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Radiological predictors of successful therapeutic wide local excision of DCIS: findings from the Sloane project

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The Sloane project is a UK-wide multi-centre prospective audit of the management of screen detected Ductal Carcinoma *In Situ* (DCIS). The aim of this analysis was to ascertain if mammographic uni-dimensional measurement, bi-dimensional product measurement, calcification morphology and pathological grade are helpful in predicting which patients could be offered a successful single therapeutic wide local excision (WLE) of their DCIS.

Description: The study group was 505 patients with DCIS whose mammograms showed calcification, and in whom a pre-operative diagnosis had been obtained and a WLE attempted. Mammographic calcifications were measured in two planes at 90 degrees on the oblique view, classified morphologically as comedo, granular or punctate and classified pathologically as high, low or intermediate nuclear grade.

Summary of results: 342 patients had a successful first WLE and 163 patients had further surgery. A uni-dimensional measurement of <35 mm and a bi-dimensional product of <799 mm was associated with successful excision at first operation (69% vs 54%, $p=0.02$ and 70% vs 27%, $p=0.0001$ respectively). Mammographic calcification morphology and histological nuclear grade did not influence the chance of a successful first WLE (67%, 72%, 59% and 66%, 69%, 80% respectively). The bi-dimensional product maintained significance in subgroups based on calcification morphology and nuclear grade more frequently than uni-dimensional measurement.

Conclusion: Bi-dimensional product is a powerful radiological predictor of successful wide local excision of DCIS at first operation.

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EGFR activity in Her-2 overexpressing metastatic breast cancer: evidence for simultaneous phosphorylation of Her-2/neu and EGFR

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Background: Her-2/neu over-expression is an important prognostic parameter in breast cancer patients and has become a response predictor for trastuzumab treatment. Nevertheless, while trastuzumab is highly effective in many Her-2/neu over-expressing tumors, some do not respond. The reason for the differential effect is unknown, but it has been hypothesized that the complex interactions between Her-2/neu and other members of the EGFR family are involved in trastuzumab resistance.

Methods: Using IHC we have analyzed the protein expression of Her-2/neu, EGFR, and their activated forms ptyr-1248 Her-2/neu, ptyr-845 EGFR and ptyr-1173 EGFR in 57 Her-2/neu over-expressing breast tumors and investigated potential correlations between the receptors. We then measured serum EGFR and Her-2/neu by ELISA.

Results: We found that ptyr-845 EGFR was significantly co-expressed with Her-2/neu and ptyr-1248 Her-2/neu ($p=0.043$, and $p=0.040$, respectively), while ptyr-1173 EGFR was only correlated to Her-2/neu expression ($p=0.042$). Interestingly, EGFR and its activated forms were all significantly inversely correlated with PgR expression ($p=0.011$, $p=0.033$, and $p=0.032$, respectively), and ptyr-845 EGFR was in addition also inversely correlated with ER expression ($p=0.006$). While we have previously shown that serum levels of the extracellular component of Her-2/neu are associated with tumoral ptyr-1248 Her-2/neu expression, we did not find a similar relationship between serum EGFR and intratumoral total/activated EGFR. We did, however, observe significantly higher

levels of serum EGFR in women with 3+ overexpression of Her-2/neu ($p=0.047$).

Conclusions: Taken together, we have demonstrated the activation pattern of EGFR and Her-2/neu in Her-2/neu over-expressing breast cancer. We suggest that EGFR inhibition might enhance the efficacy of trastuzumab by preventing cross-phosphorylation.

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HIF-1alpha is closely linked to an aggressive phenotype in breast cancer

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Purpose: The aim of this study is to examine the expression of Hypoxia-induced factor 1alpha (HIF-1alpha) in relation to invasive breast cancer. HIF-1alpha is a key hypoxia-regulated gene that is also modulated by signal transduction via growth factors.

Experimental design: We examined, by immunohistochemical analysis, the expression of HIF-1alpha in normal breast tissue, benign disorders and breast cancer. In invasive breast cancer, we investigated the correlation between expression of HIF-1alpha and clinicopathological and biological factors. We also studied the prognostic value of HIF-1alpha in breast cancer.

Results: HIF-1alpha was mainly detected in tumor cell nuclei. In the 171 cases of invasive breast cancer examined, nuclear HIF-1alpha expression was detected in 72 (42.1%) cases. Immunoreactive nuclear HIF-1alpha was correlated with tumor size ($p=0.002$), lymph node metastasis ($p<0.0001$), tumor stage ($p=0.021$) and histological grade ($p=0.0031$). Elevated HIF-1alpha levels were also associated with hormone receptor negativity ($p=0.0001$), HER2 overexpression ($p=0.0028$), high Ki67 labeling index ($p<0.0001$), increased levels of VEGF ($p<0.0001$), COX-2 overexpression ($p=0.0029$) and increased nuclear p53 ($p=0.0023$). In terms of the possible use of HIF-1alpha as a prognostic indicator, patients who had increased HIF-1alpha levels in their tumor showed shorter disease-free survival ($p<0.0001$) and overall survival ($p=0.0002$) than those lacking HIF-1alpha in univariate analysis. In multivariate analysis of disease-free and overall survival, HIF-1alpha was identified an independent prognostic factor.

Conclusions: These findings suggest that HIF-1alpha is closely linked to an aggressive phenotype in breast cancer. It may be useful to study the expression of HIF-1alpha using immunohistochemical analysis for better understanding of the tumor characteristics of breast cancer.

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Breast volume and mammographic extent of DCIS as predictors of surgical procedure: findings from the Sloane project

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Introduction: The Sloane project is a UK multi-centre audit of the management of screen detected Ductal carcinoma *In Situ* (DCIS). The aim of this analysis was to ascertain if breast volume and mammographic bi-dimensional measurement of micro-calcification are predictive of the choice of mastectomy as the primary therapeutic operation, and to ascertain whether they are predictive of a single successful operation in those undergoing therapeutic wide local excision (WLE).

The study group consisted of 522 patients whose mammograms showed calcification and in whom a pre-operative diagnosis of DCIS had been obtained. Mammographic calcifications were measured in millimetres (mm) in two planes at 90 degrees on the oblique view and a bi-dimensional product (BDP) was calculated. Breast volume in milliliters (ml) was estimated from the oblique mammograms using the formula for the volume of a cone.

Summary of results: 110 patients underwent mastectomy and 412 patients underwent WLE as their primary therapeutic operation. A BDP ≥ 400 mm was a predictor of the initial choice of mastectomy as therapeutic option (63% vs 9%, $p<0.01$). In addition, women with a BDP ≥ 400 mm were more likely to have a mastectomy if they had a breast volume of less than 1000ml (71% vs 52%, $p<0.05$).