142 Poster

Prognostic effect of serum 25-hydroxyvitamin D levels in breast cancer patients

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Background: There is increasing evidence that vitamin D has been linked to breast cancer risk, but prognosis effect are unknown. We investigated the possible association between vitamin D and breast cancer prognosis by comparing serum vitamin D level.

Materials and Methods: From June to December 2006, serum 25 OHD were measured in 310 Korean women with breast cancer at the Asan Medical Center. Clinical, Pathologic, and dietary data were accessed to examine prognostic effects of serum 25 OHD.

Results: Mean age was 48.7 years, mean serum 25OHD was 31.4±16.1 ng/ml. 25OHD levels were deficient (<20 ng/ml) in 24.2%, insufficient (20−29 ng/ml) in 30.6%, and sufficient (30–150 ng/ml) in 24.0%. Mean follow up was 30 months: 31 had recurrences. Women with deficient 25 OHD levels had an increased risk of recurrence (HR = 2.93; 95% CI = 1.27 to 6.77) compared with those with sufficient levels. 25OHD levels were inversely associated with prognosis of hormone receptor positive tumors, but not with hormone receptor negative tumors (HR = 5.73; 95% CI =1.82 to 18.06 for hormone receptor positive tumor, HR = 1.142; 95% CI = 0.33 to 3.92 for hormone receptor negative tumor). The association remained after individual adjustment for age, tumor size, nodal status, estrogen receptor status (HR = 4.13; 95% CI = 1.77 to 9.61).

Conclusions: Vitamin D deficiency may be associated with poor outcomes in hormone receptor positive breast cancer patients.

143 Poster

The prediction of lymph node metastasis in ductal carcinoma in situ with microinvasion by assessing lymphangiogenesis

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Background: The reported incidence of ductal carcinoma in situ with microinvasion (DCISM) is 5%-10% of breast cancer and the presence of axillary lymph node metastasis in DCISM is variable (0%-14%). To ascertain the role of lymphangiogenesis in lymph node metastasis in DCISM, we compared the lymphatic vessel density with the presence of lymph node metastasis in a group of patients that underwent axillary dissection with breast surgery due to DCISM.

Material and Methods: We identified 46 patients with a diagnosis of DCISM who underwent breast surgery with axillary dissection to evaluate lymph node status from June 1996 to March 2008. The number for blood vessel density (BVD) and lymphatic vessel density (LVD) was counted by immunohistochemical staining with two markers, CD34 for angiogenesis, and D2−40 specific for lymphatic vessels.

Results: LVD was lower than BVD in both metastatic and non-metastatic groups. LVD of the patients with lymph node metastasis was significantly higher than that of the patients without lymph node metastasis ($p = 0.04$). However, BVD bore no relation with lymph node metastasis. Correlation in the total score of progesterone receptor (PR) and LN metastasis was also noted ($p = 0.017$). There was no statistically significant relation between LVD and clinicopathologic parameters such as size and type of underlying DCIS, nuclear grade, presence of lymphovascular invasion, estrogen receptor (ER), PR, and HER-2 status.

Conclusion: Lymphangiogenesis may be significantly associated with lymph node metastasis in DCISM. This is the first attempt to predict axillary lymph node metastasis in DCISM by quantifying the LVD.

144 Poster

The cell cycle profile (C2P) test is a prognostic indicator for breast cancer patients treated with postoperative 5-fluorouracil-based chemotherapy

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Background: Our previous study has suggested that the novel cell cycle profile (C2P) test is an independent prognostic indicator for early breast cancer patients. To further clarify prognostic value of the C2P test, we apply this test to breast cancer patients treated with postoperative 5-fluorouracil (FU)-based chemotherapy.

