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Tumor size and vascular invasion predict distant metastasis in stage I breast cancer. Grade distinguishes early and late metastasis

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Background: In a recent Dutch guideline, adjuvant systemic therapy (AST) is offered to women with high grade stage I breast carcinoma ⩾1 cm. High grade is defined as Bloom and Richardson grade 3 (B&R3), Nottingham modification, or a mitotic activity (MAI) ⩾10/1.59 mm^2. We felt that corroborative studies were needed with respect to the selection of these histological prognostic factors and the exclusion of others that are mentioned in the literature.

Materials and Methods: We used a case-control study design in which fifty cases with stage I breast carcinoma that developed distant metastases were selected from the regional cancer registry (IKR). They were matched for time of diagnosis to fifty controls without distant metastasis. None of the patients received AST. All H&E slides were revised by one pathologist for several histological prognostic factors.

Results: Compared to controls, cases more often had tumors ⩾1 cm (47 vs. 40, p=0.019), B&R3 tumors (20 vs. 12, p=0.059), grade 3 nuclei (28 vs. 15, p=0.005), and vascular invasion (10 vs. 1, p=0.007). No differences were found for MAI ⩾10 (14 vs. 11, p=0.46). In a multivariate analysis, the only statistically significant variables were vascular invasion and tumor size (odds ratios 8.21 and 5.35 respectively). In a separate analysis, the 50 cases were divided in 25 patients with early distant metastasis (before the median time to metastasis of 3.7 years) and 25 patients with late distant metastasis (after 3.7 years). Compared to those with late metastasis, those with early metastasis more often had B&R3 tumors (15 vs. 5, p=0.009) and grade 3 nuclei (19 vs. 9, p=0.006). No differences were found for tumors ⩾1 cm (25 vs. 22), vessel invasion (6 vs. 4) or MAI ⩾10 (10 vs. 4). Under the present Dutch guideline for AST, based on B&R3, 20 cases and 11 controls would have received AST. Based on MAI ⩾10, 14 cases and 11 controls would have received AST.

Conclusions: The present study shows that tumor size and vessel invasion are the best prognostic factors for disease free survival in patients with stage I breast cancer. It also demonstrates that the Dutch selection criteria for adjuvant systemic therapy for these patients need to be improved. In addition we show that some prognostic factors are time-dependent which makes the use of these factors as selection criteria for adjuvant systemic therapy more complicated.

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Results of surgical treatment of patients with breast sarcoma in relation to tumor size

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Aims: Breast sarcoma is a rare and heterogenous disease. Surgical resection is a primary treatment. However, due to rarity of the disease the further details of best treatment option are unknown. The aim of this study was to assess the results of surgical treatment of breast sarcoma patients in relation to tumor size.

Methods: Survival data of all 29 women treated between 1977 and 2001 were collected from hospital records. Twenty eight had mastectomy; in one case wide local excision was performed. No residual microscopic disease and no metastases in regional lymph nodes were found. Median size of the tumor was 10 cm (range: 3–30 cm). The diameter of breast tumor was bigger than 5 cm in 22/29 cases (76%). Cystosarcoma phyllodes was the most common histopathological type (48%). Mean and median disease-free survival times were calculated by the product-limit estimate method. Disease-free and overall survival probabilities were calculated according to Kaplan-Meier method for estimation of survival functions.

Results: The disease relapsed in 11 patients (38%); 8 of them died during follow-up (28%). The probability of disease free survival was 0.55 at 5 years and 0.44 at 10 years. The median length of disease free survival was 119 months. The overall survival probability was 0.69 at 5 years and 0.61 at 10 years, with a median length of overall survival of 137 months. Most of the patients whose disease recurred (10/11; 91%) and all who died had tumors larger than 5 cm. The majority of relapses were observed within two years after surgery. For patients with tumors not bigger than 5 cm the five-year overall survival probability was 1.00, the ten-year overall survival probability was 1.00. Survival estimates could not be computed for these patients since all observations were censored. For patients with tumors bigger than 5 cm the five-year overall survival probability was 0.60, the ten-year overall survival probability was 0.52; the median overall survival was 129.0 months (mean, 118.7 months).

