

Celecoxib significantly decreases COX-2 protein expression and increases the rate of apoptosis in human DCIS and is a promising adjuvant therapeutic strategy for Ductal Carcinoma In Situ.

### O-52. Activated c-Src in ductal carcinoma in situ correlates with high grade and HER2 expression

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**Background:** The non receptor tyrosine kinase c-Src is downstream of HER2 and activation of c-Src influences response to Herceptin, and tumour progression and metastasis.

**Aim:** To determine the expression of activated c-Src in pure DCIS and determine if activated c-Src correlates with HER2 expression and clinicopathological parameters in DCIS.

**Method:** Immunohistochemical expression of activated c-Src using Clone 28 monoclonal antibody was evaluated in 78 patients (median age 55 years, range 39–71 years) with “pure” DCIS and a median follow-up of 60 months (range 24–240). HER2, HER4, ER and Ki67 levels were evaluated by immunohistochemistry. A HER2/HER4 score  $\geq 2$  was considered positive.

**Results:** Forty-three (out of forty-seven) HER2 positive tumours expressed active c-Src ( $p < 0.015$ ). Strong expression of activated c-Src was also associated with high tumour grade ( $p < 0.0005$ ) in 78 DCIS examined, but not epithelial proliferation (measured by Ki67,  $p = 0.450$ ), tumour size, ER status and HER4 expression.

Characteristic	% DCIS Activated c-Src	P value
HER2 score $\geq 2$	91% (43/47)	0.015
HER4 score $\geq 2$	88% (22/25)	0.549
ER positive	67.6% (52/77)	0.499
Tumour grade		
Low	10.3% (8)	
Intermediate	32% (25)	
High	57.7% (45)	$P < 0.0005$

**Conclusion:** Activation of c-Src is seen in high grade DCIS lesions with HER2 expression. Interruption of c-Src signalling with small molecule inhibitors may be therapeutically useful.

### O-53. Accuracy of mammography in predicting histological extent of DCIS

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Mammographic (MMG) extent is the main determinant for offering wide local excision for DCIS. It is recognized that this does not always correlate accurately with histological (HIST) extent. The aim of this study was to define the degree of variance between MMG and HIST measurement of DCIS and analyze the factors predicting a significant discrepancy.

The HIST and MMG data for 174 cases of DCIS were reviewed. The MMG size was bigger than the HIST size in 97(55.7%) and there was  $>10$  mm difference in 18 (10.3%)

of cases. The HIST size was bigger than the MMG size in 69 (39.7%) of cases and  $>10$  mm difference in 30(17.2%) of cases.

The association between a variance in MMG/HIST extent and various factors is shown in the table below.

	MMG > HIST		HIST > MMG	
	$>10$ mm	1–10 mm	1–10 mm	$>10$ mm
Mean MMG size in (mm)	26.6	14.6	12.6	19.1
% High Grade	61.1	59.5	66.7	70.0
% Dense MMG	5.9	15.6	18.4	13.3
% Involved Margins	16.7	17.9	23.7	80

The only statistically significant finding was that cases with a HIST  $>$  MMG variance  $>10$  mm were more likely to require further surgery for involved margins. We were unable to find factors that pre-operatively identified these women.

The important findings of this study are that MMG under-sizes DCIS in over a third of cases and there is no reliable method for identifying this group. Other methods of pre-operative imaging should be explored.

### O-54. Factors predicting recurrence in DCIS after breast conserving surgery with clear margins

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**Background:** Factors predicting recurrence following breast conserving surgery (BCS) with clear margins for Ductal Carcinoma In Situ (DCIS) are largely unknown.

**Aim:** To determine recurrence rates and predictors of recurrence risk in patients who underwent BCS with clear margins ( $>1$  mm) for pure DCIS.

**Method:** We reviewed all patients who underwent BCS ( $n = 305$ ) for pure DCIS and then excluded patients with involved margins ( $n = 76$ ) to determine what factors predicted recurrence in patients with clear margins ( $n = 229$ ). ER, HER2, and Ki67 were measured by immunohistochemistry. A HER2 score  $\geq 2$  was considered positive.

**Results:** Margin status was a highly significant recurrence predictor ( $p \leq 0.001$ ). Overall recurrence was 13.1% (30/229) in patients with clear margins at 5 years and 31.6% (24/76) with involved margins. In the group of women with clear margins after BCS ( $n = 229$ ), high epithelial proliferation (measured by Ki67,  $p = 0.044$ ) and HER2 positivity ( $p = 0.042$ ) were associated with increased recurrence. 75% of recurrent DCIS had a Ki67  $\geq 10\%$  compared to 50% in the non-recurrent group 39% of HER2 positive DCIS recurred at 5 years compared to 16% HER2 negative. Tumour grade, size and age at diagnosis did not predict recurrence.

