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

T. Osako[1], R. Nishimura[1], Y. Okumura[1], M. Hyashi[1], M. Mine[1], N. Arima[2]. *[1]Kumamoto City Hospital, Breast And Endocrine Surgery, Kumamoto, Japan; [2]Kumamoto City Hospital, Clinical Pathology, Kumamoto, Japan*

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

V. Papantoniou[1], P. Valsamaki[2], A. Tsaroucha[1], E. Sotiropoulou[3], S. Marinopoulos[4], A. Fothiadaki[1], T. Karianos[1], A. Archontaki[1], K. Dimitrakakis[4], A. Antsaklis[4]. *[1]Alexandra Hospital, Nuclear Medicine, Athens, Greece; [2]Pammakaristos Hospital, Nuclear Medicine, Athens, Greece; [3]Sotiria Hospital, Radiology, Athens, Greece; [4]Alexandra Hospital, Gynaecology and Obstetrics, Athens, Greece*

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.

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POSTER SESSION

New drug development

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Development of novel steroidal oxime-ethers for breast cancer therapy

S. Thota[1], S. Guleria[1], R. Bansal[1], R.W. Hartmann[2], A. Palusczak[2]. *[1]Panjab University, University Institute of Pharmaceutical Sciences, Chandigarh, India; [2]Universitat des Saarlands, Pharmazeutische und Medizinische Chemie, Saarland, Germany*

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.