Conclusion: The high probability of disease relapse in patients with large-sized breast sarcomas treated surgically is high, and warrants the search for more aggressive methods of treatment.

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Breast cancer characteristics and clinical outcome in geriatric patients

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Background: Breast cancer is a major source of morbidity and mortality in elderly women. Despite this, today there is no unique breast cancer treatment approach in elderly patients.

Methods: Retrospectively were followed: breast cancer biology, type of surgical treatment and overall survival rate using Kaplan-Meier analysis in period 1990–1995 years. Patients were divided in to study (⩾65 years) and control group (<65 years).

Results: The study involved 1098 women (431 study group and 667 control group). The study group mean age was 71.3 years, and control group mean age was 50.7 years. Ductal carcinoma was the most frequently observed histological type-early stage (study group 70.3% vs. 61.92% control group). Modified radical mastectomy was the most used surgical procedure (71.46% vs. 76.46%). Kaplan-Meier analysis showed no significant statistic difference for overall survival among groups (p=0.961).

Conclusions: Breast cancer management is mostly inadequate in elderly patients. This study showed similar surgical treatment type, and no significant statistic difference for overall survival among examined groups.

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Age specific variation of oestrogen and progesterone receptor expression in 1340 primary operable breast cancers

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Background: In invasive breast carcinoma (IBC), the combined analysis of estrogen (ER) and progesterone receptor (PR) is more reliable than analysis of ER only in predicting response to endocrine therapy and prognosis. We analysed whether age at diagnosis affects differences in the combined expression of ER/PR by tumor cells.

Patients and Methods: Charts from 1340 consecutive female patients diagnosed with primary operable IBC (Jan. 2000 and March 2003) were reviewed, excluding those who received neoadjuvant therapy. Patients were divided in 5 age categories: ⩽40 y, 41–50 y, 51–60 y, 61–70 y and >70 y. IHC stains for ER (6F11/2) and PR (312) were categorised using the H-score as follows: ⩽50 (−); 51–100 (+); 101–200 (++) and 201–300 (+++). Each case was grouped according to the combined ER/PR expression (16 combinations). 233 IBCs were ER−ve/PR−ve (estrogen independent IBC). In 375 of 1107 cases with an estrogen dependent IBC (ER+ve and/or PR+ve) ER and PR belonged to the same category whereas ER and PR belonged to a different category in the remaining 732 cases. These patients were grouped as follows: ER<PR (n=20; ER<50); ER>PR (n=242; PR<50); ER<PR (n=164; ER>50); ER>PR (n=306; PR>50).

Results: 17.4% of all IBCs were ER−ve/PR−ve. The incidence of such estrogen independent IBC decreased significantly after the age of 40 (32.4% <40 y vs. 16.1% >40 y; p<0.001). Of all estrogen dependent IBC (n=1107), 1.8% were ER−ve/PR+ve, 21.8% were ER+ve/PR−ve and 76.4% were ER+ve/PR+ve. ER+ve/PR−ve tumors were significantly more frequent after the age of 50 (9.9% before 50 y vs. 23.1% after 50 y; p<0.001). In the group of ER+ve/PR+ve IBCs, those with PR expression exceeding ER expression were more numerous before than after age 50 y. This is due to the high proportion of PR+ve IBCs before age 50. After 50, there is an age dependent increase in ER expression but not in PR expression.

ER/PR by age group Total numbers	⩽40 108	41–50 323	51–60 371	61–70 328	>70 210	Total 1340
ER−ve/PR−ve	32.4%	16.7%	18%	13.4%	15.7%	233
ER−ve/PR+ve	4.7%	1.5%	1.9%	0.6%	0.5%	20
ER+ve/PR−ve	10.1%	7.7%	19.4%	26.2%	22.8%	242
ER+ve/PR+ve						
ER=PR	23.2%	31.2%	25.3%	30.1%	26.6%	375
ER>PR	14.8%	17.7%	25.2%	24.0%	30.2%	306
ER<PR	14.8%	25.4%	10.2%	5.7%	4.2%	164

Discussion: Estrogen dependent IBC show stronger PR positivity before than after age 50, when ER expression becomes increasingly dominant,

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 χ^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