were further divided into four subgroups: group 1 (HER2+, HR+) N = 34; group 2 (HER2+, HR−) N = 23; group 3 (HER2−, HR+) N = 123. Group 4 (HER2−, HR−) N = 23. The strength of the associations between the uPA/PAI-1 expression and biological characteristics/subgroups were tested with Kruskal-Wallis H test (multiple-group caomparison) and Mann-Whitney U test (paired-group comparison).

Results: Our findings indicate a positive association between HER2 status and uPA ($p < 0.002$) but no association between HER2 and PAI-1 ($p = 0.445$) was found. The levels of uPA were significantly different between the four subgroups, with the highest levels observed in HER2+HR− subgroup 2. Paired comparisons showed significantly higher uPA levels in HER2+HR− subgroup compared to HER2+HR+ ($p = 0.027$) as well as compared to HER2−HR+ subgroup ($p < 0.001$). The levels of PAI-1 were not significantly different between the four subgroups. However, pair comparisons still showed borderline difference in PAI-1 levels between HER2+HR+ and HER2+HR− subgroup ($p = 0.047$).

Conclusion: In our collective of EBC patients a positive association between HER2 status and uPA was found, however no association between HER2 and PAI-1 was confirmed. The levels of PAI-1 did not differ significantly in the four molecular subgroups defined according to both, HER2 and HR status. Our limited observation points out to a possible independent prognostic value of PAI-1 in the subsets of HER2+ EBC patients.

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Does progesterone receptor status provide a predictive value for adjuvant endocrine therapy in breast cancer patients?

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Background: The predictive value of estrogen receptor (ER) status for adjuvant endocrine therapy in breast cancer patients has been widely proven in many clinical trials reported previously. However, the predictive significance of progesterone receptor (PR) is controversial in an adjuvant setting. The aim of this study was to evaluate the efficacy of hormone therapy according to progesterone receptor expressions.

Material and Methods: The authors retrospectively evaluated clinical data of 1,642 ER-positive breast cancer patients who received adjuvant tamoxifen between January 1993 and December 2002 at Asan Medical Center. The number of patients of ER+/PR+ group was 1,242 (75.6%) and ER+/PR− group was 400 (24.4%). The tumor characteristics, incidences of recurrence and survival rates of the patients were examined.

Results: The mean age of the ER+/PR+ group was younger than that of the ER+/PR− group (46.3 vs 49.3 years, $p < 0.001$). The mean size of ER+/PR+ group was 2.81 ± 1.78 and that of ER+/PR− group was 2.63 ± 1.74 cm ($p = 0.08$). Early breast cancer proportion of the ER+/PR+ group was higher than that of the ER+/PR− group (49.8 vs 43.2%, $p = 0.03$) while advanced breast cancer proportion of the ER+/PR+ group was lower than that of the ER+/PR− group (50.2% vs 56.9%, $p = 0.03$). There were no difference in the LN metastasis and stage, HER2/neu expression between the two groups. With a median of 40 months follow-up, there was no significant difference between the two groups with regard to overall survival (OS) (94.7 vs 90.3%, $p = 0.08$). The 5-year disease free survival (DFS) for ER+/PR+ and ER+/PR− groups were 86.6 and 83.7%, respectively ($p < 0.001$). We classified the ER+ patients into three strata by age (<35, 35−50, $\geqslant$50 years). There was no significant difference in DFS and OS between the two groups in the <35 stratum and the $\geqslant$50 stratum. In contrast, the ER+/PR− group had a worse prognosis in the 35−50 stratum with regard to both DFS (<0.001) and OS ($p = 0.015$).

Conclusion: The present study suggests that PR receptor expression is predictive factor of adjuvant endocrine therapy for ER+-breast cancer patient regard to DFS and OS.

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Expression of cyclin D1 and bcl-2 in infiltrative ductal carcinoma of the breast – their correlations and clinical implications

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Background: Cyclin D1 and bcl-2 are involved in cell proliferation and apoptosis in tumor development and commonly expressed in breast cancer. A few laboratory reserches about correlation between cyclin D1 and bcl-2 expression were published but there are few clinical reports. The study was designed to analyze the expression of cyclin D1 and bcl-2 and their clinical implications in breast cancer.

Materials and Methods: Immunohistochemical expressions of cyclin D1, bcl-2 were studied in 342 infiltrative ductal carcinoma cases and were compared with clinicopathologic parameters such as age, tumor size, histologic grade, lymph node status, p53, c-erbB2 and estrogen receptor (ER) positivity.

Results: Cyclin D1 expression was found in 86 of 342 cases (25.1%). Bcl-2 was found to be positive in 227 of 342 cases (66.4%). The overexpression of bcl-2 was associated with the high expression of cyclin D1 ($p = 0.0001$). Correlation was detected between both cyclin D1 and bcl-2 and ER positivity ($p = 0.000$). There was a reverse correlation between bcl-2 and histologic grade ($p = 0.001$). bcl-2 overexpression group had better disease free survival in 3 year follow up.

