

Results: 10/49 patients (20%) allocated to AC were N+ whereas 16/51 patients (32%) randomised to SNM alone were N+. These 16 were then converted to complete axillary dissection at a second operation and 12 (75%) had no further positive nodes. Patients randomised to AC had a mean hospital stay of 6.8 days (range 4–10). Those with SNM stayed for 3.6 days (2–7) and those having two operations because of SNM+ a stay of 9.5 days (6–13).

Conclusions: 82% of patients suitable for the Trial were happy to be randomised. This percentage may dwindle once public perception of the value SNM becomes more wide spread. 184 of 250 patients with invasive disease were potentially eligible for SNM outside the context of a Trial (75%). An estimated 317 bed days will be saved by the introduction of the technique into this Unit in one calendar year. Applied across the country this would have a significant implication in the cost of delivering breast cancer surgery.

O-61. CHANGES IN PROLIFERATION IN BREAST CANCER WITH TAMOXIFEN AND CORRELATION WITH TUMOUR RESPONSE

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Before using MIB-1 which has been used as a cell cycle marker as a parameter of response to neoadjuvant therapy, it was thought important to assess the effect of variables such as the nature of the tumour specimen being examined and the variability of results which might be found in specimens taken at the same or different points of time without any intervening treatment.

A study was then carried out to assess the effect of neoadjuvant tamoxifen on proliferation of breast cancer and correlated changes on sequential biopsies and tumour response. Immunohistochemistry for MIB-1 was carried out using avidin-biotin technique and assessed quantitatively using a computerised image analyzer. The variability of MIB-1 measurements in breast cancer was assessed in histological sections from core excision biopsies taken simultaneously in 13 cases and sequentially (with an intervening period of 2-3 weeks) in 17 cases. 50 post-menopausal women with large ER breast cancers were treated with 20 mg/day of tamoxifen for 3 months. Tumours were monitored clinically and radiologically. Response was defined as 25% reduction in tumour volume. Quantitative immunohistochemistry using MIB-1 antibody was performed on biopsies obtained at diagnosis, 10–14 days and 3 months on treatment using image analysis.

Results show no significant differences in values between cores and sections whether taken simultaneously or sequentially. Individual pairs of cores and sections occasionally demonstrated substantial differences. Mean ratio of MIB-1 scores between cores and sections was 0.97 (95% confidence intervals [CI] = 0.68–1.38). However 95% confidence intervals for ratios within individuals were 0.14–6.68. 38 of 50 patients (76%) responded to tamoxifen. MIB-1 staining was significantly reduced at 10–14

days ($p = 0.0015$) and 3 months ($p = 0.0003$) in responding tumours but not in non-responders. At 10–14 days 28/38 (74%) of responding tumours compared with 3/12 (25%) on non-responding tumours showed a decrease in staining, a significant difference between groups, $p = 0.005$.

Changes in proliferation can clearly be detected in biopsy samples at both time points following tamoxifen treatment. These changes differ significantly in responding and non-responding tumours and predate clinical assessment of response; a minority of tumours however show paradoxical changes. Tumour heterogeneity limits the utility of these changes in proliferation in precisely predicting response to treatment in individual cases.

O-62. MORPHOLOGICAL ASSESSMENT OF HEAT SHOCK PROTEIN 27 AND OESTROGEN RECEPTOR ALPHA, POTENTIAL MARKERS OF BREAST CANCER RISK

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The search is continuing for new markers to predict breast cancer risk. Early dysregulation of oestrogen receptor (ER α) and oestrogen regulated heat shock protein 27 (hsp27) may represent an early event in mammary carcinogenesis. Having assembled a cohort of benign lesions with a known outcome, we investigated their morphological and biological markers of risk and survival probability. A case-control study was conducted on benign breast biopsies from 502 patients received at the Royal Liverpool University Hospitals from 1979 to 1999. Morphological classification and the uni- and multivariate analyses were done and the relative risk was assessed for all benign categories including blunt duct adenosis and hyperplasia of usual type (HUT). Foci of HUT ($n = 16$) and surrounding normal lobules ($n = 91$) from cases ($n = 21$) and controls ($n = 28$) were then stained using monoclonal antibodies for hsp27 and ER α and % of positively stained cells was quantified using morphometric image analysis. The expression of hsp27 and ER α was significantly higher in HUT foci from cases compared with controls ($P < 0.001$ and 0.015 respectively). The mean ER α + cells in HUT was 57% in cases and 30.27% in controls. Among cases, a significant overexpression of hsp27 was found in HUT foci compared with normal lobes ($P < 0.001$). Our data highlight a novel role mediated by hsp27 during mammary carcinogenesis and suggest that overexpression of both hsp27 and ER α may define a subset of hyperplastic phenotypically benign lesions likely to progress to breast cancer. This subset might benefit from selective anti-oestrogen approach.

O-63. COEXPRESSION OF EGFR, HER2, HER3 AND HER4 IN PRIMARY HUMAN BREAST CARCINOMA

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Overexpression of the Human Epidermal Growth Factor Receptor family members HER1 (EGFr) and HER2 (c-erbB-2) are asso-

ciated with a poor prognosis in breast cancer. The HER family comprises four receptors (HER1-4) which heterodimerise following ligand binding to activate intracellular signal transduction pathways.

