O-31 ACCURACY OF UNIDIMENSIONAL AND VOLUMETRIC ULTRASOUND MEASUREMENTS IN PREDICTING GOOD PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER PATIENT

I. Gounaris [a], R. Sinnatamby [b], K. Taylor [b], M. Wallis [b], L. Hiller [c], A.-L. Vallier [d], E. Provenzano [b], M. Iddawela [b], G. Wishart [b], H. Earl [b], P. Britton [b]. [a] *Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK.* [b] *Cambridge Breast Unit, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK.* [c] *Warwick Clinical Trials Unit, University of Warwick, Coventry CV4 7AL, UK.* [d] *Cambridge Cancer Trials Centre, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK*

Background: Pathologic complete response (pCR) is an important predictor of long term survival in patients with breast cancer receiving neoadjuvant chemotherapy.

Methods: Unidimensional and volumetric ultrasound measurements prior to, after 4 cycles (mid-treatment), and at the end of 8 cycles (end-treatment) of chemotherapy were available from a subset of 55 patients enrolled in Neo-tAnGo, a phase III neoadjuvant chemotherapy trial. Changes in proportional longest diameter (LD) and volume as well as absolute residual size thresholds were examined for their ability to predict pCR or pCR plus minimal residual disease (pCR/MRD). Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) and likelihood ratios (LRs) were calculated. Receiver–operator characteristic (ROC) curves and logistic regression models were constructed.

Results: At mid-treatment, neither complete radiological response, nor proportional LD or volume changes were found predictive of final pCR. Residual tumour volume $\leqslant 1\ cm^3$ was associated with pCR/MRD ($p = 0.014$). Sensitivity, specificity, PPV, NPV, LR+ and LR– values were 61%, 77%, 61%, 77%, 2.62 and 0.51 respectively. The area under the ROC curve (AUC) was 0.689 ($p = 0.03$). Volume $\leqslant 1\ cm^3$ was found significant in a univariate logistic regression ($p = 0.011$), but not in multivariate analysis. At end-treatment, no ultrasound measurements were found predictive of pCR or pCR/MRD.

Conclusions: Proportional tumour size changes were not found predictive of good pathologic response, yet residual volume $\leqslant 1\ cm^3$ after 4 cycles of chemotherapy was found predictive. Multiple volume and LD thresholds were examined and uncorrected *p*-values presented, increasing the possibility of type I errors. Replication in an independent dataset is required.

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O-32 D-DIMER AS A MARKER FOR EARLY PROGRESSION IN PATIENTS COMMENCING NEOADJUVANT CHEMOTHERAPY

C.C. Kirwan, C.N. McCollum, N.J. Bundred, G.J. Byrne. *University Department of Surgery, University Hospital of South Manchester, UK*

Objective: D-dimer, the end product of coagulation, is increased pre-operatively in abdominal cancers with poor prognosis, and in early breast cancer is associated with lymph node positivity. However, d-dimer as a marker of response to treatment has not been investigated.

Methods: In early breast cancer patients receiving neoadjuvant chemotherapy ($n = 11$), d-dimer was measured prior to commencement of chemotherapy and at 6 months following commencement of treatment. Clinical and radiological follow-up of breast cancer was at 3, 6, 12 and 24 months. We compared baseline d-dimer, d-dimer at 6 months, and change in d-dimer in response to treatment in patient with relapse compared to those remaining disease free at 2 years.

Results:

	Relapse at 2 years	Disease free at 2 years	*P*-value
D-dimer pre-chemotherapy, ng/ml (SD) (*n*)	1328 (1183) (3)	259 (91) (7)	0.03
D-dimer at 6 months, ng/ml (SD) (*n*)	1364 (221) (2)	454 (224) (5)	0.005
Change in d-dimer in response to chemotherapy, ng/ml (SD) (*n*)	717 (345) (2)	177 (188) (5)	0.04

(Upper limit of normal 500 ng/ml).
No patients had clinical evidence of relapse at 6 months.

Conclusions: Despite no clinical evidence of disease, d-dimer remains elevated at 6 months following breast cancer treatment in patients with early relapse. D-dimer, prior to treatment and following treatment, may act as a marker for early relapse in breast cancer.

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O-33 AN ARTIFICIAL NEURAL NETWORK BASED ALGORITHM FOR PREDICTING CONTINUOUS TIME TO EVENT DATA IN BREAST CANCER

Lee Lancashire, Andy Sutton, Robert Rees, Graham Ball. *Campandia Ltd/Nottingham Trent University, Nottingham, UK*

Introduction: Development of gene signatures usually focuses on changing time dependent data into binary categories, for example 5 year survival. Predicting actual time to an event has the potential to be much more powerful. Here we introduce a novel algorithm termed Risk Distiller that aims to overcome the splitting of data into arbitrary categories by using artificial neural networks to predict a continuous response variable describing the actual time to event.

Methods: Time to recurrence data (0–14 years) for a series of breast cancer patients was made available in a study described by Van de Vijver et al. We applied our method to those cases with known events to identify an optimal panel of genes with the ability to predict the actual time to recurrence. The gene signature started as a single gene and was grown upwards until the optimal model was determined.

Results: The optimal signature contained 28 genes. There was a statistically significant correlation between actual versus predicted time to recurrence for blind data (rho = 0.975; $p < 0.0001$). A prospective Kaplan–Meier plot was generated which showed no significant difference to the actual Kaplan–Meier plot for this dataset ($p > 0.955$).

Discussion: For the first time gene expression signatures have been identified that predict actual time to event data rather than placing patients into arbitrary risk groups. Coupled with the ability to derive prospective Kaplan–Meier plots, this tool has the potential for assessing prognosis and determining treatment regimens on a case by case basis.