Conclusions: Higher expression of cyclin D1 was associated with bcl-2 overexpression. Positive expression of ER was associated with high cyclin D1 and bcl-2 expression. Bcl-2 has tendency to have a positive clinical outcome.

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HER2 and SPARC status in tumors may play an important role in the relative effectiveness of nanoparticle albumin-bound (nab®) paclitaxel versus polysorbate-based docetaxel

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Background: *Nab*-paclitaxel (Abraxane®) is an albumin-bound 130-nm particle form of paclitaxel that demonstrated higher efficacy and was well tolerated compared to solvent-based paclitaxel (Taxol®) and docetaxel (Taxotere®) in clinical trials for metastatic breast cancer. *Nab*-paclitaxel enhances tumor targeting through gp60 and caveolae-mediated endothelial transcytosis and the association with the albumin-binding protein SPARC in tumor microenvironment. HER2, which is overexpressed in about 25−30% of breast cancers, is associated with increased tumor survival and resistance to paclitaxel. SPARC, which is overexpressed in about 50% of breast cancers, is associated with increased tumor invasion and known to be a poor prognostic factor in breast cancer. The goal of this study was to evaluate the importance of HER2 and SPARC status in determining the relative efficacy of *nab*-paclitaxel compared with solvent-based docetaxel.

Materials and Methods: Maximum tolerated dose (MTD) of *nab*-paclitaxel and docetaxel were previously determined as >120 mg/kg and 15 mg/kg respectively on a q4d$\times$3 schedule. HER2 and SPARC status in tumors was analyzed by immunohistochemistry. The antitumor activity of solvent-based docetaxel (15 mg/kg) was compared to *nab*-paclitaxel in breast tumor xenografts MX-1 (equidose level of 15 mg/kg, qwk$\times$3), MDA-MB-231 (120 and 180 mg/kg, q4d$\times$3) and MDA-MB-231/HER2+ (50 and 120 mg/kg, q4d$\times$3). Additional tumor xenografts (LX-1 lung, PC3 prostate, and HT29 colon) were also studied. Tumor volume and body weights were monitored.

Results: MDA-MB-231 and MX-1 breast cancer and the LX-1 lung cancer lines were HER2 negative and low in SPARC. The HER2 positive tumors had variable SPARC expression, with MDA-MB-231/HER2+ < PC3 < HT29. *Nab*-paclitaxel at sub-MTD dose was significantly more effective than solvent-based docetaxel at its MTD in the three HER2-negative tumors. In HER2-positive tumors, *nab*-paclitaxel was equal to or better than solvent-based docetaxel in tumors with medium to high SPARC levels (PC3 and HT29), but not in MDA-MB-231/HER2+ tumors with low SPARC expression.

Conclusions: The relative efficacy of *nab*-paclitaxel vs. solvent-based docetaxel was significantly higher in HER2-negative tumors. In HER2 positive tumors, the relative efficacy of *nab*-paclitaxel increased with increasing SPARC expression. HER2 and SPARC expression may be useful biomarkers in determining antitumor effectiveness for taxanes.

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External validation in ONCOPOOL of updated survival according to the Nottingham Prognostic Index (NPI)

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From Nottingham City Hospital (NCH) data the NPI was described and validated in the early 1980's. Case survival has markedly improved and new survival figures for cancers treated in the 1990's NPI groups have been published (n = 2235).

ONCOPOOL is a dataset of primary breast cancer assembled as an EC FP5 project in 12 European Breast Units. 17,604 cases treated in the 1990's were available for this analysis.

There are no significant differences in survival in any NPI group between the NCH set and ONCOPOOL nor do overall distributions to prognostic groups differ significantly.

ONCOPOOL gives an excellent intercentre and international validation of the new survival figures according to NPI of women treated to modern protocols.

NPI Group	% Selected		10 Year BCS	
	NCH	ONCOPOOL	NCH	ONCOPOOL
EPG	14	19	96±2	94±2
GPG	21	26	93±2	91±2
MPG I	28	27	81±4	84±2
MPG II	22	18	74±4	76±4
PPG	10	9	55±8	53±6
VPG	4	5	38±12	40±8
Overall	77		81±0.4	

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The prognostic factors for the breast cancers with 10 or more lymph node metastases

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Background: The presence of axillary lymph node metastasis is the most important prognostic factor in breast cancer. The locally advanced breast cancer patients have very poor prognosis with very low disease free and overall survival. Even high-tech diagnostic tools have been developed, locally advanced breast cancers consist of about 10% of all breast cancers. Thus, we investigated the prognostic factors in 10 or more axillary lymph node metastasis.

Materials: Between April, 1986 and December, 2004, a total of 290 breast cancer patients including 44 patients who had neoadjuvant chemotherapy, were reported to have 10 or more axillary lymph node metastasis. It consisted of 5.9% of all breast cancers. All patients' medical records were reviewed. Disease free (DFS) and overall (OS) survival curves were generated using Kaplan–Meier method, with comparison of curves with log-rank test. Cox regression test were used for multivariate statistical analysis.

