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Primary tumour Ki67 predicts endocrine sensitivity in ER positive metastatic breast cancer (MBC)

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Background: Baseline and dynamic changes in primary tumour Ki67 expression have predictive value for response to neoadjuvant endocrine therapy. We sought to investigate whether Ki67 expression in primary breast cancer predicts for sensitivity to first line endocrine therapy at relapse with MBC.

Methods: Institutional databases were searched (1991 to 2007) for cases of metastatic breast cancer treated with first line endocrine therapy. Cases were excluded if combination chemo-hormonal therapy was used. Eligible cases required data on immunohistochemical (IHC) analysis of Ki67, ER and PgR in the primary tumour performed either at initial diagnosis or at relapse with MBC. Ki67, ER and PgR were scored as the percentage of positive staining malignant nuclei per 1000. Case notes and pathology reports were reviewed to obtain details on tumour type and grade, Her2 and EGFR expression, and clinical factors including time to progression (TTP). Analysis of TTP was by Kaplan–Meier log rank test. Cox regression analyses were performed treating Ki67 as a continuous variable and multivariate analysis performed on Ki67, ER and PgR.

Results: 101 eligible cases were identified. All were ER positive and 92 (91%) were PgR positive. EGFR and Her2 were available for 94 and 85 cases respectively. 91/94 (97%) tumours were EGFR negative and only 9/85 (11%) were Her2 IHC3+. Histology was ductal (69%), lobular (15%), mixed (14%) and mucinous (2%). Grade was I in 11%, 2 in 53% and 3 in 36%. Mean Ki67 was 25.9% (range 1.6−68.6%). Median TTP was 12 months and 83/101 (82%) patients had progressed at analysis. Both ER and PgR expression were positively associated with TTP ($p = 0.001$ and 0.0005 respectively by log rank test), whereas grade and Her2 expression were not ($p > 0.17$ for both). After categorising Ki67 as low (<25%, $n = 50$), moderate (25−35%, $n = 29$) and high (>35%, $n = 22$) a significant inverse relationship between Ki67 and TTP was evident ($p = 0.025$; log rank test). Treating Ki67 as a continuous variable the hazard ratio (HR) for progression was 1.22 for every ten unit increase in Ki67 ($p = 0.02$). In multivariate analysis with ER and PgR this effect persisted but was weakened (HR 1.15; $p = 0.09$).

Conclusion: Ki67 expression of primary breast cancers is inversely related to their sensitivity to first line endocrine therapy on relapse. Ki67 assessment along with ER and PgR may help guide treatment selection and follow up strategies on therapy.

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Improved NPI for breast cancer prognosis

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Background: Currently, the Nottingham Prognostic Index (NPI) is used to classify breast cancer patients into risk groups indicating the chance of disease recurrence. Research shows the importance of estrogen (ER), progesterone (PR) and human epidermal growth (Her2) receptors for early breast cancer relapse. This study investigates the possibility of improving the NPI with one or more of these factors.

Material and Methods: Data concerning 1928 patients with primary operable breast cancer treated in the University Hospital of Leuven between 2000 and 2005 with known NPI, ER, PR and Her2 status were used in this study. The NPI was calculated as $0.2 \times$ size (cm) + grade + nodal score. The grade was scored from 1 to 3, according to the Ellis and Elston grading system. The nodal score equals 1, 2 or 3 in case of 0, less than 4 or more than 3 positive lymph nodes respectively. Multivariate Cox regression was performed to find improved prognostic models. We compared performances of a model with NPI as only predictor with models including NPI and ER, PR and/or Her2. Statistical significance was tested with a t-test for corrected resampling. The disease free survival (DFS) of risk groups defined by the corrected NPI score (cNPI) was compared with the DFS of NPI risk groups using Kaplan–Meier's method.

