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HER-2/neu Overexpression as Prognostic Factor in Small Size Breast Cancer (pT1, N0, M0)

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Background: Breast cancer patients, classified as pT1, N0, M0 usually have a good prognosis, but 20−30% of these presents recurrence of disease. Approximately 25% of breast cancers are HER-2/neu overexpressed and/or amplified both being prognostic and predictive factors associated with worse disease-free and overall survivals. According to international guidelines, in tumors with a size <1 cm, HER-2/neu-positive, the use of adjuvant therapy with Trastuzumab may be problematic because there are no published clinical trials on the subject. The aim of our study was to evaluate the molecular features of pT1, N0, M0 tumors and to correlate them with the follow-up in order to identify risk factors for recurrence of disease.

Material and Methods: 300 women (median age: 56 years) with small invasive breast cancer, pT1, N0, M0 (2004–2010), entered in the study. 192/300 tumors (64%) were pT1c, whereas 108 tumors (36%) were pT1a and b. ER, PgR, Ki-67 status were evaluated using immunoistochemistry (IHC) and scored according to St. Gallen conference guidelines. HER-2/neu protein expression was investigated by IHC (HercepTest, DAKO), HER-2/neu gene status was assessed by FISH (PathVysion HER-2 DNA Probe Kit, PathVysion Kit) and scored accoding to FDA guidelines.

Results: 86/108 cases (79.6%) cases were ER+/PgR+, 18 (16.7%) were ER−/PgR−, 24 (22.2%) were Ki-67 $\geqslant$20, 8 (7.4%) had triple negative (TN) biological features. 158/192 cases (82.3%) were ER+/PgR+, 32 (16.7%) were ER−/PgR−, 76 (37.6%) were Ki-67 $\geqslant$20. 14 (7.3%) were classified as TN. Different Ki-67 expression, in two subset (pT1a-b VS pT1c) is associated with tumor size.

24/192 pT1c (12.5%) cases and 10/108 pT1a-b (9.3%) cases evidenced HER-2/neu overexpression. Subset overexpressing HER-2 tumors (34/300, 11.3%) showed a high proliferative activity (Ki-67 index: $\geqslant$20%) regardless of tumor size. Follow up data (mean FU: 77.5 months; range 12–168 m months) were available only in 20 patients overexpressing HER/Neu (10 pT1a-b, 10 pT1c). Were evidenced two relapse (10%): one case, classified pT1b, shows local and metacronous cancer relapse, in a woman only treated with radio therapy. One case, classified pT1c, in a woman treated with Tamoxifen, this case showed TN biological features.

Conclusions: HER-2/neu overexpression could represent a significant marker of high risk of relapse and could be a prognostic and predictive factor also in small breast node-negative carcinomas.

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Osteopontin as a Potential Serum Marker in Early Breast Cancer − Preliminary Results

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Introduction and Aim: Osteopontin is a glycoprotein playing a role in carcinogenesis, tumour progression and metastasis. The immunohistochemical studies show its over expression in tumour tissue which is correlated with its serum level and tumor stage. High serum osteopontin level correlates with higher risk of relapse and shorter survival and is used as a prognostic marker in same cancers. The aim of this study was to evaluate the level of serum osteopontin in early breast cancer patients and to observe its changes while treatment.

Materials and Methods: The analysis was performer in the group of 73 patients with early breast cancer treated in Institute of Oncology in Gliwice between 2005–2007. Median age was 58 (range 38−72). All tumours were diagnosed in I or II clinical stage. The stage distribution was as follows: T1 − 55%, T2 − 45%, N0 − 75%, N1 − 25%. All patients were treated with radical surgery (mastectomy or wide excision with ALND) and adjuvant systemic therapy and radiotherapy if indicated. The control group consisted of 50 healthy women. To assess the serum osteopontin level the Elisa method was used (R&D System). The measurements were performed three times: at diagnosis, after surgery and 1 year after the treatment was completed. To identify the differences in ostepontin level in diagnostic and control group the Kruskall-Wallis test was used and Wilcoxon test to assess its changes during treatment. To correlate the changes in osteopontin level with clinical parameters test $\chi 2$ was used.

