 0.0001$). Breast conserving surgery was more frequently performed in pts with tumors ⩽2 cm compared to pts with tumors >2 cm ($p < 0.0001$) and in N0/N1−3 pts compared to N⩾4 pts ($p = 0.0003$). Grade 3 BCs were more frequently associated with ER0/PR0/HER2:0 phenotypes than grade 2 BCs ($p = 0.03$). Pts with N⩾4 more frequently experienced disease relapse than pts with N0/N1−3 ($p = 0$), especially bone and liver metastases ($p < 0.0001$ and $p = 0.0002$, respectively). There was no difference in DFS and OS in subgroups divided according to age, menopausal status, tumor histology, size and grade, HR/HER2 phenotype, and type of adjuvant CHT. N0/N1−3 pts subgroups had significantly better DFS (Log-Rank test; $p = 0$) and OS (Log-Rank test; $p = 0$) than N ⩾4 subgroup.

Conclusion: Nodal status was the only prognostic discriminator for 2-year outcome in pts with stage 1/2 TNBC.

309 Poster

PR Negative Tumors ñ Prognosis and Results of Oncotype Dx

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Several studies demonstrated that breast cancers that are ER positive/PR negative carry a worse prognosis than ER/PR positive tumors if treated only by adjuvant hormonal therapy. In these studies PR was assessed by methods that measure protein content. Oncotype Dx measures mRNA expression. In clinical trials the discrepancy between IHC and RT PCR for the expression of PR was about 20%, but this was not assessed in a community setting. The meaning of high levels of PR mRNA without detectable PR protein is unclear. This discrepancy might result from technical issues or might be explained by a biological mechanism such as translational inhibition of PR by miRNA's.

We sought to verify the prognostic value of the expression of the progesterone receptor by IHC in women with early stage HER 2 negative, ER positive BC treated with systemic hormonal therapy only at our institution. Next, we aimed to characterize the results of Oncotype Dx in ER positive, PR negative HER 2 negative tumors.

Methods: 1st cohort: Files of consecutive patients with ER positive HER 2 negative tumors that were treated by adjuvant hormonal treatment during 2000–2006 were reviewed.

2nd cohort: The characteristics of PR negative tumors tested by Oncotype Dx during 2007–2011 were analyzed.