Results: Out of 1928 patients 9.44% developed disease recurrence between inclusion and September 2006. Considering any nuclear staining as positive 86.93% and 75.52% of cases had positive ER, PR respectively and 11.93% of cases were Her2 positive. The cNPI was calculated combining NPI, Her2 and PR status. In case of positive Her2 status or negative PR status, cNPI score was elevated with 1 point. Further inclusion of ER did not give additional information. NPI risk boundaries lie at 3.4 and 5.4; for the cNPI the first boundary was shifted towards 2.4. Comparison of survival curves showed a lower disease free survival for cNPI high risk than for NPI high risk groups. For the low risk groups the survival was better in the cNPI group, but differences were not as pronounced as in the high risk groups.

Conclusions: This study shows the relevance of incorporating PR and Her2 in a prognostic index for prognosis of short DFS. Since the prognostic value of PR and Her2 is thought to be less relevant at longer follow up (FU) it should be evaluated if the cNPI remains valuable for longer FU. The cNPI should be validated on an independent test set.

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Response of basal-like tumors defined by ESR1, Her-2/neu, MLPH and MMP7 to neoadjuvant chemotherapy

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Background: Neoadjuvant therapy allows for precise evaluation of tumor response in vivo and thereby the assessment of prognostic and predictive markers. ER negative tumors are reported to have higher rates of pathologic response to primary systemic therapy. Conversely, patients with Estrogen receptor (ER) negative tumors suffer from shorter disease free and overall survival.

Here, we have analyzed ER negative tumors displaying basal-like characteristics as determined by MMP7 and MLPH status and correlated with response to chemotherapy within two neoadjuvant multicenter trials.

Methods: We used paraffin-embedded breast cancer tissue from core needle biopsies from patients enrolled into the neoadjuvant TECHNO-Trial (Her2/neu positive) and Prepare-Trial (Her2/neu negative). All received neoadjuvant therapy with 4 cycles of Epirubicin/Cyclophosphamide (90/600 mg/m) and 4 cycles of Paclitaxel (175 mg/m). Patients enrolled in the Techno-Trial recieved additionally neoadjuvant trastuzumab (6 mg/kg). Tissue cuts were deparraffinized and nucleic acid extracted by an automated method based on DNA/RNA binding to magnetic beads from Siemens Medical Solutions Diagnostics GmbH. Quantitative RT-PCR has been performed to assess expression levels of ESR1, Her2/neu, MMP7, cKit and MLPH Our goal was to establish a small set of predictive and prognostic markers for response to primary antracycline based chemotherapy superior to clinical predictors in a finding cohort of 57 patients from the TECHNO- ($n = 230$) and PREPARE-Trial ($n = 850$), which is subsequently evaluated in all enrolled patients.

Results: Transcription levels of the basal-type marker MMP7 mRNA showed significant negative correlation with ESR1 expression (Spearman $r = -0.41$; $p = 0.001$), while the inversely related marker MLPH exhibited positive correlated with ESR1 (Spearman $r = 0.59$; $p < 0.0001$). Interestingly, MMP7 expression significantly correlated with the stem cell marker c-KIT (Spearman $r = 0.43$; $p = 0.0005$). The tumors with pathologic complete response showed a 2.6 fold higher median of transcription of MMP7 in both trials, while the difference was 5.4 fold in the Her-2/neu negative PREPARE trial. In addition, 3 of 4 pathological complete responders in the PREPARE trial were MLPH negative, while only 3 of 18 non responders were MLPH negative. All basal-like tumors as defined by low RNA expression of ESR1, Her-2/neu and MLPH but high expression of MMP7 achieved a pathological complete response.

Conclusions: Determination of ESR1, Her2/neu, MLPH and MMP7 mRNA has the potential to predict response to neoadjuvant chemotherapy. At time of abstract we started to confirm these findings with regard to response prediction achieved by neoadjuvant treatment in the remaining 797 tumor samples of the TECHNO and PREPARE-trial. Further results will be provided.