Results: The analysis showed higher levels of osteopontin in the breast cancer patients at diagnosis in comparison to control group ($p = 0.0003$). There was no difference in osteopontin level when clinical stage (I vs II) was concerned. After surgery we observed the decline of osteopontin level ($p < 0.0005$) but even if we assume that surgery was radical its level did not change in 20% of pts. We identified two patterns of osteopontin change during treatment. The first with the 5 fold decline after surgery ($p = 0.0005$) and its rise one year after but still to lower level than the initial ($p < 0.002$). The second one with non regular changes or stable level of osteopontin. We tried to find the correlation between the patterns of osteopontin changes with clinical parameters: tumour size, nodal stage, grade, histological type, steroid receptors, Her status, hemoglobin and leukocyte levels. The only clinical parameter which correlated with osteopontin level changes was N stage ($p < 0.05$). All patients with a decline in osteopontin level after surgery were pN0.

Conclusions: These preliminary data show that osteopontin is a potential diagnostic and prognostic serum marker for early breast cancer. The data should be re-evaluated in larger group of patients and correlated with survival.

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Prognostic Factors Male Breast Cancer

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Background: Male breast cancer is a rare disease, accounting for less than 1% of all breast cancers worldwide, associated with the aggressive course and worst prognosis.

The goal of present study − analyze the influence of certain clinical-morphological factors for the prognosis of the disease.

Material and Methods: Analyses of data of 168 male patients with breast cancer were treated at the Armenian National Center of Oncology in the period between 1981 and 2006.

Results: These datas show that 5-year-long survival rate is lower among patients with regional lymph node metastases (23.5% and 67.1% respectively, $P < 0.002$). This information permits us to identify lesion of regional lymph nodes as an extremely important prognostic factor for disease progression. At the beginning of treatment 98 patients(58.3%) out of 168 had metastases in regional lymph nodes, which is a disturbing sign and indicates increase in aggressive potential of breast cancer among men. The 5-year survival rate is also strongly correlated with tumor size. Tumors smaller than 2 cm were correlated with higher survival rates than tumors ranging from 2 to 5 cm and more 5 cm (66.7%, 49.3%, and 30.1% respectively, $P < 0.05$); 89.3% of the men in Armenia began treatment course with tumors larger than 2 cm. The most common histological type was invasive ductal carcinoma which made up (76.8%) in 129 out of 168 patients. We didnt observe such prognostically favorable histological types as mucinous carcinoma and glandular carcinoma. The study also focused on the grade of gystological malignance for the prognosis of the disease. Its increase significantly shortened 5-year survival rate of patients (87.5% − I, 56.3% − II, 22.9% − III respectively, $P < 0.05$).

Conclusions: Lymph node status, tumour size and gystological malignance are very important clinical-morphological factors of the prognosis for men with breast cancer, which can be used for selecting appropriate schemes of treatment for such group of patients. More than half of the patients in Armenia begin treatment in the latest stages(with metastases in regional lymph nodes and size of tumor more then 2 cm), that's why the results of treatment are not effective enough.

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Prognostic Role of Preoperative Serum CA15.3 and Its Association with Clinicopathological Parameters

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Background: CA15.3 is the most widely used tumor marker in breast cancer. The aim of this work was to identify: (i) any relationship between preoperative CA15.3 serum levels and various clinicopathological parameters and (ii) the prognostic value of pre-surgical CA15.3 levels in patients with primary breast cancer.

Materials and Methods: During 2004–2007, 247 women (median age 52.9±11.49 years, range 20−83) with pT1−2 invasive breast carcinoma were reviewed retrospectively, whereas patients with confirmed pT3−4 pathology or metastatic disease were excluded. The serum values of CA15.3 were investigated at the time of primary diagnosis by means of immunoradiometric assay. The median follow-up period of patients was 62 months. Each patient was further assessed for Her-2/neu, ER, PR, histological grade, histological type, tumor size, nodal status and age at diagnosis. Statistical analysis was performed by Pearson's chi-square test, univariate (Kaplan-Meier) and multivariate (Cox regression) models using the SPSS (Statistical Package for the Social Sciences) 15.0.1. P-value

of less than <0.05 was considered as indicative of statistically significant difference.

