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HER-2 expression and lympho-vascular invasion in breast cancer

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Background: Lympho-vascular invasion (LVI) has been suggested to be a significant prognostic indicator in breast cancer. LVI means that cancer cells were found invading lymphatics in the breast parenchyma adjacent to or well beyond the margin of the invasive tumor, which can be an indicator of increased likelihood that cancer could spread, as evidence by the positive lymph nodes. HER-2 overexpression has become an increased proliferative activity of tumor cells in breast cancer. Also overexpression of the HER-2 was reported to predict lymph node involvement in breast cancer. The objective of this study was to determine whether HER-2 overexpression is associated with LVI in breast cancer.

Material and Methods: Expression of HER-2, Ki-67, P53, estrogen receptor and progesterone receptor was determined immunohistochemically in 120 patients of breast cancer, including 77 patients with absent of LVI and 43 patients with present of LVI.

Results: LVI was noted in 43 patients (35.8%) in 120 patients of breast cancer. Of 77 patients with absent of LVI, the number of stage III patients (13 patients, 16.9%) was lower than that of stage I (25 patients, 32.5%) and stage II patients (39 patients, 50.6%) of breast cancer. Of 43 patients with absent of LVI, the number of patients was 5 patients (11.6%), 13 patients (30.2%), and 25 patients (58.2%) in stage I, II, and III, respectively. There was a significant correlation between LVI and stage ($P<0.000$). Strong expression (+3) of HER-2 was seen in 17 (39.5%) of the 43 patients in whom LVI was seen and in 15 (19.5%) of the 77 in whom LVI was not seen. Overexpression of Ki-67 was noted in 42 (97.7%) of the 43 patients in whom LVI was seen and in 64 (83.1%) of the 77 in whom LVI was not seen. HER-2 and Ki-67 overexpression was associated with significantly LVI ($P=0.027$ and $P=0.018$, respectively). LVI did not correlate with the expression of P53, estrogen receptor status and progesterone receptor status. There was a strong association of LVI and lymph node status ($P<0.000$). Finally, LVI was associated with tumor size ($P=0.014$) and with nuclear grade ($P=0.022$).

Conclusions: This study demonstrates the potential value of lymph nodal status, tumor size, stage and nuclear grade in the assessment of lympho-vascular invasion; and the overexpression of HER-2 and Ki-67 as a strong indicator of LVI in invasive ductal carcinoma of breast.

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No correlation between tissue concentration and plasma levels of invasion factors urokinase-type plasminogen activator (uPA) and its inhibitor PAI-1

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Introduction: Tumor levels of urokinase-type plasminogen activator (uPA) and of its inhibitor plasminogen activator inhibitor type 1 (PAI-1) are strong and independent prognostic factors in lymph node negative breast cancer. Patients with high levels of uPA and/or PAI-1 in their primary tumors, determined by enzyme-linked immunosorbent assay (ELISA), had statistically significant shorter disease-free survival (DFS) and overall survival rates than patients with low tumor levels. Meanwhile these factors are validated at highest level of evidence (LoE 1a) such that guidelines now recommend their use in clinical routine. We studied the correlation of uPA and PAI-1 in tissue concentration levels with two different kits. In addition, we measured the plasma concentration of uPA and PAI-1 in the same cohort.

Methods: In 75 samples taken from primary breast cancer tumors, tissue concentration was measured using Imubind ELISA (#821 and #894 ADI, Stamford CT) and OSDI ELISA (#12 and #17, Oncogene Science, Greenwich CT). From the same patients, also blood was drawn prior to surgery and plasma levels of uPA and PAI-1 were measured using the OSDI kits (#12 and #17).

Results: We found a strong correlation between tissue concentration levels for both uPA ($r=0.898$, $p<0.0001$, Pearson) and PAI-1 ($r=0.873$, $p<0.0001$) measured with either Imubind or OSDI. Plasma levels of uPA and PAI-1 did not correlate with the tissue concentrations of uPA and PAI-1 using the methods described above. uPA and PAI-1 tissue levels showed an inverse correlation to steroid hormone receptor status but no correlation to tumor size and grading, as described in previous publications. In contrast, uPA and PAI-1 plasma levels showed correlation to none of these traditional prognostic factors.

Conclusions: The plasminogen activator system plays an important role in tumor invasion and metastasis. Tissue measurement of uPA and PAI-1 can be reproduced by assays from different manufacturers. However, cut-off

values for prognostic assessment are only available for one of these kits. Plasma levels of these factors do not correlate to the tissue concentrations. Therefore, only tissue measurement of uPA and PAI-1 should be used for prognostic assessment of node-negative breast cancer patients.

