

Levels of PTHrP and its receptor mRNA were significantly higher in bone metastases than in primary breast carcinomas (protein: $P = 0.004$; receptor: $P = 0.0053$) but significantly lower in other metastases (protein: $P = 0.0001$; receptor: $P = 0.0003$). There was no significant difference between levels of expression of IL-6 and its receptor in bone metastases and primary tumours. Other metastases had significantly lower levels of IL-6 than bone metastases ($P = 0.008$) but were not significantly different from primary tumours. However, IL-6 receptor mRNA levels were significantly higher in other metastases than either bone metastases ($P = 0.003$) or primary tumours ($P = 0.04$). IL-1 α was over-expressed in all metastases.

These results demonstrate a differential expression of growth factors in metastases to different sites. This could explain the variable response of metastases at different sites in the same patient to systemic therapy.

0-84. Is measurement of CEA of benefit during follow up in patients with primary breast carcinoma

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Tumour markers have a recognised role in the management of breast carcinoma but controversy exists as to which are of most benefit or whether a combination should be used in each individual patient. The aim of this study was to examine the usefulness of CEA during follow up of patients with breast carcinoma and to compare this to CA15-3. The tumour markers CA15-3 and CEA were measured in 125 patients undergoing follow up of breast carcinoma using a standard ELISA technique. During the course of follow up 10 patients developed metastatic disease and a further 13 developed loco-regional recurrence. The mean levels of each of the tumour markers are given in the table, together with the number (percent) of patients with elevated levels of tumour markers.

Disease status	Number	CEA	CA15-3
No recurrence	102	6 (5.8%)	10 (9.8%)
Loco-regional recurrence	13	3 (23.1%)	5 (38.5%)
Metastatic disease	10	5 (50%)	8 (80%)
No recurrence	102	9.9 (1.9)	37.6 (3.3)
Loco-regional recurrence	13	12.4 (3.6)	44.4 (5.3)
Metastatic disease	10	15.3 (3.5)	95.4 (37.7)

Results as mean (SEM) or number (%)

Three of the thirteen patients with loco-regional recurrence had elevated levels of CEA, however all of these and two additional patients had elevated levels of CA15-3. Five of the 10 patients with metastatic disease had elevated levels of CEA, however all these patients had elevated levels of CA15-3.

In conclusion the measurement of CEA provided no additional information to CA15-3 assessment and was of little benefit in patients undergoing follow-up of breast carcinoma.

0-85. Role of radiotherapy in early breast cancer and the salvaging of patients with local relapse

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Between August 1985 and December 1992, 707 patients with early breast cancer (less than 4 cm diameter with clinically node negative axillae) were

treated with wide local excision only and then randomised to receive immediate post-operative radiotherapy to the breast and axilla or observation only. All patients received adjuvant tamoxifen for a minimum of two years.

After a median follow up of 7 years, 530 patients are still alive and 37 have died from conditions unrelated to carcinoma of the breast. In terms of overall survival, there is no significant difference between those receiving radiotherapy (93%) and those who were subsequently observed (92%) ($\chi^2 = 1.81$, $P = 0.18$). There is, however, a significant difference in the two year actuarial relapse rate, 8% in those who received radiotherapy and 18% in those who did not ($\chi^2 = 24.1$, $P < 0.0001$). Patients who did not receive radiotherapy were more likely to present with local relapse (96/132 relapses compared to 35/80 in the radiotherapy group), with local relapse defined as recurrence in the breast and/or axilla, while remaining relapses were in distant sites.

The median time to relapse was 24 months for both local and distant relapse in the no radiotherapy group compared to 33 and 37 months, respectively, for the radiotherapy group. It is important to determine if patients who have not received adjuvant radiotherapy can be adequately salvaged at relapse. 71% of patients who relapsed locally in the no radiotherapy arm were salvaged by surgery, 18% with radiotherapy, 3% chemotherapy, 3% hormonal and 1% combination therapy. Survival from relapse is significantly better for the no radiotherapy group compared to those who received adjuvant therapy ($\chi^2 = 14.42$, $P = 0.0001$), an unsurprising result as $\frac{2}{3}$ of these patients relapsed locally as opposed to $\frac{1}{4}$ of those receiving adjuvant radiotherapy. Thus when stratifying for the site of relapse, there is no survival benefit from relapse for the no radiotherapy group ($\chi^2 = 2.1$, $P = 0.15$). These data clearly demonstrate that patients who did not receive radiotherapy and who relapsed locally, can in fact be adequately salvaged.

0-86. Local recurrence of breast cancer: new concepts about its biology and clinical relevance

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It is believed that breast cancer is multicentric and although multicentric foci (MCF) are present all over the breast, 90% of them are found in the index quadrant. In randomised clinical trials of breast conservative therapy it was found that > 90% of early breast recurrences were found to occur in the index quadrant and therefore it was believed that local recurrence arose from MCF and that all MCF correctly deserved treatment with whole breast radiotherapy.

Results of our recent analysis of spatial distribution of MCF within the breast in 2- and 3-dimensions suggests that the relative distribution of primary tumour and MCF in the 4 breast quadrants is significantly different ($P = 0.034$). MCF were present beyond the index quadrant (25% of breast volume including the tumour) in as many as 79% (15/19) of breasts that harboured MCF; and, in half the cases (15/30) when all breasts were considered. Although the number of patients in the present series is small, the probability of our finding being due to play of chance is 1 in 1500. In 15 out of 19 breasts that harboured MCF, the lesions were present beyond 25% of breast volume including the tumour (index quadrant), and in half the breasts (15/30) when all cases were considered. When the 19 breasts which actually harboured MCF were considered, then, as many as 79% (15/19) harboured MCF beyond 25% of breast volume including the tumour (index quadrant). When all patients were considered, half (15/30) harboured MCF beyond the index quadrant. If MCF were giving rise to the early breast recurrence half would have occurred in other quadrants; but 90% of such recurrence occurs in the index quadrant, whether or not radiotherapy is given and irrespective of clear margins suggesting that

it does not arise from either MCF or overlooked tumour, respectively. We propose that local recurrence arises a) from circulating metastatic cancer cells (local relapse does harbingers a poorer prognosis) or b) from local transfection of surrounding breast epithelium by nuclear material released from the original malignant clone resulting in insertional mutagenesis. The recent report of the loss of heterozygosity in morphologically normal tissue around breast cancer supports the latter view.