Results: Pretreatment CA15.3 levels ranged from 3.3 to 237.6 U/ml. Elevated CA15.3 levels (>28 U/ml) were found in 21 (8.5%) patients. Statistical analysis revealed that preoperative serum CA15.3 levels were directly related to tumor size (p = 0.015) and lymph node involvement (p = 0.009), while no significant relationship between CA15.3 measurements and age, histological type, grade, HER2/neu positivity, ER and PR status was observed. In the univariate analysis, high CA15.3 levels were significantly associated with a lower probability of disease free survival (DFS) in the overall group of patients (p = 0.0001). On the contrary, multivariate regression method showed that CA15.3 was not an independent risk factor for a shorter DFS, with a hazard ratio of 0.177 (95% CI 0.074–0.422; p = 0.001).

Conclusions: In this study of 247 cases of pT1−2 infiltrating breast carcinomas, high preoperative CA15.3 levels correlate with large size tumors and the presence of lymph node metastases and suggest that this antigen could be possibly used as a complementary prognostic marker.

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TNBC Has Disproportionately Poor Prognosis Among AJCC Stages

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Background: Subtypes defined by clinicopathological criteria are similar to but not identical to intrinsic subtypes and represent a convenient approximation. Not only previous known prognostic factors, such as lymph node status, tumor size, and patient's age but also molecular subtypes might be some correlations with breast cancer's prognosis, especially similar stages.

Methods: 1305 women diagnosed and/or treated with invasive breast cancer during 1989–2004 at Asan Medical Center were studied. Primary endpoint (locoreginal, and distant metastasis) and secondary endpoint (OS) were evaluated using chi-square tests and Cox proportional hazards models. Breast cancer samples were categorized into molecular subtypes based on immunohistochemical profiles. Samples that were ER- or PR-positive and Her-2/neu-negative were classified as luminal A, samples that were ER- or PR-positive and Her-2/neu-positive were classified as luminal B, samples that were ER- and PR-negative and Her-2/neu positive were classified as Her-2/neu-enriched, and samples that were ER-, PR- and Her-2/neu-negative were classified as triple-negative.

Parameter	TNBC	Her-2/neu	Luminal A	Luminal B	*p*-value
Number	256(19.6)	220(16.9)	564 (43.2)	265 (20.3)	
Tumor size (mm)	27.0 (±19.7)	32.6 (±23.4)	27.2 (±17.2)	24.9 (±12.4)	<0.001
Age(years)					<0.001
<35	40(15.6)	19(8.6)	36(6.4)	26(9.8)	
35−49	143(55.9)	110(50.0)	361(64.0)	151(57.0)	
>50	73(28.5)	91(41.4)	167(29.6)	88(33.2)	
Stage					<0.002
I	84(32.8)	72(32.7)	178(31.6)	83(31.3)	
II	155 (60.5)	111 (50.5)	343 (60.8)	148 (55.8)	
III	13 (5.1)	32 (14.5)	40 (7.1)	32 (12.1)	
IV	4 (1.6)	5 (2.3)	3 (0.5)	2 (0.8)	
p53					<0.006
−	135 (52.9)	90 (40.9)	492 (87.4)	199 (76.0)	
+	120 (47.1)	130 (59.1)	71(12.6)	63(24.0)	
Type					0.01
IDC	254 (99.2)	219 (99.5)	545 (96.6)	260 (98.1)	
ILC	2 (0.8)	0	19 (3.4)	5 (1.9)	
Others	0	1 (0.5)	0	0	
Chemotherapy					<0.001
no	25 (9.8)	31 (14.1)	203 (36.4)	93 (35.4)	
yes	229 (90.2)	189 (85.9)	354 (63.4)	170 (64.6)	
unknown					
OP					<0.001
BCO	79 (30.9)	31 (14.1)	148 (26.2)	45 (17.0)	
MRM	177 (69.1)	189 (85.9)	416 (73.8)	220 (83.0)	
LN					<0.021
(−)	158 (62.5)	120 (55.6)	286 (51.7)	131 (50.8)	
(+)	95 (37.5)	96 (44.4)	267 (48.3)	127 (49.2)	

Results: Triple negative breast cancer was 256 patients (19.6%), luminal A; 564 (43.2%), Her-2/neu positive breast cancer 220 (16.9%), and luminal B 265 (20.3%) (Table 1). Median follow up was 60months, triple negative breast cancer carried worse prognosis than other typed breast cancer before 3 years but it was so disproportionately represented among each stages after 3 years, and luminal A breast cancers were better survival than other typed breast cancer every stages Triple negative breast cancer carries a poor prognosis so is disproportionately represented among all stages. On multivariate survival analyses, AJCC stage, lymph node status, and breast cancer subtypes were independent prognostic factors.

