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

A.J. Evans[1], K. Clements[2], A. Maxwell[3], H. Dobson[4], M. Wallis[5], G. Lawrence[6], H. Bishop[7]. *[1]Nottingham Breast Institute, Nottingham City Hospital NHS Trust, Nottingham, United Kingdom; [2]West Midlands Cancer Intelligence Unit, Birmingham, United Kingdom; [3]Royal Bolton Hospital, Bolton Breast Unit, Bolton, United Kingdom; [4]The West of Scotland Breast Screening Programme, Glasgow, United Kingdom; [5]Coventry & Warwickshire Hospital, Warwickshire, Solihull & Coventry Breast Screening Service, Coventry, United Kingdom; [6]West Midlands Cancer Intelligence Unit, Birmingham, United Kingdom; [7]Royal Bolton Hospital, Bolton Breast Unit, Bolton, United Kingdom*

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 punctuate 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

D. Gschwantler-Kaulich[1], G. Hudelist[2], W.J. Koestler[3,6], K. Czerwenka[4], R. Mueller[1], E. Ruecklinger[5], E. Kubista[6,7], C.F. Singer[6,7]. *[1]Medical University of Vienna, Special Gynaecology, Vienna, Austria; [2]LKH Villach, Obstetrics and Gynaecology, Villach, Austria; [3]Medical University of Vienna, Oncology, Vienna, Austria; [4]Medical University of Vienna, Gynaecopathology, Vienna, Austria; [5]Ruecklinger KEG, Statistical Analysis Consulting, Vienna, Austria; [6]Medical University of Vienna, Special Gynaecology, Vienna, Austria; [7]Ludwig Boltzmann Institute, Clinical Experimental Oncology, Vienna, Austria*

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 = 0.008). 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

Y. Yamamoto, M. Ibusuki, T. Kawasoe, Y. Okumura, K. Kai, H. Iwase. *Kumamoto University, Department of Breast & Endocrine Surgery, Kumamoto, Japan*

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 was 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

A.J. Evans[1], A.J. Maxwell[2], K. Clements[3], H. Dobson[4], M. Wallis[5], G. Lawrence[6], H. Bishop[7]. *[1]Nottingham Breast Institute, Nottingham City Hospital NHS Trust, Nottingham, United Kingdom; [2]Royal Bolton Hospital, Bolton Breast Unit, Bolton, United Kingdom; [3]West Midlands Cancer Intelligence Unit, Birmingham, United Kingdom; [4]The West of Scotland Breast Screening Programme, Glasgow, United Kingdom; [5]Coventry & Warwickshire Hospital, Warwickshire, Solihull & Coventry Breast Screening Service, Coventry, United Kingdom; [6]West Midlands Cancer Intelligence Unit, Birmingham, United Kingdom; [7]Royal Bolton Hospital, Bolton Breast Unit, Bolton, United Kingdom*

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).

129 women who underwent WLE required one or more further therapeutic operation. For women with BDP < 400 mm there was no significant difference in the number requiring more than one operation between women with <1000ml and ⩾1000ml breasts (29% and 28% respectively). Of those with BDP ⩾ 400 mm, 68% of women with breast volume <1000ml required one or more further operations compared to 40% of those with breast volume ⩾1000ml. This difference just fails to reach statistical significance (p = 0.06).

Conclusion: The combination of breast volume assessment and bi-dimensional measurement of DCIS on mammography is a useful predictor of successful therapeutic surgery.

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The triple negative profile dilemma and its clinical outcome in early breast cancer

E. Azambuja, G. Castro Jr., V. Durbecq, M. Paesmans, G. Ismael, D. Larsimont, C. Sotiriou, M. Piccart, F. Cardoso. *Jules Bordet Institute, Medical Oncology Clinic, Brussels, Belgium*

Background: Gene expression studies have consistently identified several breast cancer subtypes including the basal-like (BBC). The BBC subtype is associated with a poor prognosis and in the majority of cases also with negativity of ER, PgR and HER-2 receptors. Therefore, the so-called triple negative breast cancer phenotype is frequently used as a surrogate for the BBC subtype.