In any case, if MCF do not give rise to breast recurrence then why should we treat them with either mastectomy or whole breast radiotherapy? It is as necessary or as unnecessary as treating the contralateral breast! We have begun pilot studies of a clinical trial to test whether radiotherapy to the index quadrant alone can achieve good local control.

0-87. Assessing the adequacy of mastectomy by flap biopsies

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Local recurrence occurs in 2-5% of patients following mastectomy. This may occur many years after surgery even for small tumours. This suggests that local recurrence may not be completely explained by the presence of residual malignant cells at the time of mastectomy. Another possible explanation is that local recurrence could be due to new tumour growth arising from residual breast tissue left on the flaps at the time of surgery.

The aim of this study was to assess the adequacy of mastectomy in removing all breast tissue from the skin flaps at the time of surgery and assessing the relevance of this to our clinical practice.

Seventy-six patients with a diagnosis of invasive breast cancer were studied. Once the mastectomy flaps had been dissected two biopsies of the most prominent areas of the under surface of the flaps were located by the assistant and sent to pathology to look for epithelial elements. In 10 patients breast epithelium was present in the flap biopsies and this was operator independent. To determine the relevance of this to our practice we then retrospectively looked at the nodules of local recurrence excised following mastectomy in the preceding two years. Twelve cases were identified; in 2 cases ductal carcinoma in situ was identified and in 5 cases normal breast tissue was adjacent to the 'recurrence' therefore in 7 of the 12 cases the recurrence may have been a new tumour developing in residual breast tissue.

We conclude that even when a deliberate attempt is made to cut thin flaps there is still a considerable risk of leaving residual breast tissue at the time of mastectomy. We have demonstrated that this may be a contributory factor in the development of local recurrence.

0-88. Reducing cardiac doses in post-operative irradiation of breast cancer patients

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We presently employ a radiotherapy technique with 2 dimensional planning of wedged glancing fields to the breast or chest wall for post-operative radiotherapy of breast cancer. Left sided breast irradiations inevitably encompass heart within the treatment volume, resulting in late mortality which may negate the cause-specific survival advantage of the therapy. It is not clear whether late cardiac mortality is related to maximum or mean cardiac radiation dose. A move from central slice radiotherapy plans to sophisticated 3 dimensional planning, may resolve these problems. However, as an initial step we have investigated the effect of varying the treatment position to try and minimise the heart dose. We then proceeded

to investigate the additional reduction in cardiac dose obtainable by individualised 3 dimensional planning. All cardiac doses were calculated from dose-volume histograms using a 'Helax' planning system.

The effect of positioning was studied in 11 patients with left sided tumours and 5 with right sided tumours. Using the same arrangement of glancing fields the optimum patient positioning resulted in a reduction in cardiac dose compared to our standard patient treatment position. On the left side the reduction in mean cardiac dose was 60%, and in maximum dose was 32%, and on the right was 17% and 31% respectively. Using this optimum treatment position, a further 10 patients with left sided tumours then had the cardiac doses investigated, comparing our standard glancing-field set-up with 3-dimensional planning. A further reduction of 12% in the mean cardiac dose was achieved and 5/10 patients had a further small reduction in the maximum dose of 4.6%. One patient had a further reduction in maximum dose of 58%.

In conclusion, sophisticated radiotherapy planning can reduce cardiac doses, but optimum patient positioning is of greater importance.

0-89. A randomised controlled trial of early versus standard discharge after breast cancer surgery

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Early discharge after breast cancer surgery would reduce hospital costs and stay but its effect on physical and psychological morbidity is unknown. We have performed a randomised controlled trial comparing early discharge at two days post-op with a standard discharge policy.

Patients have had physical morbidity (infection, seroma, shoulder movement) and psychological morbidity (Rotterdam Symptom Questionnaire, Checklist of Concerns, Hospital Anxiety and Depression Status) compared for each discharge policy pre-op and at 1 and 3 months post-op. To date 100 women have been randomised into the trial, 20% undergoing mastectomy and axillary node clearance and the remainder breast conservation surgery.

Women discharged early had significantly greater shoulder movement at one month post-op than standard discharge patients but no difference in infection or seroma development was noted. At one month a significantly lower Rotterdam Symptom Score was seen in patients undergoing early compared to standard discharge ($P \leq 0.03$) and generally psychological morbidity was lower in patients discharged early.

	Early	Standard	
n	50	50	
Median hospital stay (range)	2 (2-8)	5 (3-13)	($P \leq 0.01$)
Restricted arm movement	89%	63%	($P \leq 0.01$)
Rotterdam Score at 1 month	10.4 (0-54)	14 (12-51)	($P = 0.03$)

Early discharge after breast cancer surgery is feasible and does not increase physical or psychological morbidity.

0-90. Association of vascular endothelial growth factor (VEGF) and its receptor (FLT-1) with microvessels density in invasive ductal carcinoma of the breast

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Angiogenesis is critical for growth and metastasis of breast tumours.