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Agreement Between Visual and Automated Assessment of HER2 Overexpression and Ki67 Labeling Index in Breast Cancer − Comparison of Core Biopsy and Surgical Specimens

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Background: Correct immunohistochemical assessment of HER2 and Ki67 expression is a crucial diagnostic procedure to select the appropriate treatment for breast cancer patients. Although several image analysis systems have been developed for scoring prognostic and predictive breast cancer markers, most of these focused on evaluation of ER and PgR expression. Therefore, the present study investigated agreement between visual and automated HER2 and Ki-67 assessment. Additionally we analyzed the impact of sample types (core biopsy versus surgical specimen) on the reliability of the two assessment methods.

Materials and Methods: In the present study we evaluated matched pairs of core biopsy samples and surgical specimens of 96 breast cancer patients that were immunohistochemically stained for expression of HER2 and Ki67. Visual assessment was performed in accordance with recent guidelines by two experienced pathologists. Automated analysis was carried out using Ventata Image Analysis System (VIAS). For Ki-67, a cutoff of 10% between low and high proliferative cases was chosen. Cohen's kappa coefficients (κ) were calculated using SPSS version 17 for agreement between different analytical methods and core biopsy vs. surgical specimen as well. Results were further evaluated according to the method of Bland and Altman.

Results: For HER2, agreement between visual and VIAS assessment was higher for surgical specimens than for core biopsy samples, reaching κ-values of 0.927 and 0.795, respectively. Agreement between core biopsy and surgical specimens was comparable for both methods with κ-values of 0.897 for visual and 0.865 for VIAS-assisted determination.

Agreement between Ki-67 assessments for the two methods was nearly identical with rather low κ-values of 0.595 and 0.578 for core biopsy and surgical samples, respectively. However, 95% limits of agreement according to Bland and Altman were higher for VIAS (40%) than for visual determination (21%). All strongly divergent cases represented invasive ductal carcinomas of intermediate or low grade of differentiation (G2-G3) with Ki67 values ranging from 6−75%. Agreement between core biopsy and surgical specimens was low in general, but higher for visual than for automated determination with κ-values of 0.537 and 0.418, respectively.

Conclusions: Visual and VIAS-assisted determination are both accurate methods for determination of HER2, whereas agreement between visual and automated assessment was higher in surgical specimens than in core biopsy samples. Ki67 assessment could be optimized upon assessment of a greater proportion of the primary tumor as core biopsy samples or selected areas might not be representative of the entire tumor sample.

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The EORTC 10041/BIG 03−04 MINDACT Trial Quality Assurance Program − Results of the Questionnaire for Pathologists

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Background: MINDACT investigates the added clinical value of Mammaprint™ to standard Clinicopathological criteria for the accurate selection of breast cancer (BC) pts for adjuvant chemotherapy. The trial logistics involve especially local pathologists for tissue collection, preparation of frozen samples and histopathological workup. As part of the MINDACT Quality Assurance (QA) program a questionnaire (Q) was created aiming to describe the characteristics and practices of participating pathologists and laboratories (labs).

Material and Methods: A non-compulsory, web-based Q was submitted to the pathologists of each participant centre between Sep. 2011 and Oct. 2012. The Q comprises 40 questions on 4 main topics: demographic and accreditation, MINDACT logistics, techniques for hormone (HR) and HER-2 receptors and integration of pathologists in clinical trials.

Results: A hundred five centres in 9 European countries enrolled a total of 6694 pts in the trial. Of them 83 (79%) replied the Q, which represents 85.9% (5752) of total pts enrolled. Nearly 71% of pathologists work at a tertiary high complexity hospitals, with 58% big-sized (>450 beds) facilities. About 69% of labs are affiliated to a university, 70% have a pathology residence program and 75% serve a cancer centre. Around 88% of labs have some accreditation (i.e. health authority, professional organization, societies, ISO). In 89% of centres the lab staff has knowledge of the trial tissue handling standard operation procedures. For 93% of pathologists, the 1 h timeline for freezing the tissue samples is easily achieved. HER-2 IHC and FISH/CISH tests are performed in house in 92% and 73% of labs respectively. HR results are reported by percentage in 64% of labs and 22% use Allred score. HR positive is defined as $\geqslant$ 1% stained cells in 42% of labs and $\geqslant$ 10% for another 42%. In about 95% of centres, pathologists participate in BC multidisciplinary meetings. For 78% of the pathologists, the logistics and timelines of MINDACT are feasible in clinical practice. Finally, 78% of pathologists actively participate in clinical trials but 10% don't feel integrated.

Conclusions: Pathologists and corresponding labs have an important role in biomarkers-based clinical trials. We reported the current state of practice in BC pathology of 83 European labs participants in MINDACT trial. QA programs that focus on the variability between participating centres/labs are of the most value for current clinical trials.

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PROFFERED PAPER

Patient Related Factors and Responsive Therapy

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Relationship Between Body Mass Index (BMI) and Outcomes in Node-positive Breast Cancer Patients Receiving Chemotherapy − Results From CALGB/Intergroup 9741

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Background: Observational studies suggest that obesity at diagnosis is associated with poor prognosis in women with breast cancer, but there is debate regarding potential confounding effects of treatment-related factors, particularly with regard to chemotherapy dosing of obese individuals. We sought to examine the relationship between BMI at diagnosis and outcomes in CALGB 9741, an adjuvant study which mandated that patients receive chemotherapy dosed according to actual body weight.

Methods: CALGB 9741 evaluated dose-density and sequence in a 2×2 factorial design in lymph-node-positive breast cancer. All patients received doxorubicin, cyclophosphamide and paclitaxel based on body surface area without a cap or adjustment. Height and weight at diagnosis were abstracted from patient records. The relationship of BMI with relapse-free (RFS) and overall survival (OS) was evaluated using multivariate proportional hazards regression after adjusting for number of involved nodes, estrogen receptor (ER) status, tumor size, menopausal status, drug sequence and dose density. Additionally, we graphically displayed the univariate relation of BMI with each outcome. Due to the variability of BMI data, BMI was smoothed using a moving average of 200 patients.

Results: 2005 women were enrolled in CALGB 9741 between September 1997 and March 1999. Baseline height and weight were available for 1909 patients, with median follow-up of 11 years. Overall, 49% of patients were premenopausal, 65% had ER positive cancers, and 70% received tamoxifen. Mean baseline BMI was 28.5 kg/m^2; 1.2% of patients were underweight (BMI <18.5 kg/m^2), 32.6% normal weight (18.5–24.9 kg/m^2), 32.9% overweight (BMI 25–29.9 kg/m^2), and 33.3% obese (BMI $\geqslant$30 kg/m^2). The graphics of smoothed BMI with RFS and OS each described a linear relationship with approximately the same slope. In adjusted analyses, BMI was significantly related to both RFS (P = 0.010) and OS (P = 0.022). Table 1 shows the 5- and 10-year RFS and OS by BMI