We have studied the four members of this growth factor receptor family in tissue from 220 randomly selected patients who were treated for breast cancer between 1984 and 1993. Follow up data was available for all these patients. Expression was assessed by immunohistochemistry using specific antibodies to each of the family members.

Elevated expression of EGFr (HER1) was observed in 16%, HER2 in 23%, HER3 in 18% and HER4 in 12% of breast cancers. Patients with elevated expression of EGFr, HER2 or HER3 had significantly reduced survival ($p = <0.001$). Patients with high levels of HER4 had increased survival ($P = 0.01$) relative to patients with low levels of HER4. Expression of any 2 of EGFr, HER2, HER3 further reduced survival. HER4 was rarely associated with other members of the HER family (2% of cases). Cox's multiple regression analysis showed that EGFr, HER2, HER3 and HER4 are independent of size and grade and HER2 is independent of stage.

These results show that expression of members of the HER type I receptor tyrosine kinases in breast cancer is more complex than investigation of individual members of the family may suggest. Combinations of HER1-3 can further impact on patient prognosis. The role of HER4 remains poorly understood and the mechanism underlying the apparent prolonged survival in patients expressing this protein is not known. The development of agents specifically targeted against HER2 (Herceptin), EGFr (Iressa) and members of the downstream signalling pathways activated by the HER family provide new possibilities in the treatment of breast cancer. However the complex interactions highlighted by this study further suggest that we should be taking a pathway oriented approach to analysis and treatment of breast cancer

O-64. THE PROGNOSTIC VALUE OF CONTRALATERAL, METACHRONOUS, AND BILATERAL, SYNCHRONOUS BREAST CANCER IN BREAST CANCER PATIENTS

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In the Twente-Achterhoek region breast conservative treatment (BCT) is the treatment of choice since 1984 for patients with T1 and T2 (3 cm breast carcinoma). Until 1998 1545 patients with breast cancer were treated with BCT.

Forty-four patients presented with an already treated tumour in the contralateral breast. Forty patients presented with bilateral, synchronous breast cancer (BBC). Sixty-three patients developed contralateral breast cancer (CBC) in the follow-up. The follow-up ranged from 3 to 206 months with a median of 68 months. A significant relation was seen between CBC and the different clinical and histopathological factors such as age, family history, and histology. From the 63 patients with CBC 17.5% was (40 years

($p = 0.009$), and 36.5% had a positive family history ($p < 0.001$), compared to 8.1% and 20.1% respectively for the rest. This was in contrast to BBC where no significant relation was seen to clinical and histopathological factors.

The overall recurrence rate was 34.9% for CBC and 30% for BBC compared to 16.2% for the rest ($p < 0.001$ and $p = 0.021$). The local recurrence rate was respectively 17.5% and 3.6% for CBC versus the rest ($p < 0.001$), and the distant metastasis rate respectively 25.4% versus 14.6 % ($p = 0.016$). Only the distant metastasis rate was significantly higher for BBC versus the rest ($p = 0.006$).

In a multivariate logistic regression analysis for the presence of distant metastasis for BBC, taking into account all relevant factors, bilaterality did not show significance (O.R. 2.1; 95% Conf. Interval 0.7–5.6; $p = 0.163$).

In a multivariate logistic regression analysis CBC was the strongest factor for local recurrence (O.R. 5.2; $p < 0.001$; 95% Conf. Interval 2.4–11.3).

The 5-year disease specific survival for the 63 patients with CBC versus the rest was 92.4% versus 91.3% respectively. For the patients with BBC this was 81.5% compare to 91% for the rest of the patients (log rank $p = 0.0017$).

The 5-year local recurrence free survival (LRFS) was 88.9% for patients with CBC and 97% for the rest ($P < 0.001$). In a multivariate Cox-regression analysis for LRFS, taking into account all relevant factors contralaterality did show significance (H.R. 3.1; 95% Conf. Interval 1.5–6.2; $p = 0.002$).

The 5-year disease free survival (DFS) for BBC versus the rest was 72.3% and 85.6% respectively (log rank, $p = 0.011$). In a multivariate Cox-regression analysis for DFS, taking into account all relevant factor bilaterality did not show significance (H.R. 1.6; 95% Conf. Interval 0.7–3.6; $p = 0.279$).

Conclusion: This study shows a difference in predictive factors and prognostic value for patients with CBC or BBC versus unilateral breast cancer. The presence of BBC seems to have no major prognostic value. There is a significant relation between CBC and local recurrence.

O-65. IMMEDIATE BREAST RECONSTRUCTION USING THE LATISSIMUS DORSI MYOCUTANEOUS FLAP (LDF): LONG TERM RESULTS AT 15 YEARS PLUS

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Although early results of immediate reconstruction using LDF are satisfactory, long term consequences are not well known. The aim of this study was to assess by questionnaire the effects of immediate breast reconstruction 15 years plus after the procedure. Between 1983 and 1995 78 patients underwent a mastectomy and immediate reconstruction using LDF. In 1987, 47 were surveyed by questionnaire (EQ) (exclusion: 11 deceased, 5 lost to follow up, 15 non-responders). In December 2000 33 of the 47 took part in a later questionnaire (LQ) (exclusion 6 deceased, 2 lost to follow up, 6 non-responders). In this longitudinal study