Results: The average of positive axillary lymph nodes was 18.3 (10−68 in range). Mean age was 47 years (22−81). Median follow-up was 58.8 months (6.1–224.0). The 5-year and 10-year disease free survival (DFS) rates were 46.9% and 36.0%, respectively. Also, overall 5-year and 10-year survival (OS) rates were 58.1% and 45.6%, respectively. In multivariate analysis, age (<35 vs $\geqslant$35, relative risk = 1.816, p = 0.0070), having neoadjuvant chemotherapy (relative risk = 2.413, p = 0.0001), more than 20 nodes involvement (relative risk = 2.105, p = 0.0001), type of adjuvant chemotherapy (CMF vs Anthracyclines or taxane, relative risk = 1.753, p = 0.0001), local recurrence (relative risk = 3.090, p = 0.0001) were revealed to be independent variables for disease free survival. And having neoadjuvant chemotherapy (relative risk = 2.446, p = 0.0001), more than 20 nodes involvement (relative risk = 2.189, p = 0.0001), type of adjuvant chemotherapy (CMF vs Anthracyclines or taxane, relative risk = 2.253, p = 0.0001) were revealed to be independent factors for overall survival.

Conclusion: As expected, previous neoadjuvant chemotherapy, extensive lymph nodes involvement, and regimens of adjuvant chemotherapy are significant factors associated with either disease free or overall survival. It would be better to change the chemotherapy regimens in patients who did not respond well to neoadjuvant chemotherapy. For this high risk group, more potent regimens are expected to improve the outcomes. Additional studies to find out molecular markers are mandatory.

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New cutoff points of tumor size discriminates patients' survival time more precisely than T classification of the 6th AJCC cancer staging system of breast carcinoma

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Background: Tumor (T) classification is one of the most important components of TNM system, and provides information regarding prognosis and treatment options for patients with breast carcinomas. Therefore, in order to estimate more precise outcome of patients, application of the more refined staging system is necessary.

Materials and Methods: We evaluated tumor size in 609 patients of breast carcinoma by measuring only infiltrating breast carcinoma component, and compared this evaluation to survival time and other clinical and pathologic parameters, including the current T classification of AJCC cancer staging system.

Results: A complex pattern of survival time versus the tumor size was observed by censored local regression. The recursive-partitioning technique was coupled with the log-rank test to identify 2 significant cutoff points for the tumor size, 3 cm and 5 cm, which segregated patients into 3 groups with statistically significant decreasing 5 year survival rates (3 cm and 5 cm, 65%, P2 cm and 5 cm, 65%).

Conclusion: Based on the present data, we propose that the T classification of breast carcinoma should be changed to incorporate this measurement: T1 (3 cm and 5 cm).

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Epidermal Growth Factor Receptor (EGFR) in primary breast cancer – protein expression, but not gene copy number, gives important prognostic information in tamoxifen treated patients

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Background: EGFR is a tyrosine kinase receptor being overexpressed in several epithelial malignant tumours (breast, colorectal, lung) and associated with an aggressive phenotype. Targeted therapies are today introduced in order to inhibit EGFR's negative effect and the predictive information achieved by EGFR protein expressesion and gene copy number are thus being explored in different malignancies.

Material and Methods: Tumours from patients operated for primary breast cancer stage II treated with adjuvant endocrine therapy with tamoxifen for two years were included in a tissue microarray. EGFR protein expression was assessed by immunohistochemistry and membrane staining was scored semiquantitavely considering both fraction and intensity on a scale 0−7 and EGFR gene copy number by FISH. FISH positivity, increased gene copy number, was definied as either amplification with EGFR/CEP7 ratio >2.0 or high polysomy as >4 copies per cell. 297 tumours were evaluable by IHC, 252 by FISH and 237 tumours by both IHC and FISH.

Results: EGFR protein overexpression (score 7) was found in 11% of the patients and correlated with ER negativity and PgR negativity, high S-phase fraction, and inversely correlated with nodal metastases. In univariate analysis, EGFR protein overexpression was associated with shorter distant disease free survival (DDFS) (hazard ratio 2.1; p = 0.017) at 5-years follow-up, and reached borderline significance in a multivariate analysis, adjusting for ER, menopausal and lymph node status, tumor size, and HER2 (p = 0.057). Only two patients had amplified tumours, whereas 27 (11%) displayed high polysomi and the two groups were analysed together. By a linear regression model, there was a significant correlation between EGFR protein overexpression and EGFR gene copy number, p = 0.002. EGFR gene copy number was significantly correlated to ER- and PgR negativity, but not to any other of the clinicopathological variables and did not add prognostic information in terms of DDFS.

Conclusion: EGFR protein overexpression is associated with an aggressive phenotype in primary breast cancer and contributes to a shorter DDFS in patients treated with adjuvant tamoxifen. Increased EGFR gene copy number is correlated with hormonereceptor negative breast cancer, but adds no prognostic information in tamoxifen treated breast cancer.

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Prognostic significance of basal and luminal markers in triple-negative breast cancer

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Background: Recently, many efforts had been focused on classification of breast cancers according to molecular features, with particular emphasis on triple-negative (TN) (estrogen receptor-negative, progesterone receptor-negative and HER2-negative) breast cancers. In this study, we examined