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Characteristics of Non-invasive Ductal Carcinoma of the Breast

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Background: It is important for survivors of breast carcinoma, who hope to become pregnant in the future, to determine if adjuvant hormonal therapy is necessary even when diagnosed with non-invasive ductal carcinoma (DCIS). Pathological characteristics of DCIS have been reported in Europe and the United States, but not in Japan where the population of breast cancer patients is younger and more often hormonal receptor positive, and whose contralateral breast carcinoma event (CBTR). Our study was intended to determine clinicopathological characteristics of non-invasive carcinoma in Japanese patients.

Materials and Methods: Of 5,731 patients who underwent breast resections in our facility from 1993 to 2008, 400 (6.9%) were diagnosed pathologically with DCIS or micro-invasive ductal carcinoma <5 mm. Clinicopathological characteristics retrospectively analyzed for 368 (6.4%) patients included age, menstruation, body mass index (BMI), family history, bilateral carcinoma, size, type, structural atypia, nuclear atypia, mitotic count, necrosis, hormonal receptor (HR) and HER2-neu subtypes, surgical method, ispilateral event (IBTR), CBTR and distant recurrence.

Results: Partial mastectomies were performed on 146 patients (39.7%) (Group PM) and 222 patients (60.3%) underwent total mastectomies (Group TM). There were six cases of IBTR (4.1%) and 17 cases of CBTR (4.6%) among all 368 patients. With respect to univariate analysis of IBTR cases, there were significant differences in age (<40 years; $p = 0.04$) and margin (<1 mm; $p = 0.002$). As for multivariate analysis, there was a significant difference in margin (<1 mm; odds ratio [OR]: $8.6x10^6$, 95% confidence index [CI]: 2.15-; $p = 0.01$). Among the PM Group, there were no significant differences between hormonal therapy and radiation therapy while in stratification for age (<40), BMI and margin (<1 mm) were significantly different in (Group PM. Significant differences with univariate analysis for CBTR cases included type (non-comedo; $p = 0.002$), necrosis (negative; $p = 0.03$), size (>1.3cm: $p = 0.06$) and nuclear grade (NG1; $p = 0.07$). In terms of multivariate analysis, there was a significant difference in type (non-comedo; OR: $10.9x10^7$, 95% CI 6.53-; $p = 0.007$).

Conclusions: Our findings indicate that there are different risk factors for IBTR and CBTR events and the risk for CBTR events may depend on unknown factors that keep a widespread non-invasive ductal carcinoma both low grade and without invasion.

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Flat Epithelial Atypia: Its Management and Outcome in Four Dutch Teaching Hospitals

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Background: Flat Epithelial Atypia (FEA) is a presumably neoplastic alteration of terminal duct-lobular units, characterized by the replacement of native luminal epithelium by ductal cells demonstrating low-grade cytologic atypia. The architecture shows stratification of epithelial cells. FEA is often accompanied by microcalcifications and therefore discovered in biopsies following screening mammography. FEA is frequently seen in association with ADH, DCIS, lobular neoplasia and invasive tubular carcinomas. There is emerging evidence suggesting FEA may represent a precursor to DCIS. The risk of subsequent breast carcinoma remains to be defined. The aim of this study is therefore to inventorise the management and outcome of solitary FEA in histological biopsies in four Dutch teaching hospitals.

Materials and Methods: Data of this retrospective multicentre study were collected in a database. Local pathology databases were screened with the terms: 'FEA', 'Flat Epithelial Atypia', 'columnar atypia' and Dutch equivalents. Results were manually screened, only including solitary FEA. Patient files were viewed for information on presentation, mammography, ultrasound and management: surgery vs follow-up. In case of excision, definitive pathology was added.

Results: The search resulted in 184 cases, of which 78 solitary FEA. The management of these patients consisted of follow-up for 45 patients (58%) and lumpectomy (n = 76) or mastectomy (n = 2) for 33 (42%). No incidents occurred in the follow-up group so far. Definitive pathology of excision showed no abnormalities or solitary FEA in 19 patients; other findings were ADH in 6, LCIS in 3 and DCIS in 6 patients. Invasive disease (ID) was found in 3 patients. Reason for choosing mastectomy was contralateral malignant disease; definitive pathology showed no abnormalities.

Conclusions: No consistent management exists concerning solitary FEA. DCIS or ID was discovered in 18% of all surgical patients. Therefore, FEA can be seen as a red flag, indicating the possible presence of a more malignant lesion. Also, one hospital used the diagnosis of FEA inconsistently and interchangingly with other terms. A shortcoming of this study is the retrospective gathering of data, which hampers the identification of reasons for chosen management. Additional research is warranted, preferably as a multicentre randomized controlled trial comparing surgery vs follow-up.

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Are Bilateral Breast Cancers Different From Breast Cancers Coexisting with Ovarian Cancer?

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Background: Bilateral breast cancers and breast cancers coexisting with ovarian cancer are associated with genetic predisposition more frequently than sporadic cases. The aim of our study was to compare the morphological and immunohistochemical characteristics of bilateral breast cancers and breast cancers coexisting with ovarian cancer.

