ABSTRACTS

8th Nottingham International Breast Cancer Conference

16–19 September 2003

O-1. Breast cancer treatment in nine hospitals in Southeast Sweden 1986 to 1999. Comparison of outcome

Tejler G, Einarsson E, Nordenskjöld B *and the Southeast Sweden Breast Cancer Group*

Southeast Sweden with 976,000 inhabitants is served by nine hospitals with specialized breast surgeons collaborating with four pathology units and two departments of oncology. The hospitals serve areas with populations from 46,000 to 167,000 inhabitants.

7892 women had their first invasive breast cancer diagnosed between 1986 and 1999, 60% were diagnosed within the mammography screening programme. All patients were treated according to a management program specifying principles for diagnostic procedures, surgery, radiotherapy and adjuvant medication. Ten years breast cancer specific survival for the entire population was 75%. For stage I it was 91%, for stage II NO 76%, for stage II N+ 62% and for stage III 38%.

The results were equal in all hospitals and in an international comparison very good. There was a non-significant trend towards better results in smaller hospitals.

Our data show that breast cancer survival was not related to hospital size.

O-2. Goserelin vs CMF in premenopausal women with node +ve breast cancer: ZEBRA trial survival results

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The Zoladex Early Breast Cancer Research Association (ZEBRA) trial compared the efficacy and tolerability of goserelin ('Zoladex') vs CMF pre-/perimenopausal women with node +ve, early breast cancer (BC). From 1990-1996, 1640 pats (aged <50 yrs) received goserelin (3.6 mg every 28 d for 2 yrs; n = 817) or CMF (6 × 28-d cycles; n = 823) for the adjuvant treatment of BC. We present an updated analysis of disease-free survival (DFS), distant DFS (DDFS) and overall survival (OS) [median follow-up 7.3 yrs]. A competing risk model investigated whether the treatments have a different influence on isolated locoregional recurrence, distant metastases/death without previous recurrence or new primaries as first events.

An initial analysis showed a significant interaction/between treatment and oestrogen receptor (ER) status ($p < 0.01$). In pts with ER-ve tumours (n = 1189) goserelin continues to be equivalent to CMF for DFS (HR 1.05; p = 0.75; 95% CI 0.88-1.24; p = 0.60) and for DDFS (HR 1.03; p = 0.75). Median DFS was 7.9 yrs of goserelin and 8.0 yrs for CMF.

Non-inferiority of goserelin vs CMF was shown for as in patients with ER+ve turnOutS (HR 0.94; p = 0.62).

In pts with ER-ve disease (n = 304) goserelin was expectedly inferior to CMF for DFS, DDFS and OS.

The competing risk model demonstrated a close similarity between treatment groups for all 3 classes of first events in ER-ve pts. This analysis confirms the previous outcomes from the ZEBRA trial and that goserelin is an effective alternative to CMF in pts with ER+ve, node +ve early BC.

O-3. Tamoxifen combined with Goserelin vs CMF in the treatment of premenopausal patients with hormone responsive breast cancer: an update from the ABCC Trial 5

Jakesz R *on behalf of the Austrian Breast and Colerectal Cancer Study Group Trial 5 investigators*

The Austrian Breast and Colorectal Cancer Study Group Trial 5 compared the efficacy of tamoxifen combined with goserelin ('Zoladex'; T+Z) vs treatment with standard chemotherapy. Assessable patients (n = 1034) with hormone-responsive stage I or II breast cancer were randomised to goserelin (3.6 mg every 28 days for 3 years) plus tamoxifen (20 mg every day for 5 years; n = 511) or cyclophosphamide, methotrexate and fluorouracil (CMF; × 28-day cycles; n = 523). Stratification criteria -included tumour stage and grade, number of involved nodes, type of surgery, and steroid hormone receptor content. Relapse-free survival (R;FS) was defined as time from randomisation to first relapse, local recurrence, or contralateral incidence, and overall survival (OS) as time to date of death.

