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Identification of key breast cancer phenotypes

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Background: Breast cancer is a heterogeneous disease, of which several forms have been identified on the basis of their gene expression characteristics. However, translation of this molecular genetic approach into routine clinical practice remains elusive or prohibitively expensive. We have previously demonstrated that protein expression characteristics can be used to identify comparable classes. In this study, we extend this approach and further define the key criteria for class membership.

Material and Methods: Expression of twenty-five proteins, with known relevance to breast cancer, have been assessed in a series of 1,076 patients. This large data set has been examined by four alternative data clustering techniques [Hierarchical, K-means (KM), Partitioning around medoids (PAM), Adaptive resonance theory (ART)]. Concordance between techniques was used to elucidate 'core classes' of patients which could be well characterised.

Results: A total of 663 (62%) of the 1076 patients were assigned to six core classes, while 413 (38%) patients were of indeterminate or mixed class. Three core classes correspond to well known clinical phenotypes (luminal A, luminal B and HER2). Two classes correspond to the well known basal phenotype, but exhibit a novel differentiation into two sub-groups. The last class appears to characterise a novel luminal subgroup.

Conclusions: Key clinical phenotypes of breast cancer can be identified using standard, widely available immunocytochemistry technology. The main luminal and basal breast cancer phenotypes appear to be heterogeneous, containing distinct sub-groups. The six clinical phenotypes determined in this study are a new luminal group, luminal N, the new basal sub-groups, basal p53 altered and basal p53 normal, as well as the previously well-established luminal A, luminal B and HER2 groups.

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High expression of p130Cas/BCAR1 significantly associated with early relapse in hormone receptor positive, axillary node positive breast cancer patients

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Background: Tamoxifen is a still major drug to reduce the risk of recurrence and to prolong the survival of receptor positive breast cancer patients. Even if most patients benefit from tamoxifen, many tumors become resistant. The adhesion-associated molecule p130Cas/BCAR1 is known to promote resistance to tamoxifen. We have studied the expression of mRNA and protein by RT-PCR and immunohistochemical (IHC) staining about BCAR1 and correlation with early relapse in node positive, hormone positive breast cancer patients.

Materials and Methods: We have conducted this study in both retrospective and prospective ways. Retrospectively collected 87 tumors, 61 tumors from disease free patients more than 2 years of tamoxifen and 26 tumors from who showed recurrence within 2 years, were analyzed by IHC expression of EGFR1, Her-2/neu, p53 and BCAR1. BCAR1 was the only one significantly related with early relapse (Odds ratio:4.08, p = 0.0056). Then, prospective study was designed with consecutive 190 node positive, hormone positive breast cancer patients from October 2001 through December 2005. All patients received standard operations, adjuvant or neo-adjuvant chemotherapy, with or without radiation therapy and followed by tamoxifen therapy. The expression of BCAR1 mRNA was checked by semi-quantitative RT-PCR in peripheral blood sample and evaluated with protein expression by IHC staining of primary tumor. We also analyzed correlation between the expression of BCAR1 and clinicopathologic parameters and early relapse.

Results: Mean follow up time was 32 months and 16 recurrences developed. The expression of BCAR1 mRNA in peripheral blood and IHC staining of primary tumor was significantly correlated (p = 0.044). The patients who had higher expression of BCAR1 mRNA showed poorer outcome of disease-free survival (p = 0.0001) than those of non-detectable or weak expression. The patients who had strongly positive estrogen receptor and weak expression of BCAR1 mRNA showed the best outcome of disease-free survival (p = 0.0001) in multivariate analysis.

Conclusions: High expression of p130Cas/BCAR1 significantly associated with early relapse in hormone receptor positive, axillary node positive breast cancer patients.

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Clinicopathologic characteristics of triple negative breast cancer in early stages

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Background: Triple negative breast cancer (estrogen receptor-negative, progesterone receptor-negative, and c-erb B2 receptor-negative) is associated with high risk of recurrence and poor clinical outcome. Clinicopathologic characteristics of triple negative breast cancer is important to prediction of prognosis and decision of treatment guideline. We investigated the characteristics of triple negative breast cancer in early stages.

Materials and Methods: We reviewed the records of 821 early stage (stage I and II) breast cancer patients who treated at our hospital from 1995 to 2005. We examined difference between triple negative group compared with non triple negative group in relation to clinicopathologic characteristics.

Results: Of 821 early stage breast cancer patients, 200 cases (24.4%) were of triple negative group. The mean age of triple negative group was 47.9 and non triple negative group was 48.9. Both histologic grade and nuclear grade of triple negative group were significantly higher than those of non triple negative group (p = 0.000). Large tumors (T2 and T3) in triple negative group were significantly more than those in non triple negative group (p = 0.042), but there was no significant difference in lymph node involvement between two groups (p = 0.933). As of May 2007, with a median follow-up time of 50 months, there have been 50 local recurrences, 98 distant metastases, and 65 deaths. There were significant high rates of local recurrence (n = 21, 10.5%) and death (n = 25, 12.8%) in triple negative group (p = 0.006, p = 0.010 respectively).

