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

B.J. Song<sup>1</sup>, S.H. Chang<sup>1</sup>, H.S. Kim<sup>2</sup>, J.S. Kim<sup>3</sup>, S.S. Jung<sup>3</sup>. <sup>1</sup>Ilisan Paik Hospital, Medical College, Inje University, Department of surgery, Koyang-si, Korea; <sup>2</sup>Ilisan Paik Hospital, Medical College, Inje University, Department of pathology, Koyang-si, Korea; <sup>3</sup>College of Medicine, The Catholic University of Korea, Department of surgery, Seoul, Korea

**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 evidenced 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 node 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**

M. Bader, I. Witzel, V. Müller, F. Jänicke, F. Thomssen. University Hospital Hamburg-Eppendorf, Gynecology, Hamburg, Germany

**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**

G. Burkadze, G. Turashvili. Tbilisi State Medical University, Pathological Anatomy, Tbilisi, Georgia

**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 and histological 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**

G. Turashvili<sup>1</sup>, G. Burkadze<sup>1</sup>. <sup>1</sup>Tbilisi State Medical University, Pathological Anatomy, Tbilisi, Georgia

**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  $27.4 \pm 3.5$ , AgNOR-dots per cell –  $2.4 \pm 0.6$ , sex chromatin containing cells – 100%. In DIN1b the mean number of AgNOR-positive cells was  $34.5 \pm 4.1$ ,

AgNOR-dots per cell –  $3.1 \pm 0.6$ , sex chromatin containing cells – 100%. In DIN1c the mean number of AgNOR-positive cells was  $48.5 \pm 3.6$ , AgNOR-dots –  $3.9 \pm 0.45$ , cells with sex chromatin – 89%. In DIN2 the mean number of AgNOR-positive cells was  $60.4 \pm 2.5$ , AgNOR-dots –  $5.5 \pm 0.4$ , sex chromatin containing cells – 86%. In DIN3 the mean number of AgNOR-positive cells was  $87.4 \pm 3.6$ , AgNOR-dots per cell was  $7.8 \pm 0.6$ , sex chromatin containing cells – 74%.

**Conclusion:** AgNOR counts are relevant for differentiation between the grades of DIN. Therefore, objective and reproducible data obtained by AgNOR analysis may allow better evaluation of the prognostic significance of these lesions. This may give insight into the biological background of DINs, grade and progression and may also underlie the independent prognostic value of AgNORs.

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#### Risk of breast cancer following mantle radiotherapy for Hodgkin's disease

K. Valassiadou<sup>1</sup>, F. Yuille<sup>2</sup>, E.D.C. Anderson<sup>2</sup>. <sup>1</sup>Leicester University Hospitals, Breast Care Centre, Leicester, UK; <sup>2</sup>Western General Hospital, Edinburgh Breast Unit, Edinburgh, UK

**Background:** Radiation therapy was the first treatment modality to demonstrate cure of Hodgkins Disease (HD). Women with HD who receive mantle radiotherapy (MRT) are at increased risk of developing breast cancer (BC) but this association is difficult to quantify.

**Methods:** The medical records of female patients who received MRT for HD between 1974 and 1998 inclusive were retrospectively reviewed.

**Results:** Of the one hundred and twelve women on the database, eight developed BC within a follow up period of 0.2–29 years (median 12.3 years): 3 of 59 patients aged <30 at the time of MRT, 5 of 21 patients aged 30–40 at MRT and 0 of 32 patients aged >40 at MRT. The median age of MRT was 28 years (min13 – max77 years), median time to BC 17.2 years (min11 – max27 years) and median age of BC 40 years (min22 – max58 years). The actuarial incidence of breast cancer in 15, 20 and 28 years following MRT (Kaplan-Meier tables) was 5%, 15% and 30% respectively. This rate remains stable when correlated with the age of MRT (log rank test for trends=0.547). The breast cancer incidence within the current age groups <40, 40–50 and >50 is 11.4%, 7.5% and 2.7% respectively.

**Conclusions:** Long-term survivors from HD that received MRT are at very high risk of developing breast cancer. As these long-term survivors are more likely to have received MRT at a young age and may develop BC before they reach the recommended breast screening age, it is essential that they are identified as a high risk group to be offered breast screening.

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#### Clinical and prognostic features of myoepithelial carcinoma

K. Behranwala, N. Nasiri, G. Gui. Royal Marsden Hospital, Breast Surgery, London, UK

**Introduction:** Myoepithelial cell carcinoma of the breast is a rare tumour of controversial histogenesis. Little is known about its natural history and long term outcome following treatment.

**Methods:** All patients with myoepithelial carcinoma treated at our institution between 1970 and 2001 were studied with respect to pathological features, outcome and prognosis.

**Results:** Six patients were identified. The median age was 60 (40–66) years and median follow-up was 34.5 months (range 14–76) months. Four tumours were T1 and one was T2 (one tumour size unknown). There were two moderately differentiated and three well-differentiated tumours (grade could not be assessed in one patient). Oestrogen and progesterone receptor could be assessed in five patients and all were negative. Primary treatment was wide local excision with clear radial margins. Lymph node assessment was negative in all patients. One patient received adjuvant radiotherapy. Three patients developed local recurrence at 15, 38 and 50 months and two patients developed distant metastasis at 30 and 79 months. The local recurrences were treated by further excision but two patients developed distant metastasis at intervals of 15 and 26 months respectively. Two patients have died of the disease and four remain well. The 2 year and 5 year survival was 88% (SE=6) and 55% (SE=16) respectively. Large tumour size is a prognostic indicator of poor outcome.