Materials and Methods: Tumor morphology and expression of 6 immunohistochemical markers was assessed in a tissue microarray (TMA) containing cores from 174 tumors from patients with bilateral breast cancer (B), 23 breast tumors from patients with breast-ovarian cancer syndrome (O) and 2 breast tumors from patients with coexisting ovarian and bilateral breast cancer (BO). Markers analyzed included hormone receptors (ER, PgR), HER2, CK 5/6, E-cadherin and vimentin.

Results: Majority of tumors in all subgrous (B, O, BO) were invasive ductal cancers (83,3%, 91,3%, 100%). Grade 3 tumors were more common in O (60,9%), compared to B (35,6%). 82,6% of O and 58,6% of B had no intraductal component; extensive intraductal component was present in 25,3% of B and in none in O. Strong ER and PgR expression was present in 72,8% and 56,1% of B, and 55% and 36,4% of O, respectively. HER2 was overexpressed (3+) in 18,2% and 4,8% of B and O, respectively. 6% and 15,8% of B and O had triple negative phenotype. Strong expression of CK5/6 (>10% of cells) was present in 47,6% of O and 19,1% of B, no expression was found in 51,6% of B and 28,6% of O. Weak expression of vimentin (<1% of cells) was present in 69,2% of B and 33,3% of O. No differences in E-cadherin expression were identified between subgroups.

Conclusion: Breast cancer tumors from patients with breast-ovarian cancer syndrome are characterized by higher incidence of high grade, ER, PgR and HER2 negativity, strong expression of CK5/6 and lower incidence of intraductal component compared to with bilateral breast cancers.

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Clinicopathological Pattern and Prognostic Influence of Neuroendocrine Differentiation in Breast Carcinomas

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Background/Objectives: Neuroendocrine differentiation (NED) has been found and suggested as a marker of poor prognosis in a subgroup of a variety of carcinomas including a significant minority of breast carcinomas. The need to develop more effective therapies for breast cancer has led to investigations in understanding the molecular mechanisms of their differentiation process, in particular NED based on a theoretical assumption that NE-differentiated tumours may be associated with an adverse prognosis, earlier dissemination and greater chemosensitivity.

This study was designed to assess the immunohistochemical expression of NE markers, chromogranin A (CgA) and neuron specific enolase (NSE) and compared it with the histidine decarboxylase (HDC) immunohistochemistry in various subtypes of breast carcinomas in our female patients.

Material and Methods: About 225 patients (mean age 45±6 years) presenting with variable morphology, histological grades and clinical stage of the breast carcinomas during January 2006 to January 2008 were included. The patients were assessed both clinically as well as expression of ER, PR and NE markers was determined by indirect immunohistochemistry. Positive staining was asserted following the criterion proposed in previous literature. The patients were followed up clinically from the departmental record for 3 years till January 2011.

Results: The findings of our study revealed that immunohistochemical staining of the histological tissue sections of 10.2%, 7.4% and 15.1% breast carcinomas demonstrated focal areas with mild to strong cytoplasmic staining of the tumour cells by CgA, NSE and HDC respectively. Individual subtypes when assessed revealed that most of the ductal carcinomas stained positively and strongly than other varieties. Our findings also depicted that HDC expression in detecting the NE foci in breast carcinomas was stronger and more sensitive than CgA and NSE ($P = 0.0063$) and that too even in PD tumours of which 8.2% were strongly positive as compared to CgA (2.0) and NSE (1.3%) ($P < 0.001$). No significant association was found between the NED of breast carcinomas and clinico-pathological or hormonal receptor status of the patients. As per the follow-up record of 3 years, either univariately nor taking account of various known prognostic factors, does focal NED appear to carry a special prognostic significance as disease recurrence occurred locally in 01 patient and distant metastases was found in none.

Conclusion: Out results suggest that NED, though present in breast carcinomas, particularly of ductal type, may characterize a subgroup of these tumours with no significant impact on patient prognosis. However, more perspective analyses with prolonged follow up should be carried out in our female patients to assess these NE differentiated carcinomas in terms of their prognostic implication and therapeutic choices.

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Impact in the Management of Patients After Pathology Second Opinion in Breast Cancer

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Background: A second opinion in pathology may be requested by clinicians, when a patient is referred from another hospital for diagnosis and treatment. In patients with breast cancer, the pathology report contains valuable information about the diagnosis, but also related to prognosis and therapeutic response. We report the experience with second opinion in breast pathology, in selected patients consulting the Breast Oncology Unit at our institution.

Materials and Methods: Two hundred and four cases referred to the Breast Oncology Unit were selected for second opinion after clinical evaluation, between 2002 and 2011. The cases reviewed included 92 core needle biopsies, 98 surgical biopsies, and 14 fine needle aspiration cytologies. A case was classified as major change in second opinion when the findings had the potential for significant change in treatment or prognosis. A case was considered to represent minor change, when these did not alter significantly the treatment or prognosis.