At a median follow-up of 60 months, 88 (17.2%) patients receiving T+Z relapsed compared with 109 (20.8%) patients treated with CMF. Local recurrences emerged in 24 (4.7%) patients treated with T+Z compared with 42 (8.0%) patients treated with CMF. Secondary malignancies in the opposite breast were similarly lower in patients receiving T+Z (3 patients) compared with those receiving CMF (12 patients). RFS (p = 0.037) and local recUrrence-free survival (p = 0.015) differed significantly in favour of endocrine therapy, with a similar trend observed in OS (p = 0.195). The significant advantage for RFS associated with T+Z was maintained after an extended 72-month follow-up, with a rate of 78.1 % for the combination vs 73.7% for CMF (p = 0.045). Local RFS was also significantly greater with T+Z (92.6% vs 88.8% with CMF; p = 0.008) at the 72-month follow-up. Cox analysis of RFS showed significant interactions for treatment, age, tumour stage, nodal status and PgR status (all $p < 0.001$). In conclusion, these data confirm that the combination of goserelin and tamoxifen is significantly more effective than CMF in the adjuvant treatment of premenopausal patients with stage I and II hormone-responsive breast cancer.

O-4. CMF vs tamoxifen (TMX) plus goserelin (GOS) as adjuvant treatment of ER positive (ER+ve) premenopausal breast cancer. Updated results of a multicentric trial

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Between January 89 and January 97,244 premenopausal ER+ve early breast cancer patients were randomly allocated to receive either 6 cycles of 'classical' CMF or 5 years of TMX (20 mg/d) plus GOS 3.75 mg q4w for 2 years (37 patients chose

oophorectomy or ovarian irradiation instead of pharmacological castration). 120 patients were assigned to chemotherapy (CT) and 124 to endocrine therapy (ET). Groups were well balanced in respect to age, T size, T grade, N involvement and primary treatment.

At a median follow-up time of 10 years (1-14), 102 patients experienced a disease recurrence (48 in the CT group and 54 in the ET group) and 57 died (26 and 31, respectively). 10-year PFS was 57% and 59%, respectively. Failure ratio did not differ according to age at entry, T size and N status. However, there was a significant trend in favour of CMF among the patients with undifferentiated tumours. Similarly, there was no difference in 10-year overall survival between groups (78% in both groups). However again patients affected by G3 tumours appeared. to do better with CMF. Adjusted Odd ratios of recurrence and death for the patients treated with ET were 0.98 (0.66-1.47) and 0.99 (0.58-1.71), respectively. Multivariate analysis confIrmed age, nodal status and T grade to be independent predictors of the risk of recurrence or death.

This long-term analysis confirms that the combination of TMX with GOS or other forms of ovarian suppression is a safe and effective adjuvant treatment for premenopausal ER+ve breast cancer, namely for women with G1-G2 tumours.

O-5. Same gain, less pain? Premenopausal women's preferences for either adjuvant chemotherapy or Goserelin

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Considerable data have emerged recently from RCTs showing that hormone therapy that includes ovarian suppression may be at least as effective as CMF in premenopausal women with early, hormone-receptor positive breast cancer. Despite these data and the different impact the treatments have on quality of life, many clinicians do not routinely even offer women the option of goserelin. We are conducting a survey of 200 healthy premenopausal women aged 25-49 to establish their hypothetical preferences for either chemotherapy or goserelin. Scenarios describing the pros and cons of each treatment were constructed using published data and information from cancer charity websites. These were modified following feedback from 5 experienced consultants and 3 specialist breast cancer nurses and incorporated into a questionnaire which was given to volunteers from a variety of socio-economic backgrounds. We examined the reasons women gave for their preferences and the relationship of these with other demographic variables. Data from 155 women have been collected and analysed to date and show an overwhelming preference for goserelin over chemotherapy ($p < 0.0001$). Women viewed the side effect profile of goserelin as more acceptable and valued the chance to retain fertility. A further important feature was the mode of administration with injections administered by the GP seen as less disruptive to everyday life. The few women who chose chemotherapy were less concerned about fertility loss and felt prepared to accept the side effects as a trade-off for completing treatment more quickly. At this stage preferences do not appear to be related to age. Patient involvement in decision- making following a full appraisal of the potential benefits and harms is important and these preference data may be useful to clinicians when discussing options for adjuvant treatment.

O-6. Predictors of metastasis in higher-echelon nodes when sentinel lymph node is positive in breast cancer

Goyal A, Mansel RE, Douglas-Jones A. *Department of Surgery UWCM Cardiff on behalf of the ALMANAC study group*

Background: Even though the status of the axilla is known to be the single most important prognostic factor, there is clearly no benefit to removing normal lymph nodes. In approximately 50% to 65% of patients the sentinel lymph node (SLN) is the sole site of regional node metastasis.