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O-34 DYNAMIC CONTRAST-ENHANCED MRI REVEALS CORE SIGNALLING PATHWAYS IN BREAST CANCER

S. Mehta [a], N.P. Hughes [b,d], F.M. Buffa [a], R.F. Adams [c], S.S. Gambhir [b,e], A.L. Harris [a]. [a] *Weatherall Institute of Molecular Medicine, Oxford, UK.* [b] *Institute of Biomedical Engineering, University of Oxford, Oxford, UK.* [c] *Oxford Breast Imaging Centre, Churchill Hospital, Oxford, UK.* [d] *Molecular Imaging Program, Stanford University, USA.* [e] *Department of Bioengineering, Stanford University, USA*

Dynamic contrast-enhanced MRI (DCE-MRI) is a widely used imaging modality for the management of breast cancer patients. At present, there is little understanding of how imaging patterns on DCE-MRI relate to the molecular pathways that drive tumour growth.

To address this issue, we performed a retrospective study of 65 patients with primary breast cancer, for whom pre-treatment DCE-MRI scans and formalin fixed paraffin embedded (FFPE) core biopsies were available. We used pharmacokinetic modelling of DCE-MRI to quantify the rate constant k_{ep} governing contrast agent washout from the tumour extravascular extracellular space. By computing the median k_{ep} over tumour volume an overall tumour leakiness score was derived. We extracted RNA from FFPE cores and measured gene expression using Affymetrix Human Plus 2.0 arrays. Following normalization and pre-processing, we used permutation tests to determine which genes were significantly correlated with median k_{ep}. Pathway analysis was performed using GeneCodis with the KEGG database.

Setting the False Discovery Rate to 5% resulted in 1258 genes that were significantly positively correlated with tumour leakiness including integrins B1 and A6, TGFBR1, HIF1 and 2A, SMAD4, HES1, JAG1. Interestingly, pathway analysis revealed that the p53 ($P < 0.004$), Wnt ($P < 0.004$) and Notch signalling pathways ($P < 0.006$), which are known to have important roles in angiogenesis, were all significantly associated with tumour leakiness.

These results illustrate how the combination of non-invasive imaging and gene expression profiling can reveal the molecular correlates of radiological features and provide insight into the mechanisms driving tumour growth and angiogenesis.

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O-35 SERPINB3, A BIOMARKER OF TAXANE BENEFIT IN BREAST CANCER

Elaina S.R. Collie-Duguid [a], Kathleen Sweeney [a], Keith Stewart [b], Iain Miller [b], Steve Heys [a]. [a] *Cancer Medicine, University of Aberdeen, UK.* [b] *Department of Pathology, University of Aberdeen, UK*

Background: Lysosomal cathepsin proteases function in a programmed cell death (LPCD) pathway. Although there is evidence for the importance of this pathway in cancer cell survival, it has not been exploited in anti-cancer therapeutics. Hsp70 and serpinB3 can block this pathway and promote cell survival. Furthermore, serpinB3 is associated with lack of response to chemotherapy. Cathepsin mediated cell death is observed in response to anthracyclines or taxanes, which are widely utilised in breast cancer treatment.

Methods: We evaluated serpinB3 and Hsp70 by immunohistochemistry in 255 surgically resected breast tumours from patients treated with either CVAP or CVAP and docetaxel prior to potentially curative resection. The study was performed with the approval of the regional research ethics committee.

Results: SerpinB3 and Hsp70 were significantly correlated with poor pathological response ($P = 0.014$ and $P < 0.0001$, respectively). SerpinB3 positivity is a poor prognostic factor ($P = 0.029$; mean survival 88.8 vs. 100.4 months) and this is independent in multivariate analysis ($P = 0.023$). Patients with serpinB3 positive tumours have poor survival if treated with anthracycline ($P = 0.026$) but not if they are also given a taxane ($P = 0.786$). Furthermore, only patients with serpinB3 positive tumours benefit from taxane treatment ($P = 0.008$).

Conclusions: SerpinB3 and Hsp70 are predictive biomarkers, potentially blocking breast tumour response to chemotherapy by preventing LPCD. SerpinB3 is prognostic and may prevent anthracycline-, but not taxane-, mediated cytotoxicity in breast tumours. Patients with serpinB3 negative tumours have a good prognosis when treated with anthracycline-based therapy alone. In contrast, patients with serpinB3 positive tumours benefit significantly from the addition of docetaxel.

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O-36 RECRUITMENT OF INSULIN RECEPTOR SUBSTRATE-1 BY ErbB3 IMPACTS ON IGF-IR SIGNALLING IN OESTROGEN RECEPTOR-POSITIVE BREAST CANCER CELLS

J.M. Knowlden [a], J.M.W. Gee [a], D. Barrow [b], J.F. Robertson [b], I.O. Ellis [b], R.I. Nicholson [a], I.R. Hutcheson [a]. [a] *Tenovus Centre for Cancer Research, Cardiff University, UK.* [b] *Professorial Unit of Surgery, Nottingham City Hospital, Nottingham, UK*

We have shown that insulin receptor substrate 1 (IRS-1) can associate with epidermal growth factor receptor (EGFR), with activation of EGFR promoting recruitment and phosphorylation of IRS-1 in an oestrogen receptor (ER)-positive tamoxifen resistant breast cancer (BC) cell line. In this study, we examined recruitment of IRS-1 by another erbB receptor family member, erbB3 in three ER-positive BC cell lines. Our studies revealed an interaction