Results: Concordant results were found in 162 (79.4%) diagnoses. In 42 cases (20.5%) the pathology review showed changes. Twenty-eight (13.2%) patients were classified as major changes. In 4 of this 28 patients, breast cancer metastasis diagnosed in an axillary node turned to be non mammary breast cancer (one was a melanoma, two were lung metastasis and one was a cutaneous anexal tumor). Another patient with a diagnosis of breast cancer metastasis in a brain biopsy was changed to lung metastasis to the brain and the last one diagnosed as breast cancer was changed to lung metastasis in the breast. Two patients diagnosed with breast cancer changed to benign breast lesions. In 4 patients there was a change in estrogen receptor status, three from negative to positive, and one in the opposite way. The Her2-neu status changed from positive to negative in five cases. Five patients with a diagnosis of infiltrating ductal carcinoma (IDC) turned to be carcinoma in situ (DCIS) in three, and microinvasive in two. Four patients classified as CDIS changed to IDC, and two cases changed from microinvasive carcinoma to DCIS. Fourteen patients (6.8%) had minor changes after the pathology second opinion. Most of them included changes in atypical hyperplasia to typical. Others reviews resulted in changes in progesterone receptor status that did not change treatments.

Conclusions: Second opinion in breast pathology may uncover significant discrepancies that impact in patient management and prognosis. Major discrepancies are most frequently related to the assessment of the degree of invasion of breast carcinoma and the result of immunohistochemical studies. However, the assessment of axillary lesions and distant metastasis in patients suspected of having breast cancer that may reveal non-mammary tumors, together with the diagnosis of benign proliferative lesions that simulate malignancy, may also severely affect the patient's treatment and prognosis.

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Ductal Carcinoma in Situ of the Breast − Modified Black Nuclear Grading System Revisited

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Background: This study aims to determine the pathologists agreement of modified Black nuclear grading system and Holland classification applied to cases of ductal carcinoma *in situ* (DCIS) of the breast.

Materials and Methods: Forty-three cases of breast lesions diagnosed as DCIS were selected to interobserver analysis. Twelve pathologists received the same set of digitized images from microscopy of the DCIS cases, and answered a questionnaire containing the criteria to compose the modified Black nuclear grading system and Holland classification system. In order to determine interobserver agreement and diagnostic accuracy, a web-based survey was created. It organizes the information collected from each pathologist providing the histological grading of the cases in both classification systems.

Results: The reliability for the modified Black nuclear grade applied to cases of DCIS was acceptable, with Kappa value of 0.23±0.02. Comparing the two classification systems studied, there was a similar agreement among both schemes, showing Kappa value of 0.27±0.03 for the Holland classification. Analyzing a subgroup of pathologists rated according to their interest in breast pathology, a higher diagnostic reproducibility was found for the group of breast pathology experts in relation to the pathology residents only for the modified Black nuclear grading system ($\kappa = 0.43 \pm 0.07$ vs. $\kappa = 0.11 \pm 0.05$; $p = 0.002$). The agreement among all pathologists and the gold standard pathologist similarly followed the results of the interobserver concordance, showing to be acceptable, with Kappa for the overall mode value 0.32±0.10 for both classifications. The findings of Kappa for the mode values among specialists in breast pathology and pathology residents were, respectively, 0.34±0.11 (acceptable) and 0.19±0.08 (weak) for the modified Black nuclear grade and 0.33±0.11 (acceptable) and 0.19±0.08 (weak) for Holland classification.

Conclusions: Breast pathology specialists showed greater reproducibility than pathologists not devoted to this subject for both evaluated classification systems. The diagnostic accuracy was similar for the modified Black nuclear grading system and the Holland's classification system.

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Histopathological Grading of Ductal Carcinoma in Situ of the Breast − Validation of a Web-based Survey Through Intraobserver Reproducibility Analysis

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Background: This study aims to develop a method of systematic application of the diagnostic criteria that compose the histological grades of ductal carcinoma *in situ* (DCIS) of the breast through a questionnaire available in a website, and to determinate its reliability and applicability in clinical practice.

Materials and Methods: The most important criteria to grade DCIS lesions in histopathological bases were selected to compose the point scoring system according to their relevance to three different DCIS classifications. A software was created in order to be accessed through Internet, in website format (http://mayer.art.br/cainsitu/site3). This website offers a questionnaire containing the characteristics used to compose the three DCIS classification systems evaluated in our study, and also the digitized microscopy images of 43 DCIS cases selected. Three pathologists, who are specialists in breast pathology, analyzed the same set of digitized images in this web-based survey. In the first phase, they answered a questionnaire with the characteristics used to compose the modified Black nuclear grade system and the classification systems of Holland and Van Nuys. After at least 6 months, the pathologists read again the same images, but without the help of the questionnaire, indicating subjectively the diagnoses, using the grading system of their daily practice. The intraobserver agreement analysis was used to validate this innovative web-based survey.