Methods: In the ALMANAC audit phase, 31 surgeons in 17 centres throughout the UK operated on 842 breast cancer patients. The SLN was identified using the combined technique (Nanocoll® + blue dye) followed by standard axillary dissection.

Results (see table): Of the 271 patients with a positive SLN, 151 (56%) patients had no further positive nodes in the axilla, 120 patients (44%) had additional metastasis in nonsentinel lymph nodes (NSLN) upon completion of axillary node dissection.

Predictors of axillary metastasis in the NSLN

Variable		Positive NSLN	Negative NSLN	p-value
Tumour size	<2 cm	27.9% (31/111)	72% (80/111)	0.004
	2-5 cm	44.6% (41/92)	55.4% (51/92)	
	>5 cm	66.7% (4/6)	33.3% (2/6)	
Tumour grade	1	31.3% (10/32)	68.7% (22/32)	0.030
	2	29.3% (29/99)	70.7% (70/99)	
	3	48% (36/75)	52% (39/75)	
Age (years)	Mean	55.2 (±11.2)	55.4 (±10.8)	0.443
	Median (range)	54 (27-78)	54 (32-80)	
Number of positive SLN	Mean	1.5 (±0.9)	1.3 (±0.6)	0.119
	Median (range)	1 (1-6)	1 (1-4)	
Analysis below is based on data from Cardiff Centre only (No. of patients with positive SLN = 65)				
Lymphovascular invasion	Present	56% (14/25)	44% (11/25)	0.289
	Not present	42.5% (17/40)	57.5% (23/40)	
Extranodal invasion	Present	83.3% (10/12)	16.7% (2/12)	0.007
	Not present	39.6% (19/48)	60.4% (29/48)	
Size of metastasis	<2 mm	7.1% (1/14)	92.9% (13/14)	<0.001
	2-5 mm	56.2% (9/16)	43.8% (7/16)	
	>5 mm-10 mm	38.9% (7/18)	61.1% (11/18)	
	>10 mm	100% (12/12)	0% (0/12)	

Conclusions: In patients with a positive SLN, increasing tumour size, tumour grade, size of the metastasis and extranodal invasion all significantly increase the frequency of additional positive nodes. Characteristics of the SLN and primary tumour can. provide information to determine the need for a complete axillary node dissection.

O-7. A study of 330 screening-detected breast cancer patients: implications for shorter screening intervals and less radical surgery

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Histological features of 330 screen-detected breast cancers di-

agnosed between 1997 and 2003 in one regional breast screening unit were analysed to investigate any relationship between tumour size, grade and lymph node status. Tumour size ranged from 2-27 mm. Mean tumour diameters were 14 mm grade I ductal, 15 mm grade II ductal, 17 mm grade III ductal and 19 mm lobular.

The distribution of the histological was as follows:

Ductal carcimona grade I (DC I)	Ductal carcinoma grade II (DC II)	Ductal carcinoma grade III	Lobular carcinoma	Special type
23%	46%	16%	8%	11%

Only 11% of tumours were well-differentiated and of special type while 66% were Grade II or worse.

The table below demonstrates axillary node positivity in relation to histological and tumour size:

	Tumour size mm				
Tumour grade	0-9	10-14	15-20	20-24	25 and above
DC I	0	8%	30%	60%	50%
DC II	0	13%	20%	36%	14%
DC III	0	33%	21%	17%	25%
Lobular	0	0	0	33%	8%
Special type	8%	9%	15%	0	0

% tumours With positive lymph nodes.

All ductal carcinomas of no special type and less than 10 mm in diameter were node negative irrespective of histological grade. All lobular carcinomas less than 20 mm in diameter were node negative.

The high number of large poorly differentiated tumours suggests the need to reduce the three yearly screening interval. Ductal carcinomas <10 mm and lobular carcinomas <20 mm are unlikely to be node positive and should not undergo radical axillary staging procedures.

O-8. The 2001/02 ABS at BASO audit - repeat therapeutic operations and pre-operative history

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The 2001/02 ASS at BASO audit included 10,191 cancers detected by the UK NI-1SSSP between 1 April 2001 and 31 March 2002. Overall, 89% of cancers were diagnosed pre-operatively. 93% of invasive cancers and 73% on non-invasive cancers had a pre-operative diagnosis. 25% of B5a (Non-invasive) cancers, and 92% of C5 cancers were found 1 to be invasive following surgery. 98% of B5b (invasive) cancers had surgical confirmation of invasive cancer.