Patients and Methods: We performed a retrospective analysis of 323 patients with primary early breast cancer treated at the Jules Bordet Institute during the year of 2001 for whom follow up data was available. Data from histological features, immunohistochemical (IHC) findings for HER-2, estrogen (ER), and progesterone (PgR) receptors, and clinical outcome were collected. The clinical outcome of the patients with triple negative breast cancer was compared to the rest of the population.

Results: From the 323 patients selected (median age 57 years (range 28–96 years), 66.2% postmenopausal and 59.1% node negative)), 23 patients (7.1%) were classified as triple negative breast cancer after central pathology review. With a median follow up period of 43 months, the triple negative subgroup had a significantly worse disease free interval (DFI) (HR = 3.01; CI 95% 1.44–6.53, p = 0.01). Using a backward selection of variables in multivariate analysis for DFI, triple negative status remains a significant variable (HR = 3.82; CI 95% 1.72–8.48, p = 0.001) together with node positive (HR = 3.02; CI 95% 1.57–5.81, p = 0.001) and adjuvant chemotherapy (HR = 3.05; CI 95% 1.32–7.02, p = 0.01).

Conclusions: Triple negative status is associated with a poor outcome in early BC. Tailored therapeutic approaches associating chemotherapy and biological agents are warranted for this particular subgroup of patients.

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Reproducibility and validity of the Claus-Extended Formula in a British cohort of women with a family history of breast cancer

C.E. Jacobi[1], G.H. De Bock[1,2], J.C. van Houwelingen[3], A. Shenton[4], D.G. Evans[5], C.J. van Asperen[6]. *[1]Leiden University Medical Center, Dept. Medical Decision Making, Leiden, The Netherlands; [2]University Medical Center Groningen, Dept. Epidemiology and Biostatistics, Groningen, The Netherlands; [3]Leiden University Medical Center, Dept. Medical Statistics, Leiden, The Netherlands; [4]Christie Hospital NHS Trust, Cancer Research UK, Dept. Medical Oncology, Manchester, United Kingdom; [5]St. Mary's Hospital, Academic Department of Medical Genetics, Manchester, United Kingdom; [6]Leiden University Medical Center, Center for Human and Clinical Genetics, Dept. Clinical Genetics, Leiden, The Netherlands*

Background. Risk estimation in breast cancer families in clinical practice is often performed using the Claus Tables. Previously, we constructed a new risk estimation method especially for clinical practice: the Claus-Extended Formula [1]. This formula uses the Claus Tables (CT) and information on the presence of bilateral breast cancer (BBC), ovarian cancer (OC), and multiple (more than 2) breast cancer cases (MC) in the family and is formulated as follows: 0.08 + 0.40*CT + 0.07*OC + 0.08*BBC + 0.07*MC. It was constructed using a Dutch cohort of breast cancer families. Correlations and agreements between the Claus-Extended Formula and the Claus Model, the Claus Tables, and the Jonker Model were satisfying.

Aim. The aim of this study was to validate the Claus-Extended Formula using a British cohort of families with breast and/or ovarian cancer.

Methods. We analysed family histories of 2156 counselees selected from a British Family History Clinic. We estimated lifetime risks of breast cancer using the Claus Model, the Jonker Model, the Claus Tables and the Claus-Extended Formula and considered correlations and agreements

between these methods to evaluate the reproducibility of the Claus-Extended Formula. Furthermore, we calibrated the Formula in order to evaluate whether the Formula estimates the risks accurately in this other cohort.

Results. The British counselees had on average 1.7 breast cancer cases per family (SD 0.8; range 0–6). Spearman correlations between the Claus-Extended Formula and the Jonker Model, the Claus Model and the Claus Tables were 0.768, 0.679, and 0.770, respectively. Agreements were 73%, 33%, and 63%, respectively. The calibration of the formula showed that no clinical relevant differences could be found between the lifetime risks estimated by the Claus-Extended Formula and by the Jonker model.