Patient Characteristics	Non-recurrent $n = 199$	Recurrent $n = 30$	$p$ value (Log Rank)
BCS + clear margins			
HER2 positive ( $\geq 2$ )	44	70	0.042
Ki67			
Median	10.1	13.2	
Range	0.8–38	2.5–38.8	0.044
ER positive %	77.6	61.5	0.316
Tumour Grade			
Low	16	1	
Intermediate	47	8	
High	118	21	0.496

**Conclusion:** HER2 positivity and high proliferation predicts recurrence in DCIS after BCS with clear margins. Small molecular inhibitors targeting HER2 may be beneficial in reducing recurrence after BCS.

#### O-55. Management of lobular carcinoma in situ within the NHSBSP

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**Background:** The treatment of LCIS has changed radically in line with the change in belief that LCIS is a marker of risk instead of a true disease entity.

**Aims:** To review the management of all cases of LCIS identified within the NHS breast screening programme.

**Methods:** Data on 366 cases of screen detected LCIS was collected. The clinical management of each case was reviewed including surgical and adjuvant treatment as well as the mammographic and clinical follow up of these cases.

**Results:** Of 366 cases identified, 4 women had initial unilateral mastectomies, 9 had biopsy only and 353 had a form of localisation biopsy. 1686 women-years of follow up were available on 321 LCIS cases. Of these, 51 patients had further surgery including 9 who had bilateral mastectomy, 8 had unilateral mastectomy, 28 had margin excision, and 6 had wide lump excision. 67 received tamoxifen and 9 received radiotherapy. 30/320 received mammography at an interval of > one year. 35 women received no clinical follow up and 5 women received clinical follow up of > one year intervals. Incidence of subsequent breast cancer within this population amounted to 15.4/1000/year.

**Conclusions:** Management of screen detected LCIS varied considerably. LCIS was associated with a roughly 5-fold increase in breast cancer risk suggesting these patients should be followed up clinically and mammographically more regularly than in the routine screening programme.

#### O-56. Optical diagnostics in ductal carcinoma in situ (DCIS) of the breast to differentiate between different grades of pathology

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Ductal carcinoma in situ (DCIS) is detected more often since the advent of mammography. A standardized staging and grading system does not exist. The aim of this study is to determine whether chemical finger printing using optical spectroscopy can differentiate between the existing accepted grades and improves the grading system.

At the Biophotonics Research Centre, Gloucester, a team of research scientists, surgeons and a breast specialist pathologists are working to improve the understanding of breast diseases using Raman and infrared spectroscopy. The ducts were carefully marked on a H&E section by a pathologist. Raman spectra were measured, using a Renishaw Raman Spectrometer, on a 20-micron thick consecutive frozen section.

The spectral data were analysed using Matlab. Analysis of selected regions of the duct, especially epithelial and basement membrane regions in high grade comedo DCIS and from low to intermediate group DCIS revealed increased collagen and decreased lipids in relation to specific regions. There is also some degree of differentiation in the concentrations of triolein, choline, actin and DNA between these different pathology groups in different regions. A principal component spectral model has been constructed to show the differentiating components between the two pathology groups.

Optical spectroscopy can be used to accurately differentiate between different grades of DCIS *in vitro*, and therefore shows the potential to provide an objective method to grade DCIS. Work is ongoing to increase the sample size of this study and also to assess the progression of pathology of proliferative breast lesion to malignancy.

#### O-57. Pain syndromes affect quality of life after mastectomy and breast conserving surgery

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Chronic pain following breast surgery for cancer in mastectomy patients is well described (post mastectomy pain syndrome), but there is little data on its impact on the quality of life. Pain syndromes in women undergoing breast conserving surgery (BCS) are not well described.

Modified UCSF (University of California San Francisco) quality of life pain questionnaires were given to 600 patients who had unilateral surgery (mastectomy, BCS) attending the primary breast cancer follow-up clinic from 2004 to 2005. Exclusion criteria included reconstruction, or further surgery for local/regional recurrence. All patients had a minimum of one year follow up, and were under 70 yrs.

Of 306 patients who have completed the questionnaire to date, 186(61%) complained of significant pain. In 22%, the pain was severe enough to affect the daily wearing of a bra and/or clothing. 10% needed regular analgesia to alleviate symptoms. 62% were fearful that the pain represented an indication of cancer recurrence. In analysis by operation type (mastectomy vs. BCS, 47% vs. 53%), there was a greater incidence of pain in the lumpectomy group ( $p = 0.02$ ). The pain was limited to the breast region and not the axilla ( $p = 0.05$ ). This effect persisted when controlled for radiotherapy. No significant difference was found between the types of pain (e.g. shooting, stabbing), fear of cancer recurrence, depression, and effect on personal relationships.

This study shows that pain syndromes occur in a high proportion (60%) of patients who undergo breast surgery. The long term morbidity associated with BCS is possibly under reported in the current literature. This study suggests that such pain syndrome not only affects patients' quality of life, but may also represent a psychological fear of cancer recurrence. Such patients need to be identified and offered reassurance and/or treatment when appropriate.