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THE PROGNOSTIC VALUE OF PLASMINOGEN-ACTIVATOR INHIBITOR-1 (PAI-1) AND THE METASTASIS-ASSOCIATED PROTEASES UROKINASE (uPA) AND CATHEPSIN-D IN PRIMARY BREAST CANCER: A MULTIVARIATE ANALYSIS IN 657 PATIENTS.

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Previously we reported that uPA (Cancer Res 52:6101-6105, 1992), cathepsin D and PS2 (J Clin Oncol, 1993, in press) have prognostic value in breast cancer. In the present study we investigated the prognostic value of PAI-1 (measured in routinely prepared cytosols by ELISA) by univariate and multivariate analysis including cytosolic ER and PgR (by ligand binding assays), uPA (by ELISA), and PS2 and cathepsin D (with ELSA-kits, CIS bio international, France; kindly provided by Dr. B. Thirion), tumor size (T), nodal status (N), and age. Of the 657 patients, 407 were postmenopausal. PAI-1 was positively correlated with uPA and cathepsin D ($P<0.0001$) and negatively with PS2 ($P<0.001$), PgR ($P<0.001$), ER ($P=0.004$) and disease-free survival (DFS) ($P<0.0001$) and overall survival ($P<0.001$), but not with T, N, or grade. In multivariate analysis independent factors for relapse were PAI-1, T, N (all $P<0.0001$), uPA and premenopausal age ($P=0.001$), and for death were PAI-1 ($P=0.02$), N, T, ER/PgR (all $P<0.001$) and age ($P<0.02$). In 264 N^0 patients, PAI-1 was the only independent prognosticator for DFS ($P<0.0001$). In N^+ patients uPA added to the prognostic value of PAI-1. In conclusion, PAI-1 is a strong independent prognosticator for patients with primary breast cancer. Supp. Dutch Cancer Society: DDHK 88-09/92-04; Deutsche Forschungsgemeinschaft: CSFB 207-F9/G10).

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DIFFERENTIAL INFLUENCE OF PROGNOSTIC FACTORS ON THE OCCURENCE OF METASTASES AT VARIOUS ANATOMICAL SITES IN PATIENTS WITH BREAST CANCER

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Using Cox regression analysis, the influence of various risk factors for recurrence at specific sites were studied in 788 premenopausal patients with primary breast cancer and high risk of recurrence (node positive, fascial invasion or primary tumor > 5 cm). Cox analysis confirmed that established prognostic factors were related to the recurrence of metastases in many different sites (tumorsize, differentiation, local invasion, node status, adjuvant therapy). However, Cox analyses allows only comparison of prognostic factors as to the specific anatomical site, and do not allow comparisons between sites. In order to solve this, a specific Marshall-Olkin model was applied: Most prognostic factors had a significant decreasing effect on the rate of recurrence at all sites. A high number of positive lymph nodes was associated with increased risk of metastases in all sites, except in brain where the opposite trend was found. High degree of anaplasia was also associated with a homogenous increased risk of metastases, homogenous except for brain, where a more pronounced effect of anaplasia was found. Comparison of the results reveals that the Marshall-Olkin model illustrates fewer site specific differences between the prognostic factors than suggested by the Cox models. The study shows that certain prognostic factors may be useful predictors for metastases in specific sites.

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TUMOUR PLATELET DERIVED GROWTH FACTOR (PDGF) EXPRESSION PREDICTS FOR SHORTENED SURVIVAL AND TREATMENT FAILURE IN ADVANCED BREAST CANCER.

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In a study of plasma and tissue platelet derived growth factor concentration in patients with breast cancer elevated levels of plasma PDGF were found in 11/37 (30 %) of patients. All patients with elevated plasma PDGF levels showed positive staining of tumour cells. Sixteen (43 %) had tumours which expressed AA-platelet derived growth factor and 6 patients had tumours which expressed BB PDGF on immunohistochemical staining of tumour cells. Furthermore there was a significant correlation between plasma levels of platelet PDGF and the intensity of tissue staining. Patients with stage 4 breast cancer with tumours which were positive for PDGF had a significantly lower response rate to chemotherapy as well as significantly shorter duration of survival. These results indicate that elevated plasma levels of PDGF in patients with breast cancer are derived from the tumour cells and suggest that PDGF may play a significant role in auto-stimulation of tumour cell growth.