Conclusions: Patients classified as triple negative breast cancer have poor pathologic findings and prognoses. Careful treatment and follow-up is important to triple negative breast cancer in early stages and further investigation is necessary to triple negative breast cancer.

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HER-2 overexpression does not decrease survival of breast cancer patients with brain metastases

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Background: HER-2 positivity is an increasingly recognized risk factor for development of brain metastases (BM). Approximately 10−30% with HER-2 overexpression will present BM, according to recent studies. There are not enough sufficient data on correlation between HER-2 positivity and survival of patients presenting BM. Overall survival and post-radiotherapy survival were analyzed in presented study.

Material and Method: HER-2 overexpression reported in 35% of cases between 31 breast cancer patients treated recently with radiotherapy due to BM in Krakow Cancer Institute. Whole-brain radiotherapy technique with total dose ranging from 20 to 40 Gy was used.

Results: No significant differences in overall survival (p = 0.1138) and post-radiotherapy survival (p = 0.3279) were detected between HER-2 positive (60 months and respectively 7.1 months) and negative groups (45 months and respectively 6.1 months).

Conclusion: HER-2 positivity is a known risk factor for BM development in breast cancer patients but does not affect survival among patients with detected and irradiated BM.

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Proliferation rate, microvessel density, expressions of HER-2, hormone receptors and P53 protein as predictors of tumour response to adjuvant anthracycline treatment in breast cancer patients

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Background: Among breast cancer (T1−T2, N1−N2, M0) patients treated radically with surgery and adjuvant chemotherapy based on anthracyclines, in about 60% of woman local recurrence is observed. These differences in treatment outcome indicate the need to identify biological markers of

probability of patients' disease free survival (DFS). The aim of this study was to assess the influence of tumours proliferation rate, microvessel density (MVD), expression of HER-2, oestrogen (ER) and progesterone (PR) receptors and P53 protein on 5-year DFS in the group of breast cancer patients treated radically with surgery and adjuvant chemotherapy with anthracyclines.

Material and Methods: The study was performed in the group of 94 breast cancer patients (mean age: 50.5 years; range: 27−69). Proliferation rate (labelling index of Ki-67 – Ki-67LI), MVD (CD34 antibody) and expressions of HER-2, ER, PR and P53 protein were studied immunohistochemically before treatment. These data were correlated with DFS estimated by Kaplan–Meier method.

Results: Among 94 tumours, 83.9% were positive for ER, 82.8% expressed PR and in 48.0% expression of HER-2 was detected. The mean values of Ki-67LI, P53LI and MVD were 23.0%±1.3 (SE), 10.1%±3.4 and 156.0 vessels/mm^2 ±6.6, respectively. All women (n = 13) with tumours characterized by positive expression of ER and higher proliferation rate (optimal cut off point Ki-67LI >16.5%) survived 5 years without any evidence of cancer, whereas for patients having slower proliferating tumours and without oestrogen expression DFS was significantly lower (40.0%; p = 0.003). No other significant relation was found between the assessed biological parameters and DFS.

Conclusion: The data presented here indicate that on the basis of oestrogen status and tumour proliferation rate we are able to identify breast cancer patients without risk of cancer progression during 5 years after completing of anthracycline treatment.

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Differences in outcome of young breast cancer patients according to BRCA1 mutation status

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Purpose: To investigate the clinical characteristic and outcomes of younger (<50 years old) breast cancer patients with BRCA1 mutation in comparison to patients without this germline mutation.

Methods and Materials: This is an ongoing study and patients will be enrolled till end of 2008. Till now we followed 495 breast cancer patients who were diagnosed before age 50 and were asked to provide a blood sample for BRCA1 mutation screening (5382insC, 300T/G, 185delAG, and 4153delA). We compared contralateral breast cancer and ovarian cancer incidence, disease free, metastases free, and overall survival, between BRCA1 mutation carriers and non-carriers.

Results: BRCA1 mutations were detected in 90 breast cancer patients; the remaining 405 women did not carry the mutation. BRCA1 related tumours showed higher grade, more frequent negative oestrogen, progesterone, HER2 receptor status. Patients with BRCA1 mutation had a higher incidence of bilateral breast and ovarian cancer. Multivariate Cox analysis for DFS (local-regional and distant failure) showed that node ratio >13%, tumour diameter, age >44 years and BRCA1 mutation negative patients significantly decreased DFS.

Conclusions: Patients with BRCA1 mutations have higher incidence of bilateral breast and ovarian cancer which imposes the need for frequent and careful follow-up after therapy. Node ratio and tumour diameter are the strongest prognostic factors. A final conclusion will require more patients and longer follow up.