Conclusion: Breast cancer subtypes have heterogenous effects on disease free survuval in a silimar stage, but disproportionately among all stages. Her-2/neu positive and triple negative breast cancer are seem to be independent prognostic factors in a limited sized analysis.

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Immunohistochemical P53 Over-expression and Hormonal Therapy Benefit in Invasive Breast Cancer

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Purpose: To confirm prognostic and predictive values of immunohistochemical p53 accumulation, we analyzed the prognostic role of p53, particularly in invasive breast cancer patients according to the intrinsic subtypes by hormone receptor and HER2 status.

Materials and Methods: Data about p53 immunohistochemistry results along with estrogen receptor (ER), progesterone receptor (PgR), and HER2 of 60 hospitals' own patients were retrospectively retrieved from web-based database of Korean Breast Cancer Society (KBCS). A total of 15,598 patients diagnosed between 1997 and 2004 were enrolled in this analysis. The chi square test was used to determine the differences in variables between pairs of groups. Overall survival (OS) and breast cancer specific survival (BCSS) were estimated by the Kaplan-Meier method. Log-rank tests were used for the comparison of survival curves. Multivariate analyses were performed using stratified Cox's proportional hazard regression model. A model with interaction terms of p53 by both hormonal therapy and chemotherapy was evaluated to determine the treatment benefit from both modalities.

Results: Immunohistochemical p53 over-expression was statistically associated with advanced pathological stage; higher tumor grade; hormone receptor (HR) negativity; and HER2 positivity. The median follow-up for this cohort of patients was 53 months. The 5-year OS was 88.0% for positive p53 patients, and 91.3% for negative p53 patients ($P < 0.0001$). The 5-year BCSS was 88.5% for positive p53 patients, and 91.8% for negative p53 patients ($P < 0.0001$). In a multivariate analysis, p53 over-expression was a weak but independent prognostic factor (Hazard ratio (HR) = 1.17; 95% CI, 1.01–1.34 for OS and HR = 1.39; 95% CI, 1.12–1.73 for BCSS). Its poor prognostic value was prominently valid in the luminal A (HR+ and HER2−) subtype for OS and BCSS with a hazard ratio of 1.44 (95% CI, 1.08–1.93) and of 1.47 (95% CI, 1.09–1.99) respectively, compared to those in the other subtypes. The hazard ratios of p53 over-expression for OS/BCSS were 1.27 (95% CI, 0.98–1.66)/1.26 (95% CI, 0.96–1.65), 1.25 (95% CI, 0.96–1.60)/1.21 (95% CI, 0.94–1.57), and 0.94 (95% CI, 0.73–1.20)/0.92 (95% CI, 0.71–1.18) in luminal B (HR+ and HER2−), HER2 over-expressing, and basal-like subtype, respectively. The model with interaction terms revealed that hormonal therapy has a significant interaction with p53 status (p = 0.002 and 0.007 for OS and BCSS, respectively), resulting in insignificant prognostic value of p53 status (p = 0.268 and 0.296 for OS and BCSS, respectively). The interaction between chemotherapy and p53 status was not found in this model.

Conclusions: Immunohistochemical p53 over-expression has an independent prognostic value, especially in luminal A invasive breast cancer, most likely caused by differential treatment benefits from hormonal therapy according to the immunohistochemical p53 status.

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Clinical Dilemmas in Bilateral Breast Cancer

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Background: Women with breast cancer are at an increased risk of bilateral breast cancer(BBC), a disease with a relatively poor prognosis. This review aims to highlight clinical difficulties in treating women with