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EFFECTS OF INTERFERON AND TAMOXIFEN ON IN-VIVO TUMOUR BIOLOGIC VARIABLES IN BREAST CANCER. BASIC AND CLINICAL OBSERVATIONS.

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The use of the combination of interferon α (IFN) followed by tamoxifen (TMX) was studied in 12 patients with advanced pretreated breast cancer. The aim of the study was to investigate the in-vivo changes of biologic determinants such as hormone receptor, and growth factor expression. IFN consistently increased the expression of ER and of the estrogen regulated protein P24 while decreasing the expression of the proliferation associated antigen Ki 67. Addition of tamoxifen on the other hand resulted in reduction of ER expression and rise of PR expression. Platelet derived growth factor (PDGF) expression was suppressed by IFN while the effects on TGFß expression were variable. IFN and TMX have complex effects on tumour biologic variables, some of which are consistent with predictions from in-vitro models while others are not. From the clinical point of view it might be expected that treatment which enhances ER expression will have a positive effect on response to TMX.

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TUMOR CELL DETECTION IN BONE MARROW OF PRIMARY BREAST CANCER PATIENTS

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At the Department of Obstetrics and Gynaecology, University Erlangen, a prospective trial was carried out concerning the prognostic value of tumor cell detection in bone marrow using monoclonal antibodies against EMA with respect to the probability of tumor recurrence and the duration of disease free survival.
Bone marrow punctions were taken from 228 patients with primary breast cancer and then immunocytochemically analysed for tumor cells using EMA - antibodies.
106 of the 228 patients were tumor cell positive.
The median follow up period was 32 months during which 30 patients developed recurrences, 17 of which were bone metastasis.23 of these 30 patients had positive bone marrow punctions.
Therefore positive bone marrow showed a strong correlation to the probability of bone metastasis development.
The number of recurrences and the disease free survival in EMA - positive patients was significantly higher and shorter respectively than that of EMA - negative patients.
A multivariate analysis of the results demonstrated that bone marrow punction is independant of other established prognostic criteria.
Consequently immunocytochemical cell detection in bone marrow is, according to the results above, an important and independant prognostic factor in breast cancer.However it is not to be used as an expression of micrometastases as the majority of EMA - positive patients did not develop recurrences.

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BREAST CANCER ASSOCIATED BRACHIAL PLEXOPATHY: STILL A DIAGNOSTIC AND TREATMENT CHALLANGE.

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Brachial plexopathy (BP) in breast cancer patients is a rare event, attributed mainly to radiation damage or tumor infiltration of the plexus. Differentiation between these etiologies is a diagnostic challange. Eight patients with breast cancer developed BP following the treatment of the primary disease. None of the available ancillary tests such as plain films, CT or MRI studies, EMG or tumor markers, provided reliable data regarding the cause of the BP. Biopsy, on the other hand, was not always feasible. All the patients who developed BP did not have any blood-borne metastases before developing the syndrome. In 3 of the patients BP was the first sign of recurrence. In the other 5, only local or locoregional relapse preceeded. In 7 of the 8 patients the left side was affected. Two distinguished situations are to be defined. The first is patients who have already been irradiated to the plexus. In these patients the possibility of radiation therapy induced BP is rather high. In our opinion routine chemotherapy should not be given unless a definite diagnosis of recurrent tumor is made. A relatively non-toxic agent such as tamoxifen may be used. If this fails, the possibility of "blind" chemotherapy should be discussed with the patient. As so far we are not aware of any data reporting the benefit of chemotherapy in previously irradiated patients. The second situation is naive patients, who have not yet been irradiated to the plexus. Radiotherapy, even in the absence of a definite proof for a recurrence, might be administered early in the course of the BP.