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Nottingham prognostic index confirms equivalent breast cancer survival between UK & Europe

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Background: Eurocare-4 (Lancet Oncol 2007; 8: 784−96) suggests that there are still breast cancer survival differences between the UK and mainland Europe. We have examined this in two multicentre and two breast unit datasets in UK & Europe.

Materials and Methods: The E Anglia (EA) (n = 6372) (10 breast units in East of England), Nottingham City Hospital (N) (n = 2238), Cambridge Breast Unit (C) (n = 865) and ONCOPOOL (O) (n = 6711) (12 European Breast Units) datasets of women with primary breast cancer aged <70, diam. <5 cm, treated 1998–2003 (EA & C) and 1990–99 (N & O) are presented. The EA set includes the C set and O the N. The four datasets were compared according to Nottingham Prognostic Index (NPI). Figures shown are actuarial survival for all causes of death (OS) at 84 months survival.

Results: See the table.

- The NPI separates the E Anglia, Cambridge, Nottingham and ONCOPOOL cases into six groups with significantly differing survivals.
- There are no significant differences between the four series in case numbers falling into each NPI group, nor in survival within groups, nor in all case survival.

Conclusion: These data confirm validation of the NPI in prognostic discrimination, distribution to NPI groups and survival figures in four European datasets. It also confirms that there are now no significant survival differences between breast units in the UK and the rest of Europe.

NPI	% OS at 84 months ±2SE			
	EA	C	N	0
EPG	95(2)	93(6)	96(2)	94(2)
GPG	94(2)	94(4)	90(2)	92(2)
MPG I	89(2)	93(4)	84(4)	86(2)
MPG II	77(4)	81(8)	73(4)	78(4)
PPG	62(6)	70(12)	59(6)	58(6)
VPG	48(12)	52(26)	37(12)	44(8)
All cases	84(1)	87(4)	80(2)	84(1)

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Angiosarcoma of the breast and VEGF-R expression

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Background: Angiosarcoma of the Breast (AB) is a rare tumour accounting approximately for 0.05% of all breast cancer. In this retrospective analysis of a contemporary series of patients with AB, we defined the long term outcome and the most common prognostic factors were analysed. The expression of Vascular Endothelium Growth Factor Receptor (VEGFR), with implications for targeted therapies, was also evaluated.

Material and Methods: Patients with AB that were treated at our institution between January 1996 and December 2006 were identified from an institutional database. Twenty-one patients without metastasis at the time of diagnosis were analyzed for age, association with a previous Breast Conserving Treatment (BCT) for breast cancer, size of tumour, grade, VEGFR expression and outcome.

Results: The average age of patients at diagnosis was 50 years (range 14−73). Nine patients had previously undergone BCT for breast cancer. Tumour size was >5 cm in 20% of cases (median 4.1 cm) and the higher proportion of tumours where high grade (44%), 25% were intermediate and 31% low grade. VEGFR was positive in 64% of cases and this finding was associated with low and intermediate grade tumours (P value = 0.0030). There were 6 local recurrences and 6 deaths for disease progression. The 5 years Disease Free Survival (DFS) and Overall Survival (OS) for all patients were 46% (95% confidence interval (CI): 20−72%) and 65% (95% CI: 39−90%) respectively. No factor significantly affected either DFS or OS at univariate analysis, although VEGFR positivity and tumor size >5 cm increased the risk of recurrence or death of about two folds. The occurrence of locoregional relapse increased the risk of death of approximately 3 times.

Conclusions: Multimodal therapy should be considered the standard approach to this severe disease. Despite the low number of cases require caution in drawing conclusion, in this series VEGFR expression is highly related to low and intermediate grade tumours and may have a role to predict a particular patient's clinical course. That found, we encourage the use of a targeted therapy in adjuvant setting when VEGFR is expressed.

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A study on the relationship between breast cancer molecular classification and prognosis

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Background: To investigate the relationship between breast cancer molecular classification and prognosis.

Materials and Methods: The classification of breast cancer was according to the immunohistochemical results of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2) status. Molecular classification definitions were as follows: highly endocrine responsive (ER+, PR+, HER2−), incompletely endocrine responsive (HER2−, hormonal receptor at low level or lacking either ER or PR), triple negative (ER−, PR−, HER2−) and HER2 positive (HER2+). 708 breast cancer patients were retrospectively analyzed to investigate the prognosis among different molecular classifications.

Results: The proportion of highly endocrine responsive, incompletely endocrine responsive, HER2 positive and triple-negative breast cancer was 33.2% (235/708), 23.6% (167/708), 21.3% (151/708) and 21.9% (155/708). Factors affecting the prognosis were tumor size, axillary lymph node status, molecular classification, adjuvant radiotherapy and adjuvant endocrine therapy by univariate analysis. Multivariate analysis revealed that the molecular classification and lymph node status were the independent prognostic factors with the hazard ratio 1.205 (95% CI, 1.003–1.449; P = 0.047) and 4.512 (95% CI, 2.802–7.263, P = 0.000), respectively. Survival analysis showed that highly endocrine responsive breast cancer was with superior prognosis versus others.

Conclusions: Molecular classification of breast cancer is an independent predictor of prognosis, breast cancer patients classified as highly endocrine responsive subtype had the best outcome.

	Hazard ratio	95% Confidence interval	P value
Tumor stage	1.068	0.719−1.587	0.744
Lymph node status	4.512	2.802−7.263	0.000
Molecular classification	1.205	1.003−1.449	0.047
Adjuvant endocrine therapy	0.632	0.393−1.015	0.058
Adjuvant radiotherapy	1.261	0.770−2.065	0.356

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Expression of invasive markers (uPA/PAI-1) in four different HER2, ER, PR subgroups of early breast cancer

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Background: Recent studies suggest that, in some cancers, HER2 specifically promotes the invasive capacity of tumor cells by up-regulating secretion of the proteolytic enzyme, urokinase-type plasminogen activator (uPA), or its inhibitor, plasminogen activator inhibitor-1 (PAI-1).

Aim: The purpose of this study was to evaluate the association between HER2 status and uPA and PAI-1 expression in primary tumors of early breast cancer patients (EBC) and to explore the uPA/PAI-1 expression difference in four molecular subgroups according to immunohistochemically determined HER2 and ER and PR status.

Methods: 308 patients with EBC treated between the years 2004 to 2006 at the University Hospital Maribor, were enrolled in the study. Biological characteristics: grade, ER and PR status, HER 2 status as well as tumor level of uPA and PAI-1 were accessed routinely. Patients

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.