Patients and Methods: A total of 153 breast cancer patients, who were treated with postoperative adjuvant 5-FU-based chemotherapies such as CMF (cyclophosphamide, methotrexate, 5-FU) therapy or oral 5-FU derivative therapy between 1990 and 2003 in our institute, and whose tumor samples were stored in our tumor bank, were randomly selected as the study subjects. Endocrine therapy was also given in 113 (74%) of them. Because eight patients with hormone receptor-negative tumors received endocrine therapy, they were excluded in the final analysis. Specific activities of cyclin-dependent kinase (CDK) 1 and CDK2 were measured and analyzed as previously described (Ann Oncol 19:68−72, 2008). Patients were divided into three categories (low, intermediate or high risk) based on the C2P analysis. Protocol of this study was approved by the Institutional Review Board of Kawasaki Medical School.

Results: Median age was 53 years (22−83); 71% had stage? disease; 67% received modified radical mastectomy; 98% were diagnosed as invasive ductal carcinomas; and 59% were node-positive. Positive rates for estrogen receptor (ER)-and progesterone receptor (PgR) were 66% and 59%, respectively. The proportions of the C2P categories were 39% for low risk, 10% for intermediate risk and 45% for high risk, respectively. Because of blood contamination into tumor samples and undetectable protein concentration of CDK1 or CDK2, the C2P test was not completed in 8 (5%). Univariate analyses for disease-free survival (DFS) revealed that the C2P categories were not significant prognostic factors in overall patients tested. However, they were significant prognostic factors in a subgroup of 105 patients with less than three involved nodes. Multivariate analyses for DFS also indicated that a C2P parameter (high risk versus low risk) was an independent prognostic indicator from the number of involved nodes and clinical stage in the subgroup ($P = 0.020$). Interestingly, prognostic power of the C2P test was stronger in 80 patients treated with oral 5-FU derivatives.

Conclusions: The C2P test is an independent prognostic indicator in breast cancer patients with less than three involved nodes treated with adjuvant 5-FU-based chemotherapy. This suggests that the C2P test may be useful for predicting patients with a high risk of recurrence who should be treated with stronger adjuvant chemotherapy such as anthracycline-based chemotherapies. Further clinical studies are needed to clarify the prognostic and predictive values of the C2P test.

145 Poster

A rescoring of Elston-Ellis Grade improves prognostic discrimination and consistency

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Grading by the method of Elston-Ellis has gained wide acceptance. It is semi-objective, scoring 1−3 for each of Tubule Formation, Pleomorphism and Mitoses (TPM). These are added: tumours scoring 3−5 are Grade (G) 1, 6−7 G2 and 8−9 G3.

Rationale: Both prognostic discrimination and consistency should be improved by using the scores to give more Grades.

Method: The ONCOPOOL data set of primary operable (⩽5 cm) invasive breast cancers, age ⩽70 and entered in 1990–1999, compiled in 12 European Breast Units. Only 5 Units recorded T, P and M on all cases and their data have been used for the study.

Results: A Cox multivariate analysis of all cases for survival showed that P was no longer significant and P was withdrawn from the analysis. M and T gained similar beta values.

Using only T and M, each scoring 1−3 gives 5 'New' Grades (scored 2−6). Overall % 10-year survival is in rank order: G1 (includes 8% of cases) 90±2, G2 (18%) 88±1, G3 (26%) 77±1, G4 (18%) 65±1, G5 (30%) 60±3.

'Old' Grade has only 3 grades separating to 91%, 82% and 62% survival. Discrimination of survival prospect is improved.

Consistency between units is hugely improved (Table 1).

Table 1

Unit	'New' Grade T + M (%)					'Old' Grade (%)		
	1	2	3	4	5	1	2	3
1	7	18	26	18	32	19	36	46
8	6	16	27	18	34	38	42	19
11	4	18	25	21	30	19	27	53
7	14	21	26	20	18	43	24	22
Range	4−14	16−21	25−27	18−21	18−34	19−43	24−42	19−53

Conclusion:

- Increasing the number of Grades hugely improves consistency
- Using 5 rather than 3 Grades gives improved discrimination in assessment of survival prospects.
- An additional benefit is that pleomorphism, which is subjectively scored and difficult for pathologists to estimate, is no longer required.