though most pronounced in patients with tumors ⩽10 mm and patients with node-negative disease. Patients with an interval carcinoma diagnosed before 1997 had a better OS and BCSS, whereas patients diagnosed with interval carcinomas diagnosed between 1997 and 2001 had similar outcomes compared to patients with non-screenings-related cancers in the corresponding time period.

Conclusions: Screen-detection is an independent prognostic factor and resulted in an additional BCSS benefit of 34% beyond stage migration. Therefore, method of detection should be taken into account when selecting patients for adjuvant systemic therapy.

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A focused, PCR based gene expression signature to refine grade in breast cancer

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Nottingham grading system is used to classify breast carcinomas of different histological appearance and clinical behavior into well-differentiated (grade 1), moderately (grade 2) and poorly differentiated (grade 3) subgroups. Major limitations of this system are interobserver variability and the grade 2 group of tumors which display intermediate characteristics. Further, when considering clinical behavior and treatment options this group of breast carcinomas does not compose an uniform cluster.

Recent studies suggested that grade 2 tumors can be split into high and low grade tumors with reasonable confidence, replacing the three grades with a high and low grade tumor subtype. This has been achieved with the use of microarray analysis, which is associated with a rather high cost rendering its use in routine pathological diagnosis impractical.

The genes contained in the gene expression signatures used for grade refinement show a high level of pairwise Pearson correlation coefficients (>0.7) across several breast cancer cohorts. This suggests that most grade refining genes reflect the same biological information, therefore a few appropriately selected genes will provide the same grade associated information as the tens or hundreds of genes used in the microarray analysis.

On the basis of histological grade, we evaluated 314 invasive breast carcinomas consisting of 106 grade 1, 116 grade 2 and 91 grade 3, formalin-fixed and paraffin-embedded tissue samples. After RNA purification and reverse transciption, qRT-PCR method was able to validate the proposal of the in silico analysis. We selected 5 genes (AURKA, TOP2A, FOXM1, TPX2) that are present in grade refining signatures (Sotiriou et al. J Natl Cancer Inst. 2006, Carter et al. Nat Genet 2006) and CLDN4 which is gaining more importance considering the recently described claudin-low subtype.

We present the results of our analysis which was able to split grade 2 carcinomas into low and high genomic grade clusters, thus, making it possible to reclassify breast cancer into different prognostic groups and aid therapeutic decision making.

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Unprecedented results of a clinical validation of the dedicated and highest resolution breast PET

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Background: This work aims to evaluate the first prototype of a mini-PET ring detector (MAMMI) dedicated for early cancer diagnosis. To show the first clinical images with an unprecedented spatial resolution and increased sensitivity of the MAMMI in comparison with a whole-body PET/CT.

Methods: After a pre-clinical test period the first prototype of the MAMMI mini-PET is being validated at the Netherlands Cancer Institute in a group of patients with histologically confirmed breast cancer. Images are obtained immediately after PET/CT (GeminiTF, Eindhoven, The Netherlands). PET/CT images are acquired 60 minutes after administration of 180–240 MBq 18F-FDG with the patients positioned on a special device that allows the breasts to hang down offering their maximum volume. Subsequently to the main sequence acquired with the PET/CT 10−20 min studies (depending on breast length) are performed with the MAMMI mini-PET without the need of additional dose administration. The PET/CT study counts with attenuation correction through the CT acquisition. In contrast, the MAMMI reconstruction uses 3D MLEM (voxel size of 1 mm) and an innovative attenuation correction through breast-air binarization has been obtained. Other corrections nemaly random and scatter were also satisfactorily applied during the reconstruction process. Breast lesion 18F-FDG SUVmax and tumor/background ratios were measured on PET.

Results: The new and dedicated breast PET has demonstrated to acquire images with a spatial resolution near 1.5 mm and highest physical sensitivity for this type of detectors. The mini-PET reconstructs images using a Maximum Likelihood Expectation Maximization 3D algorithm in about 15 min for a transaxial FOV of 170 mm in diameter and 40 mm axial in one shoot. However, an expanded 2D algorithm has also been developed to reconstruct the same volume within just 1 min. The whole axial FOV varies as a function of the breast length. A reliable SUV serves the user to accurately quantify the tumor and surrounding tissue.

Conclusion: An innovative dedicated breast PET ring detector with unprecedented spatial resolution aimed for early breast cancer detection has been pre-clinically tested. A clinical validation study of this mini-PET in comparison with a whole body PET/CT device is in progress at the Netherlands Cancer Institute in order to evaluate the possible advantage of the new system when related to small breast lesions.

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Outcomes of incidentally detected breast lesions on chest CT, based on histopathologic correlation

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Background: To analyze of the histopathologic findings of incidentally detected breast lesion by chest CT scan and to predict the imaging findings of suggesting malignancy.

