

thus mimicking hormone receptor distribution in normal breast cells. Whether this differential effect of age and probably more important, of menopausal status on combined ER/PR expression has a prognostic value is the object of currently ongoing studies.

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# Correlation of serum HER-2/neu extracellular domain levels in metastatic breast cancer with the expression of HER-2/neu in corresponding primary tumors

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**Background:** A positive HER-2/neu status is a requirement for antibody treatment with Herceptin in metastatic breast cancer (MBC). As a consequence, reliable and clinical relevant assessment of HER-2/neu status is a matter of interest. The aim of our study was a) to determine if HER-2/neu extracellular domain (ECD) concentrations determined at the onset of MBC reflect the HER-2/neu status of the primary tumor, b) to determine the influence of other tumorbiological factors and c) of HER-2/neu expression and ECD levels on disease-free survival and overall survival.

**Methods:** HER-2/neu ECD serum concentrations were determined at the first diagnosis of metastatic disease in 82 patients. Serum HER-2/neu ECD was quantified by a commercially available ELISA (Oncogene Science, part of Bayer Diagnostics, Cambridge, USA). ECD levels above 15 ng/ml were regarded as elevated. For HER-2/neu immunohistochemistry from paraffin-embedded tissue sections of primary tumors the monoclonal antibody CB 11 (Novocastra Laboratories, Newcastle upon Tyne, UK) was used. Staining was evaluated according to the DAKO scoring system (0, 1+, 2+ and 3+).

**Results:** a) HER-2/neu ECD levels at the onset of MBC are correlated with the HER-2/neu expression of the corresponding primary tumor ( $p=0.006$ ). b+c) In patients with non-MBC at primary diagnosis only nuclear grading and nodal status had a significant impact on disease-free survival and overall survival in the multivariate analysis ( $p<0.05$ ). In the univariate analysis patients with HER-2/neu positive tumors (DAKO-Score 2+ and 3+) tended to have a shorter disease-free-survival than patients with HER-2/neu negative tumors ( $p=0.05$ ). In patients with MBC visceral metastases correlated with shorter OS compared with bone or locoregional metastases ( $p=0.007$ ). In our group of patients, HER-2/neu ECD levels had no impact on overall survival.

**Conclusion:** HER-2/neu ECD levels correlate with the HER-2/neu expression of the primary tumor. Our results indicate that the ELISA method could be an option to obtain a real-time status of HER-2/neu in MBC. We were able to observe an impact of HER-2/neu expression in the primary tumor on disease-free survival, but not on overall survival. In our cohort of patients a prognostic relevance of HER-2/neu ECD levels in MBC was not demonstrated.

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# Menopausal status and breast cancer (BC) characteristics: analysis of 3143 consecutive patients

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**Background:** The physiological characteristics of a woman's life (age at menarche and menopause, etc.) are major factors affecting the risk of developing BC, but there are few data concerning the impact of menopausal status on its characteristics, particularly the significance of new prognostic factors such as p53, p21, BCL2 levels, vascular invasion and multi-focality.

**Materials and methods:** The aim of this study of 3143 patients was to verify the differences between the 966 diagnosed before and the 2177 diagnosed after menopause in terms of T (DCIS, T1, T2, T3, T4); nodal involvement (positive vs negative); ER and PgR (positive vs negative); Ki-67 proliferative index (low 0–15%, intermediate 16–25%, high 26–100%); grading (G1, G2, G3); c-erbB2 (positive vs negative); type of diagnosis (asymptomatic vs symptomatic); p53, p21, BCL2 levels; vascular invasion and multi-focality. Among the patients diagnosed in post-menopause the impact of age at menopause was also considered. The data were analysed using the  $\chi^2$  test.

**Results:** The BC of the patients with a post-menopausal diagnosis, compared with BC of patients with a pre-menopausal diagnosis, was less frequently DCIS (10.5% vs 14.9%;  $p<0.001$ ), G3 (29.4% vs 35.2%;

$p=0.008$ ) and c-erbB2+ (38.1% vs 48%;  $p<0.001$ ), and more frequently without nodal involvement (64.5% vs 59.37%;  $p=0.01$ ) and ER+ (83.3% vs 78.8%;  $p=0.006$ ).

There were no differences in terms of PgR, Ki-67, type of diagnosis, p53, p21, BCL2, vascular invasion or multi-focality.

Among the patients diagnosed in post-menopause, only nodal involvement correlated with age at menopause: N0=70.4% in those aged <45 years at menopause, 66% in those aged 46–50 years, 60.1% in those aged 51–55 years, and 56.6% in those aged >55 years;  $p=0.003$ .

**Conclusions:** Menopause seems to have a considerable effect on the prognostic characteristics of BC: a post-menopausal status correlates with good prognostic factors, such as no nodal involvement (particularly in patients entering menopause at a young age), ER positivity, a low grading and c-erbB2 negativity.

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# Correlation between Her-2 status in primary tumour and response to anastrozole in patients with metastatic breast cancer

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**Background:** The aim of our study was to determine the predictive value of Her-2 in primary tumour for the response to anastrozole treatment in postmenopausal patients with metastatic breast cancer.

**Patients and methods:** In a retrospective study, 60 postmenopausal females with metastatic breast cancer treated with anastrozole were included. Most of the patients (90%) had been previously treated with tamoxifen. All patients had estrogen receptor (ER) positive and/or progesterone (PR) positive primary tumours. For the study, tissue array was constructed from formalin fixed paraffin-embedded primary tumours of all patients. On tissue array sections, ER and PR were determined by immunohistochemistry (IHC) only, whereas HER-2 was analysed by IHC and FISH. Chi-square test was used for statistical analysis.

**Results:** In the group of 9 FISH positive tumours there were two immunohistochemically negative (one 0 case, one 1+ case) and 7 positive (two 2+ cases, five 3+ cases). Relatively high response rate to anastrozole (73%) were observed in both Her-2 + and Her-2 – group. If determined by IHC, response rates were similar in Her-2 + and Her-2 – cases (70% vs. 74%; NS). If determined by FISH, response to anastrozole was even better in Her-2 + than in Her-2 – patients (100% vs. 69%;  $P=0.067$ ).

**Conclusion:** According to our results, Her-2 positive tumours respond to anastrozole treatment equally good as HER-2 negative tumours. In addition, the response to anastrozole was found to be even higher in HER-2 positive tumours when determined by FISH.

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# Improved prognosis for breast cancer across the prognostic spectrum from improved therapeutic management

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The Nottingham Prognostic Index (NPI) was originally derived from multivariate analysis of prognostic factors, it recognised three groups with significantly differing survivals and was prospectively validated, intra and inter centre and internationally in series totalling over 20,000 cases. Later analysis divided patients into 5 groups. Mortality from breast cancer in the UK has fallen since the 1980s with operable 10 year survival rising in Nottingham from 55% to 77%. Earlier detection is partly responsible for this (by raising the percentages lying in the best prognostic groups and by detection of DCIS).

Group	Breast Cancer Specific 10 year % survival				
	NPI ≤	1980–86	1990–96	Reduction in deaths	
				Absolute %	Relative
Excellent	2.4	88	95	7	0.58
Good	3.4	72	90	18	0.64
Moderate I	4.4	61	79	18	0.46
Moderate II	5.4	42	71	29	0.50
Poor	6.4	14	44	30	0.34
V. Poor	7.0	12	33	22	0.24
All cases		55	77	22	0.49

Prognosis has greatly improved within each prognostic group which is largely explained by better therapeutic management (eg) adjuvant