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Evaluation of histological regression after neoadjuvant CAF chemotherapy in p53-positive and p53-negative invasive breast carcinomas of reproductive and postmenopausal women

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Background: The neoadjuvant chemotherapy is widely used for the treatment of invasive breast carcinoma. The evaluation of treatment efficacy is possible by the histological regression that is important to determine drug-resistance, possible recurrence, survival rate and etc. The aim of this study was to investigate the histological regression in p53(+) and p53(-) invasive breast carcinomas of reproductive and postmenopausal women after neoadjuvant CAF (Cyclophosphamide + Adriamycin + 5-Fluorouracil) chemotherapy.

Materials and Methods: We have studied the biopsies of invasive breast carcinomas. The paraffin sections were stained by H&E, van Gieson and immunohistochemistry with antibodies against p53, ER, PgR, visualisation system LSAB, substrate DAB (DakoCytomation). The histological grade was evaluated using Scarff-Bloom-Richardson system. In 62 ER(-)PgR(-) patients neoadjuvant CAF chemotherapy was used. These patients were divided in 4 groups: I group – 14 reproductive women with p53(+) carcinoma; II group – 16 reproductive women with p53(-) carcinoma; III group – 17 postmenopausal women with p53(+) carcinoma; IV group – 15 postmenopausal women with p53(-) carcinoma. In surgical specimens of these patients the histological regression was evaluated as follows: R0 = no regression, R1 = cytological alteration only, R2 = cytological alteration, R3 = subtotal regression, R4 = no residual carcinoma.

Results: In I group 3 patients had I grade tumors, 4 patients – II grade, 7 patients – III grade. In II group 6 patients had I grade tumors, 6 patients – II grade, 3 patients – III grade tumors. In III group 4 patients had I grade tumors, 5 patients – II grade, 8 patients – III grade. In IV group 7 patients had I grade tumors, 5 patients – II grade, 3 patients – III grade. After CAF chemotherapy in I group 6 patients had R0, 4 patients – R1, 3 patients – R2, 1 patient – R3. In II group 2 patients had R0, 4 patients – R1, 4 patients – R2, 4 patients – R3, 1 patient – R4. In III group 6 patients had R0, 5 patients – R1, 4 patients – R2, 2 patients – R3. In IV group 1 patient had R0, 2 patients – R1, 5 patients – R2, 5 patients – R3, 2 patients – R4.

Conclusions: Neoadjuvant CAF chemotherapy is more effective in p53(-) invasive breast carcinoma both in reproductive and postmenopausal patients. However, it is more effective in postmenopausal women. Therefore, p53-positivity/negativity is a possible predictor for the effect of chemotherapy.

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AgNOR counts and characteristics of a sex chromatin distribution in ductal intraepithelial neoplasias of the breast

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Background: In recent years, nucleolar organizer region (NOR) scores have been explored for potential value in the diagnosis of malignancy as the scores in malignant nuclei are seen to be higher than in benign or reactive nuclei. This technique is based on silver staining of NOR. It is much cheaper and rapid than immunohistochemical evaluation of proliferative activity. The sex chromatin incidence is markedly decreased in breast carcinoma and probably associated with AgNOR-positivity. AgNOR counts and the characteristics of a sex chromatin distribution are not well studied in ductal intraepithelial neoplasias of the breast – DIN (DIN1a, DIN1b, DIN1c, DIN2, DIN3). The aim of the present study was to determine the diagnostic and prognostic value of recently standardized morphometric analysis of argyrophilic nucleolar organizer regions (AgNORs) as well as characteristics of a sex chromatin distribution in DINs of the breast.

Materials and methods: 42 biopsies of breast DINs were investigated: 10 cases of DIN1a, 9 cases of DIN1b, 7 cases of DIN1c, 8 cases of DIN2, 8 cases of DIN3. The specimens were fixed in 10% neutral buffered formalin solution and embedded in paraffin. The paraffin sections were stained by hematoxylin-eosin and AgNOR method (Bio-Optica). Two parameters of AgNOR staining: mean number of AgNOR-stained dots per nucleus (equal to mean number of nucleoli) and mean number of AgNOR-positive cells were evaluated.

Results: In DIN1a the mean number of AgNOR-positive cells was 27.4 ± 3.5 , AgNOR-dots per cell – 2.4 ± 0.6 , sex chromatin containing cells – 100%. In DIN1b the mean number of AgNOR-positive cells was 34.5 ± 4.1 ,