Conclusion. We found that the Claus-Extended Formula provides accurate lifetime risks of breast cancer, based on estimates by the Claus model and Jonker model. The Formula is easy applicable in clinical practice. Therefore, we conclude that the Claus-Extended Formula is a valid risk estimation method for clinical practice, both inside and outside the Netherlands.

References

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Recursive partitioning analysis in breast cancer patients treated by adjuvant whole breast radiotherapy followed by external beam boost or brachytherapy boost: prognostic groups in 1485 patients

J. Hammer[1], C. Track[1], K. Spiegl[1], H.D. Thames[2]. *[1]Barmherzige Schwestern Hospital, Dept. of Radiation Oncology, Linz, Austria; [2]M.D.Anderson Cancer Centre, Dept. of Biostatistics and Applied Mathematics, Houston, Texas*

Aim: To find prognostic parameters for local failure (LF), disease free survival (DFS) and distant metastasis-free survival (MFS) derived from recursive partitioning analyses (RPA).

Patients and Method: From 1485 patients referred between 1984 and 1997 with pathologic T1–2 N0–1 breast cancer, data were analyzed. After tumorectomy, patients underwent whole breast radiotherapy and a boost either by external beams or by interstitial high dose-rate brachytherapy. Age, T-stage, grading, the number of positive axillary nodes, the ratio between the number of positive axillary nodes and the number of excised axillary nodes (n-ratio), tumor location (med/lat), the estrogen-and progesteron-receptor status (ER, PR), menopausal status, systemic therapy and the presence of surgical marker clips were included in the analyses. Cut points defining prognostic groups were estimated. For each prognostic group the relative hazard ratio (RHR) was estimated.

Results: 1238 out of 1485 patients could be used for RPA. For *LF* there were three prognostic groups. Age was the most important prognostic parameter followed by ER status and n-ratio. For *DFS*, n-ratio was the most significant factor with a cut point at 21%, followed by age. For *MFS* 4 risk groups were defined, where again the n-ratio was the most significant prognostic parameter followed by T-stage.

Conclusions: The most important factors in defining risk groups were age and node ratio (n-ratio). Whenever the n-ratio was included in the fit the number of positive nodes was not significant. For LF age was most important (with ER, n-ratio, and location also relevant), while for DFS n-ratio was most important (with age, PR/ER, and stage also relevant). For MFS n-ratio was most important (with stage, ER, and location also relevant, but not age). It is striking that high risk for DFS and MFS is defined by node ratio ⩾ 0.21, which corresponds to ⩾ 4 positive nodes in a full level I-II dissection, while the usual measure of risk, number of positive nodes, was insignificant whenever the node ratio was included in the fit.

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Outcome of invasive lobular carcinoma: the experience of the European Institute of Oncology

F. Brenelli[1], G. Gatti[1,2], G.R. Santos[1], D. Gilardi[1], A.R. Vento[1], A. Luini[1,3]. *[1]European Institute of Oncology, Breast Surgery Division, Milan, Italy; [2]Postgraduate School of General Surgery, University of Perugia, Perugia, Italy; [3]University of Milan, School of Medicine, Milan, Italy*

Invasive lobular carcinoma of the breast (ILC) is the second most common breast cancer after the invasive ductal carcinoma (IDC), and comprises approximately 10% of all breast cancers cases, ranging from 5 to 15%. Its incidence, as well as the lobular carcinoma in situ (LCIS), is increasing, predominantly in postmenopausal women. The objective of this study was to review all cases of ILC treated at the European Institute of Oncology (EIO) and compare the outcomes with those described on the medical literature. Between January 1996 until December 2003, 810 patients diagnosed with ILC were treated at the EIO. Conservative treatment was