**Conclusion:** Myoepithelial carcinoma of the breast adopts an aggressive clinical course with an outcome comparable to poorly differentiated adenocarcinoma of the breast.

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#### Risk factors for early recurrences after conventional- or high-dose adjuvant chemotherapy in breast cancer patients with extensive lymph node involvement

I.F. Faneyte<sup>1,2</sup>, J.L. Peterse<sup>1</sup>, H. Van Tinteren<sup>3</sup>, C. Pronk<sup>1</sup>, E.G.E. De Vries<sup>5</sup>, S. Rodenhuis<sup>4</sup>, M.J. van de Vijver<sup>1</sup>. <sup>1</sup>Netherlands Cancer Institute/Antoni van Leeuwenh, Pathology, Amsterdam, The Netherlands; <sup>2</sup>Netherlands Cancer Institute/Antoni van Leeuwenh, Experimental Therapy, Amsterdam, The Netherlands; <sup>3</sup>Netherlands Cancer Institute/Antoni van Leeuwenh, Biometrics, Amsterdam, The Netherlands; <sup>4</sup>Netherlands Cancer Institute/Antoni van Leeuwenh, Medical Oncology, Amsterdam, The Netherlands; <sup>5</sup>University Hospital Groningen, Medical Oncology, Groningen, The Netherlands

**Purpose:** There is limited knowledge of risk factors for breast cancer recurrence within 2 years. This study aims to predict early failure and identify high-risk patients, for prognostic and therapeutic purposes.

**Experimental design:** 739 patients from a randomized trial were studied, who had: 4 or more positive lymph nodes, age under 56, no distant metastases and no previous other malignancies. After complete surgical treatment, they received conventional-dose anthracycline-based chemotherapy or a high-dose scheme of anthracycline-based plus alkylating chemotherapy. We assessed clinical and (immuno)-histological parameters to predict recurrence within 2 years.

**Results:** Early failure occurred in 19% (n=137) and was associated with young age, large tumors, high histological grade, angio-invasion, apical node metastasis and 10 or more involved nodes. ER, PR and p27 negativity, HER2 overexpression and p53 positivity also predicted early failure. The surgical or chemotherapy regimen and histological type did not. Grade III, 10 or more involved nodes and ER negativity were independently associated with early failure and together identified a subset of patients (7%) with 3-fold increased early failure. Patients under 40 after high-dose treatment and HER2 positive patients after conventional-dose chemotherapy had decreased early failure. Median survival after early failure was limited to 0.7 years median. ER and PR negativity and visceral relapse predicted poor prognosis.

**Conclusions:** With risk factors for early failure a predictive model was formed. Young patients benefit from high-dose alkylators and patients with HER2 positive tumors benefit from increased anthracycline dosage. These findings are useful in tailoring treatment for breast cancer patients.

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#### Survival analysis and prognostic factors of breast cancer in Korea

S.H. Kang, K.Y. Chung, Y.S. Kim. Keimyung University School Of Medicine, General Surgery, Tae Gu, Korea

**Background:** Breast cancer is the most frequently occurring cancer in women in the Korea and its incidence is rapidly increasing in the past decade. Although, the actuarial survival data on western women abound in medical literature, large collections of statistics from rising prevalence areas in the orient is lacking. We have established a comprehensive breast cancer data base since 1985. We have analyzed the data according to clinical characteristics, survival and prognostic factors.

**Material and Method:** Nine hundred and eighty nine consecutive breast cancer patients first diagnosed at the Dongsan Medical Center, Keimyung University between January 1990 and December 2001 were included. Prognostic analysis was performed in 918 patients who had non-disseminated invasive carcinoma and had undergone primary surgery. Risk factor analyses for disease free survival include age, primary tumor size, number of metastatic axillary lymphnode, histologic grade, nuclear grade, family history, lymphovascular invasion and hormonal receptor status. The influence of prognostic factors on survival was explored by Cox's proportional hazard regression model using SPSS 11.0 software.

**Results:** The peak incidence age was in the 40's and the mean age at diagnosis was 48.1 years old. Forty four patients (4.4%) were in stage 0, 218 (22.0%) in stage I, 572 (57.9%) in stage II, 112 (11.4%) in stage III, and 22 (2.2%) in stage IV. The early breast cancers (stage 0 and I) were presented in 26.4%. The 5 and 10 year overall survival rates were 79.7% and 65.4%, respectively and 5 and 10 year disease free survival rates were 73.8% and 68.8%. Multivariate analysis showed that the age, tumor size, and axillary lymphnode involvement remained as significant prognostic factors for the time to recurrence and overall mortality.

**Conclusions:** This study showed that the peak age of the breast cancer in Korea was younger than that seen in Western countries. But the survival rate was similar to their Western counterpart despite the fact that our patients comprised of smaller proportion of early breast cancers. The age at the time of diagnosis, the tumor size, and the number of metastatic axillary lymphnode were confirmed to have independent influence on overall survival and disease free survival.