Materials and Methods: We retrospectively reviewed the medical records of 41 cases of breast abnormalities, detected by chest CT scan (64-detector row CT (Brilliance 64; Philips Medical Systems, Netherlands)) for screening and diagnostic CT scan (total 498 CT scans). Most of the patients were women (M:F= 3:38). The age varies from 31 to 78 years old. The clinical indication of for chest CT scan were evaluation of the chest abnormalities, detected in chest radiography (112, 22.5%), lung cancer screening (97, 19.5%), preoperative evaluation for malignancy except breast (86, 17.3%), evaluation for pulmonary metastases from other organs (75, 15.1%), work up for infectious diseases (e.g., tuberculosis, pneumonia) (61, 12.2%), clinical history of hemoptysis (49, 9.8%), unknown cause (18, 3.6%). Follow up evaluation were done by breast US and mammography. Histopathologic correlation was done if there's any finding, suggesting malignancy and over category 4a lesions and follow up breast US were done for cat. 3 lesions.

Results: Of 41 patients, 13 cases (31%) were confirmed as malignancy (8 invasive ductal carcinoma, 2 ductal carcinoma in situ, 1 mucinous carcinoma, 1 small cell carcinoma, 1 lymphoma). Remaining 28 cases were benign lesion, (19 were fibrocystic disease, 7 were fibroadenomas, 2 were intramammary lymph nodes). The CT features, suggesting malignancy were speculated margin (8/13), peripheral rim enhancement (5/13), axillary node enlargements (4/13), central low attenuation area (3/13), perilesional infiltrations (3/13). Associated calcifications, size and multifocal nodular enhancement were also shown in malignant lesions. Conversely, smooth well defined margin of the mass was more common in benign lesions (17/28 cases).

Conclusions: Based on our study, significant rates (31%) of malignancy among the detected abnormalities in chest CT scan. The most common abnormality in malignancy is invasive ductal carcinoma. The CT findings of spiculated margin and peripheral enhancement with axillary lymphadenopathy were reliable findings in predicting malignancy.

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Is 18FDG-PET CT available for detection of preoperative axillary lymph node metastasis in invasive ductal carcinoma?

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Background: 18FDG-PET/CT has been recommended as a preoperative staging modality of advanced breast cancer, but the availability of 18FDG-PET/CT is still remained controversial. This study was designed to give ideas using 18FDG-PET/CT for axillary lymph node (ALN) metastasis of invasive ductal carcinoma by comparison positive with negative result group.

Materials and Methods: The subjects are consisted of 176patients with invasive ductal carcinoma who underwent operations on Pusan National University Hospital from January 2007 to December 2008 and preoperative 18FDG-PET/CT. Among 65patients with metastatic ALN comfirmed on permanent pathologic result, 31patients with and 34 patients without

suspicious ALN metastasis on 18FDG-PET/CT scan were defined as group A and B.

Results: Group A was related with malignant potential of breast cancer (high histologic grade and score of c-erbB2, p53 expression, presence of necrosis and lymphovascular invasion) and ALN status (higher Nstage). The analysis of group statistic revealed group A had relatively large primary tumor and metastatic LN, high expression of Ki-67 and many metastatic LN than group B. In the listed categories, each cut-off values were 1.85 cm, 0.95 cm, 17.5% and 3 by ROS analysis.

Conclusion: The 18FDG-PET/CT for detecting ALN metastasis in invasive ductal carcinoma was related with high histologic grade of primary tumor. We demonstrated that the accuracy of 18FDG-PET/CT in detecting ALN metastasis is expected high when the tumor is bigger than 1.85 cm, Ki-67 is higher than 17.5%, number and maximum diameter of metastatic ALN is more than 3 and 0.95 cm. But 18FDG-PET/CT may not be necessary when ALN is bigger than 0.95 cm, because preoperative confirmation may possible by fine-needle biopsy.

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A practical approach to additional lesions at preoperative breast MRI in patients eligible for BCT − Results

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Background: Contrast-enhanced magnetic resonance imaging (MRI) detects additional breast lesions in approximately 35% of the patients eligible for breast-conserving therapy (BCT). Preoperative breast MRI is increasingly used, and the need for clinical guidelines rises. The aim of this prospective study was to evaluate the efficacy of our institutional guidelines, established to handle additional lesions at preoperative MRI.

Materials and Methods: Six-hundred-and-ninety-four patients with pathology-proven breast cancer and eligible for BCT underwent preoperative breast MRI. The incidence of additional lesions detected at MRI and impact on management were evaluated. Additional lesions were classified based on the localization with respect to the index lesion. Additional lesions were pathology-proven (using second-look target ultrasound and fine needle aspiration (FNA)/biopsy) or considered benign by follow-up. Lesions for which no pathology proof was available prior to surgery, were defined as unidentified breast objects (UBOs). Patients with UBOs in a different quadrant than the index tumour underwent BCT as planned with annual follow-up. UBOs localized close to the index tumour were excised with wider local margins.

Results: Preoperative MRI detected 143 additional lesions in 121 patients. Of these lesions, 44.1% were proven malignant. UBOs were found in 12.1% of patients. None of the UBOs resulted in malignant disease at follow-up after BCT. Most UBOs near the index tumour were malignant (78.6%). In only one patient an additional lesion in a different quadrant was considered to be malignant after ultrasound-guided FNA cytology, but turned out to be benign (fibroadenoma) at final pathology after mastectomy.

