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Surgical resection of residual microcalcification after a diagnosis of pure flat epithelial atypia on core biopsy: a word of caution

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Background: The entity of pure flat epithelial remains a challenge due to controversy of the surgical management of residual microcalcifications after core needle biopsies. Our study aims to assess the morphological data observed in immediate surgical resection specimen of residual microcalcifications after a diagnosis of pure flat epithelial atypia on mammotome core biopsy.

Material and Method: Sixty-two mammotome core biopsy with a diagnosis of pure flat epithelial atypia (flat epithelial atypia without associated atypical ductal hyerplasia, in situ and/or invasive carcinoma) were identified. From these 62 cases, 20 presented residual microcalcifications and underwent an immediate surgical excision after mammotome.

Results: Of the 20 patients with excised microcalcifications with excised microcalcifications, 8 (40%) cases had residual pure flat epithelial atypia, 4 (20%) had atypical ductal hyperplasia, 4 (20%) had lobular in situ neoplasia, no lesion was retrieved in 4 (20%) case. None of the patients had either in situ ductal carcinoma and/or invasive carcinoma.

Conclusion: Surgical resection of residual microcalcifications after the diagnosis of pure flat epithelial atypia on core needle biopsy remains still a debate. We review the literature. The present study shows no case of n situ ductal and/or invasive carcinoma on immediate excision excision of residual microcalcifications after mammotome core biopsies.

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MRI of the breast in patients with DCIS to exclude presence of invasive disease

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Background: Ductal carcinoma in situ (DCIS) is a pre-invasive breast lesion without the ability to metastasize. DCIS can, however, be associated with presence of invasive cancer. Core biopsy has been reported to underestimate presence of invasion in up to 20% of patients with preoperatively diagnosed DCIS. The aim of the current study was to evaluate the efficacy of preoperative MRI to discriminate between patients with DCIS who are at high risk of invasive breast cancer and patients at low risk.

Methods: Patients preoperatively diagnosed with DCIS on core biopsy (absence of invasion) were prospectively included. All patients underwent contrast-enhanced MRI of both breasts prior to surgery. MRI was interpreted with respect to morphology, early and late kinetics of contrast uptake. In addition clinical, mammographic, and histological features from core biopsies were assessed. All patients underwent breast surgery (wide-local excision or ablation). Univariate and multivariate analyses were performed to identify features associated with presence of invasion in the resection specimens. Chi-square statistics and receiver-operating characteristics (ROC) analyses were employed.

Results: One-hundred-and-thirty-seven DCIS lesions in 134 patients were included. Mean age was 52.6 years (range 27−84 years). Eighty-one lesions (59.1%) showed enhancement at MRI with a type-1 curve (continuous increase) in 12 (8.8%), a type-2 curve (plateau) in 22 (16.0%) and a type-3 curve (washout) in 46 lesions (33.6%). Twenty-three lesions showed invasive cancer on final histology. The most predictive features to exclude presence of invasive disease at multivariate analysis were absence of enhancement or a type-1 curve at MRI (negative-predictive value 98.5%; area-under-the ROC-curve: 0.80, $p = 0.00002$).

Conclusions: Complementing clinical and conventional imaging parameters, contrast-uptake kinetics at MRI provide high negative-predictive value to exclude presence of invasion. The technique shows potential to facilitate selection of patients with DCIS in whom sentinel node procedures should not be considered.

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Lobular and luminal ductal invasive carcinoma of the breast − comparative molecular analysis

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Background: Invasive lobular carcinoma (ILC) of the breast is the second most frequent type of breast carcinomas. The E-cadherin inactivation is an early and characteristic molecular alteration of lobular carcinogenesis.

Material and Methods: In order to get insight the other molecular alterations of ILC, comparative genomic hybridization array and transcriptomic analyses (Affymetrix U133A+B) of series of 21 lobular carcinomas and 41 ER positive luminal invasive ductal carcinomas (IDC) were performed.

Results: ILC and IDC shared highly recurrent regions of gains of the 1q12-q44 region in more than 60% of the cases, of 16pter-p11.2 (45% and 62.7% of ILC and IDC respectively) and regions of losses on chromosomes 16q11.2-q24.2 (84.4% of ILC and 67.5% of IDC) and 17pter-p12 (50% of ILC and 49% of IDC). However, ILC genomic signature was characterised by significantly more frequent losses of the 13q21.33-q31.3 region (46.5%) and the 22q11.23-q12.1 region (50%) whereas IDC showed significantly more frequent losses of 11q23.1-q23.2 region, observed in 44% of IDC. Nine different regions of high level amplifications were found in 38% of ILC cases (8/21 cases). One region of amplification is observed in five ILC, localized on chromosome 11, (11q13.2 region) encompassing the *CCND1* and *FGF3* genes. Unsupervised hierarchical clustering of transcriptomic data showed that ILC and IDC clustered apart. Genes involved in cell adhesion, cell communication and trafficking, extra cellular matrix-interaction pathways or cell mobility contributed to this clustering. Some genes involved in chromatin maintenance were also differentially expressed between the two groups. Despite these differences, the overall outcome of ILC was identical to that of IDC.