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Prognostic factors influencing on the distant relapse in axillary lymph node negative breast cancer in Korea

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Background: The axillary lymph node metastasis is one of the most important prognostic factors in breast cancer. The auther's reports are differences that the clinical or pathological factors influence on the systemic recurrence and survival in axillary lymph node negative breast cancer. Thus, we have attempted to determine the prognostic factors influence on the systemic recurrence in axillary lymph node negative breast cancer.

Materials and Methods: We reviewed the data of 1814 patients, who underwent curative surgery at Asan Medical Center, from January, 1992 to December, 2002, to determine the the prognostic factors such as age, sex, BMI, family history, operation method, size, stage, histological grade, number of resected lymph nodes, ER, PR, overexpression of c-erbB-2 and p53, adjuvant therapy, that influence on the systemic recurrence and 10 years distant relapse free survival.

Result: Systemic recurrence occurred 75 patients (4.1%) while 53.3 months median follow up period. The recurrence organ were lung 44 patients (58.7%), bone 39 patients (52.0%), liver 18patients (24.0%), brain 5 patients (6.7%) and multiple systemic recurrence patients were 29 patients (38.7%). The sex (female 4.0%; male 18.2%, p = 0.019), operation method (mastectomy 4.7%; BCS 2.6%, p = 0.047), size of tumor (T1 2.9%; T2 5.4%; T3 14.3%, p = 0.001), stage (stage I 2.8%; stage II 5.9%; stage III 16.7%, p = 0.001), ER (negative 5.4%; positive 3.1%, p = 0.017), PR (negative 5.6%; positive 2.5%, p = 0.001), overexpression of p53 (negative 1.9%; positive 5.3%, p = 0.001), bilateral breast cancer (ipsilateral 4.0%; bilateral 25.0%, p < 0.001) were statistical significances of the factors that influence on the systemic recurrence. The factors that size of tumor (T1 85.5%; T2 86.8%; T3 78.7%, p = 0.008), stage (stage I 89.0% stage II 85.6% stage III 80.0%, p = 0.005), ER (negative 82.5%, positive 89.6%, p = 0.035), PR (negative 78.4%, positive 91.5%, p = 0.001), differentiation grade (grade I 95.1%, II/III 84.4%, p = 0.015), bilateral breast cancer (ipsilateral 87.9%, bilateral 44.4%, p < 0.001) had statistical significances of the factors that 10 years distant relapse free survival.

Conclusion: Our study showed that the patient's sex, size, hormonal receptor, histological grade and bilateral breast cancer had significance as prognostic factors influencing on the distant relapse in axillary lymph node negative breast cancer.

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Prognosis effect of the pregnancy after breast cancer

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Background: Hormonal changes associated with pregnancy may worsen the outcome of breast cancer. However, prior studies have failed to detect this effect, which may be explained by a selection bias of the patients who had a full term pregnancy.

Aim: Assess the effects of pregnancy on the outcome of breast cancer in young patients.

Subjects: One hundred twenty-two young patients (<35 years) with breast cancer treated consecutively at our hospital between 1995 and 2005. Pregnancy was discouraged during the first two years, but not specific recommendation was given thereafter.

Methods: We compared the prognostic factors, treatment with adjuvant chemotherapy and follow-up of patients with pregnancy (P) vs. those who have not had subsequent pregnancy (NP).

Results: There were 17 patients that get pregnant (13%). Of them, eight (47%) decided to interrupt pregnancy, and nine (53%) gave birth to the term. Among those who decided to continue their pregnancy, one that had not knowledge of her pregnancy received tamoxifen until the second trimester. The average time between diagnosis of cancer and pregnancy was three years. Several prognostic factors, such as age (median age P31.47 years old NP31.66 years old), histological type (CDI in P82.4% NP84.6%), lymphovascular invasion (P11.8%, NP 13.1%) clinical stage (P: 0 5.9%, I 29.4%, IIA 52.9%, IIIA 11.8%; NP: 0 9.8%, I 25.5%, IIA 33.3%, IIB 15.7%, IIA 11.8%, IIIA 8.8%, IIIB 5.9%, IV 1%), overexpression of HER-2 (P36.4% NP23.4%) and use of adjuvant chemotherapy (P82.4% NP87.4%) were similar among pregnant and non-pregnant women with differences who were not statistical significance. However, hormone receptors were positive at a greater rate in patients without later gestation (P35.7% NP63.7%, vs p = 0.04). Patients with pregnancy had better disease-free interval at 5 years (P94% vs. NP67% p = 0.01) and overall 5 years survival (P100% vs. NP82% p = 0.03).

Conclusions: A significant proportion of patients diagnosed of breast cancer at young age get pregnant, many of them unwillingly. Although, pregnancy does not seem to worsen outcome, the risks of pregnancy are not completely known. Taking to account that the 53% of the pregnancies are obviously not desired, continuous contraceptive counselling should be given to patients with breast cancer at reproductive age.