Conclusions: The institutional guidelines to handle additional lesions at preoperative breast MRI proved to be sensitive to include malignant disease in the surgical planning without causing conversions to mastectomy for benign lesions in all but one patient. Yet, some adjustments are recommended to enhance the guidelines. In the light of the effectiveness of target ultrasound (and FNA and biopsy) for the management of additional lesions, we question the need for MRI-guided biopsies of UBOs.

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Utility of new brightfield dual-color in situ hybridization (BDISH) method for evaluating HER2 gene status of breast cancer patients

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Background: HER2-targeted therapy is an effective treatment for HER2-overexpressed breast cancer patients. Dual-color FISH method for HER2 gene and chromosome 17 centromere (CEN17) is utilized for the quantitative analysis of HER2 gene status. However, FISH assays are a time-consuming, extremely labor intensive, and expensive application that requires a specialized fluorescence microscope. Furthermore, it is difficult to preserve the FISH signal during a long term archive storage. In order to simplify the analysis of HER2 gene status, BDISH method has been developed recently for visualizing HER2 gene and CEN17 simultaneously on the same tissue section. Our study objective was to demonstrate the utility of BDISH method for evaluating the HER2 gene status of breast cancers by comparing BDISH results to FISH results.

Materials and Methods: HER2 BDISH results were analyzed among 52 archived breast cancer tumors that have been previously tested with HER2 FISH and HER2 immunohistochemistry (IHC). Then, two HER2 assays were reevaluated within the same small areas (5 mm in diameter) that were selected based on representative HER2 immunohistochemical staining. HER2 gene status was determined using the HER2/CEN17 ratio (Negative: HER2/CEN17 <2.0, Positive: HER2/CEN17 $\geqslant$ 2.0). HER2 IHC was scored 0, 1+, 2+, or 3+.

Results: Overall concordance rate between BDISH and original FISH results was 82.7%. Concordance rates between BDISH and FISH results based on IHC score groups were 100%, 81.3%, 57.1%, and 100% for 0, 1+, 2+, and 3+, respectively. However, when BDISH and FISH results were reevaluated within the selected small areas based on HER2 IHC staining, the overall concordance rate was 98.1%. Concordance rates between BDISH and FISH within the selected small areas based on the IHC score groups were 100%, 100%, 92.9%, and 100% for 0, 1+, 2+, and 3+, respectively.

Conclusions: The concordance rates between HER2 BDISH and FISH within the selected areas based on HER2 IHC scores were very high (98.1%). The discordance cases between BDISH and original FISH results were likely due to examining different tissue areas and possibly tumor heterogeneity. We confirmed that BDISH method is a useful new technology for examining HER2 gene status of breast cancer patients.

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Sensitivity of integral computer-aided detection (CAD) with full-field digital mammography (FFDM) for detection of breast cancer according to different histopathological types and appearance

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Background: To retrospectively evaluate the sensitivity of computer-aided detection (CAD) for full-field digital mammography (FFDM) in 360 histopathologically verified breast cancers with regard to mammographic appearance and histopathological tumor type.

Materials and Methods: 360 consecutive biopsy proven breast cancers imaged with FFDM (Senographe DS or GE Essential, GE Healthcare) from January 2001 through February 2009 were evaluated retrospectively using CAD (Hologic R2, version 8.3.17). Each case included a craniocaudal and mediolateral oblique view. In all cancer cases the malignant lesion was seen in at least one projection according to radiologist review. A CAD mark was scored true positive (TP) if it correctly indicated a malignant lesion. All other CAD marks were considered false. Cancer cases were classified as microcalcifications (64), masses (196), or both (100). Histopathological findings were classified as invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), ductal carcinoma in-situ (DCIS) or other. Sensitivity values for CAD according to mammographic appearance and, histopathological findings were analyzed using chi-squared tests.

Results: A TP mark was observed on 319 out of the 360 cancers (89%). Calcifications were significantly ($p < 0.001$) more likely to be marked than masses, 163/164 (99%) compared to 244/296 (82%). The probability of a mass TP mark was significantly related to histological type ($p < 0.001$), with sensitivity being greatest for IDC at 76% (167/221) compared to 67% (38/57) for ILC, 31% (16/51) for DCIS and 74% (23/31) for other types. The probability of a calcification TP mark was also significantly related to histological type, with sensitivity being greatest for DCIS, with 75% (38/51), compared to 43% (96/221) for IDC, 33% (19/57) for ILC and 32% (10/31) for other types. Median radiological tumor size was 15 mm. A TP mark was significantly ($p = 0.02$) more likely in tumors larger than the median (94% vs 83%). This was observed for both masses and calcifications.

Conclusion: CAD prompted the significant majority of radiological abnormalities related to cancers and was most accurate for detection of calcification and DCIS, less so for mass lesions and ILC. FFDM with integral CAD is a valuable tool for breast cancer detection, though less reliable for mass lesions and invasive lobular malignancy.