Conclusion: This molecular study highlights that lobular and luminal ductal invasive carcinomas share common genomic alterations but that lobular carcinomas present some specific biological alterations and thus represent a distinct molecular entity. In addition, these molecular specificities should help with the identification of new therapeutic targets for ILC patients.

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Incidence of ductal carcinoma in situ: in the period before, during and after implementation of a population-based screening program

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Background: The Norwegian Breast Cancer Screening Program (NBCSP), a nationwide organised breast cancer screening program for women aged 50−69 years has gradually been implemented by county in the period 1995–2004. Studies in other countries have indicated associations between implementation of screening and increased incidence of pre-invasive breast cancer (Ductal Carcinoma *in situ*, DCIS). The aim is to study the effect of organised screening on trends in incidence of DCIS in Norway.

Material and Methods: Data were obtained from the incidence database of the Cancer Registry of Norway and the screening database of the NBCSP. All new pure primary cases of DCIS in the period 1993–2007 were retrieved as the basis of the study, $n = 3167$. Information about invitation to organised screening was given for the underlying female population, $n \approx 2.5$ mill, of which a quarter of the women have been invited to screening. The gradual implementation was utilized by restructuring the data according start-up of the NBCSP. To analyse the trends in incidence descriptive analysis and Poisson regression were used.

Results: The age-adjusted incidence of DCIS increased from 4/100 000 women-years before the implementation of organised screening (1993−4) to 11/100 000 women-years in the last period after implementation (2006−7). Correspondingly, the incidence increased from 11 to 31/100 000 women-years among women in the age-group of screening (50−69 years). After restructuring the data, a 70% increase in the incidence was seen in the pre-screening period ($p < 0.01$). After the prevalence peak at start-up of the NBCSP a further 30% increase was observed in the subsequent screening period ($p = 0.44$). The proportion of DCIS detected by screening has increased with time period, whereas 85% of the cases among women aged 50−69 years were detected by screening in the last period after implementation.

Conclusions: The incidence of DCIS has risen substantially the last decades in Norway. The implementation of organised mammography screening can be considered as the main contributor to this increase, whereas other factors such as increased focus and knowledge and new technology can be considered as co-contributors.

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Clinicopathologic characteristics of invasive lobular carcinoma of the breast: analysis of 111 cases from a Japanese single institution

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Background: Invasive lobular carcinoma (ILC) is second most common type of invasive carcinoma of the breast, however, the prognostic implication of its clinicopathologic characteristics remain controversial.

Patients and Methods: Medical records were retrospectively reviewed for patients who underwent surgery for ILC in our clinic between 1985 and 2008. We had assessed the prognostic value of clinicopathologic features such as age of patients, menopausal status, tumor size, nodal status, histologic grade, peritumoral lymphovascular invasion, ER, PgR, Ki67, p53, HER2, type of surgery, and marginal involvement of resected specimens. Univariate and multivariate analyses were performed using Cox regression model and survival rates were calculated using the Kaplan-Meier method.

Results: With a median follow-up period of 137.7 months, 111 patients with ILC (3.3% of operable breast cancers) were included in this study. All the patients with ILC were diagnosed pathologically as a classic subtype except only one patient with a pleomorphic subtype. Majority of tumors were classified as ER + and/or PgR + (83.8%), HER2 − (97.3%), lower positivity (<20%) of Ki67 (69.6%) and p53 − (78.7%). Disease free survival (DFS) and overall survival (OS) for 10 years of these patients were 78.9% and 87.2%, respectively. Multivariate analysis demonstrated that nodal status was a significant prognostic factor for DFS and OS. Hazard ratios for more than 4 + nodes vs − node were 7.39 for DFS (95% CI: 1.79–30.53; $p = 0.006$) and 10.82 for OS (95% CI: 2.53–46.27; $p = 0.001$), respectively. Out of 72 patients treated between 1999 and 2008, 42 patients (58.3%) underwent breast conserving surgery (BCS) with intraoperative margin assessment. Although additional resections for 21 patients (50%) were performed during BCS, 18 patients (42.9%) were confirmed to have marginal involvement in final pathology. However, type of surgery and marginal status (negative, close, exposed) of BCS did not affect local control, DFS and OS.

Conclusion: The results of this study revealed the following. Incidence of ILC of our clinic is lower than that of Western countries. Almost all of them are identified as a classic subtype with favorable prognostic factors. Only nodal status is a significant prognostic factor of ILC for DFS and OS. ILC is very tough to achieve complete resection even if we perform intraoperative margin assessment for BCS, however, its prognosis is favorable regardless of marginal status.

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Calcitonin-gene-related-peptide (CGRP) correlates with increased breast density, 99mTc-(V)DMSA uptake and proliferation index Ki-67, estrogen receptor status negativity and lower histological grade in mixed invasive associated with extensive in situ (IDC+DCIS), but not in pure invasive (IDC) ductal carcinomas

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Background: We evaluated the variation of calcitonin-gene-related-peptide (CGRP) expression in patients with mixed invasive with extensive in situ ductal carcinomas (IDC+DCIS) and pure IDC, in relation with the mammographic breast density (%BD), the proliferation-seeking radiotracer 99mTc-(V)DMSA uptake (scintimammographic − SMM), the proliferation index Ki-67 and the estrogen receptor (ER) status. We also assessed CGRP expression with the histological grade.

Methods: We studied retrospectively 24 women with suspicious findings on mammography who were evaluated preoperatively with 99mTc-(V)DMSA-scintimammography. Histology revealed 12 IDC (grade II: 8 and grade III: 4 patients, mean size±SD: 2.6±1.3, mean age±SD = 66.5±13.1 years) and 12 IDC+DCIS (grade II: 6 and grade III: 6 patients, DCIS-component mean size±SD: 5.3±1.8 cm, IDC-component mean size±SD: 2.5±1.1, mean age±SD = 58.5±15.1 years). Immunohistochemistry for CGRP, Ki-67 and ER status was performed in all 24 surgical specimens. BD and SMM were calculated by computer-assisted methods and were statistically correlated with CGRP expression. BD, SMM, Ki-67 and ER were statistically compared between IDC and IDC+DCIS, while CGRP, Ki-67 and ER between patients with BD >25% and <25%. CGRP was also compared (t test) with grade II and grade III in both groups.

Results: Overall positive correlation was found between BD and CGRP ($r = 0.577$, $P < 0.001$). Positive correlation was established between SMM and CGRP only in IDC+DCIS (rSMM(IDC+DCIS)–CGRP = 0.634, $P < 0.05$). CGRP and Ki-67 were significantly higher in patients with BD >25% compared to <25%BD patients ($P = 0.00008$ and $P = 0.014$, respectively). BD and SMM were significantly higher in CGRP(+) than in CGRP(−) patients as well as in IDC+DCIS compared to IDC. Ki-67 was significantly higher, whereas ER significantly lower in IDC+DCIS than in IDC. In all patients, CGRP was significantly higher in grade II as compared to grade III ($P = 0.005$). In the mixed group (IDC+DCIS) grade II cancers had also significantly higher CGRP values as compared to grade III ones ($P = 0.004$). In pure IDC, no statistical difference was found between grade II and grade III ($P = 0.4$).

Conclusions: CGRP, BD, SMM and Ki-67 were significantly increased, whereas ER significantly decreased in IDC+DCIS as compared to IDC, indicating that the IDC+DCIS is an entity more aggressive, ER-independent and possibly associated with a pathway linked to stromal involvement and CGRP activity.

Thursday, 25 March 2010 18:15–19:15

POSTER SESSION

New drug development

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Development of novel steroidal oxime-ethers for breast cancer therapy

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Background: Inhibition of aromatase, a cytochrome P450 enzyme, has become of much interest in the treatment of estrogen dependent breast cancer. A number of steroidal and nonsteroidal compounds affecting estrogen biosynthesis through the inhibition of aromatase are presently in the market for the treatment of breast cancer. However, due to the lack of highly selective, orally active, side-effect free inhibitors of this enzyme, the synthesis of more powerful and more selective and safer aromatase inhibitors continues and in the process a new series of 7-hydroximino-5-androstene derivatives have been prepared and evaluated for aromatase inhibitory activity.

Material and Methods: Reduction of dehydroepiandrostane using sodium borohydride afford 3β,17β-diol derivative, which upon subsequent acetylation with acetic anhydride afforded 3β,17β-diacetoxyandrost-5-ene. Allylic oxidation and subsequent treatment with hydroxylamine hydrochloride resulted in the formation of 7-oximino-5-androstene-3β,17β-diol diacetate. Oxime-ethers were prepared by alkylation of 7-oxime steroid using hydrochloride of requisite dialkylaminoethyl chloride, which upon alkaline hydrolysis yielded their corresponding diols. Thermal fusion of 7-[*O*-(3-chloropropyl)oximino]-5-androstene-3β,17β-diol diacetate and its corresponding diol with powdered imidazole afforded imidazole substituted steroidal oxime-ethers. The aromatase inhibitory activity of the newly synthesized oxime-ethers was determined *in vitro* using human placental microsomes and [1β, 2β-^{3}H] testosterone.

Results: The imidazolyl substituted steroidal oxime-ethers exhibited strong inhibition of the enzyme and 7-[*O*-{3-(Imidazol-1-yl)propyl}oximino]-5-androstene-3β,17β-diol diacetate was found to be 50 times more potent as compared to aminoglutethimide. The imidazole nitrogen interacts with the active site of aromatase by complexing the Fe(III) of cytochrome P450 enzyme.

Conclusion: The study concludes that incorporation of an azole group containing a suitably positioned heteroatom in the steroid nucleus, capable of binding to cytochrome P450 enzymes, such that their hetero atom coordinates to the heme iron can lead to the development of new chemical entities of therapeutic value for breast cancer therapy.