Overall, 14% of invasive cancers and 20% of non-invasive cancers underwent more than one surgical operation. For invasive cancers 12% with a B5b (invasive), 15% with a C5 and 41 % with a S5a (non invasive) pre-operative diagnosis had more than one therapeutic operation. 55% of the invasive cancers with a B5b (invasive) pre-operative diagnosis had repeat operations that included conservation surgery. 6% of the repeat operations involved surgery to axillary nodes alone. Overall, 7% of invasive 1: cancers with a C5 pre-operative diagnosis and 40% with a B5a (non invasive) pre-operative diagnosis had their nodal status determined as a result of repeat operations.

Data will be presented to show how these parameters vary between regions and screening units to give an insight into differences in the treatment protocols followed within the UK NHSBSP.

O-9. Breast cancer in Southeast Sweden: incidence, treatment and survival for patients diagnosed 1986-1999

Tejler G. *for the Southeast Sweden Breast Cancer Group*

Southeast Sweden with 976,000 inhabitants is served by nine hospitals with specialized breast surgeons. These have treated breast cancer patients according to a management program and reported data to the regional cancer registry.

Population based mammography screening was introduced in 1986 for women 40 to 74 years of age. Breast cancer incidence, treatment and survival in this defined population is now reported.

7892 women had their first invasive breast cancer diagnosed between 1986 and 1999. The median size was 17 rom and 30% had axillary metastases. 52% had a modified radical mastectomy and 33% partial mastectomy and axillary clearance. 40% of the mastectomy patients and 87% of the breast conserved patients received postoperative radiotherapy in two collaborating oncology departments. Patients with receptor positive tumours stage II and III received adjuvant tamoxifen. Node positive patients under 60, and later in the study period node negative women fulfilling high risk criteria, received adjuvant chemotherapy.

Breast cancer specific survival for all stages was 83% at 5 years and 74% at 10 years. For stage I these. figures were 96% and 91% and for node positive stage n patients 78% and 62% respectively.

O-10. Do patients with breast cancer want statistics?

Maher J, Bygrave H, Hall M, Tauton N, Patterson L. *Hillingdon Breast Unit, Mount Vernon Cancer Centre*

Introduction: Hillingdon Breast unit has piloted the acceptability of a new follow up strategy. As part of the study patients were asked if they wanted to see detailed statistical charts demonstrating the prognosis of their disease based on size, grade, nodal status and hormone receptors. At the start of the study it was hypothesised that many would not want to see statistics, particularly older people and that for those with worse prognosis disease (less than 20% survival) the statistics would be worse than they expected.

Method: From June 2000-October 2002 patients completing initial treatment were offered self-managed follow up with no booked routine appointment, yearly mammography for 5 years and direct access to the clinic via the breast care nurse. A pilot study with telephone follow up was conducted to test the content of specially designed bar charts, then 200 patients were offered the opportunity to see their statistics as part of a larger Cancer Services Collaborative service redesign initiative.

Patients were asked 3 questions - do you want to see your statistics, are they better, worse or the same as you expected.

Results: More than 80% of people wanted to see their statistics with those older than 75 no less likely to want to see them. In 85% of cases statistics were better than expected or the same. Those who thought their statistics worse than expected, were distributed across the prognostic range. One patient expressed the wish that she had not seen them. Breast care nurses are now routinely using the charts before oncologists see the patients.

Conclusion: For the majority of patients with breast cancer, statistics are better than they expected and they find it helpful to discuss statistics in detail with their doctors. A larger study is now required to look in more detail the best way to present statistics and identify those patients who do not find it helpful.

O-11. Serum HER-2: predicting response and relapse

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Introduction: In breast cancers, the HER2/neu gene is amplified in 25-30% of all cases. The mechanism by which the amplification/overexpression occurs is completely unknown. This molecular alteration is associated with a poor clinical prognosis in early stage breast cancer in terms of shortened time to relapse (increasing the relative risk of relapse by a factor of tow–three for both node-positive and node-negative breast cancers), as well as shortened overall survival. In this study, we examine the relationship between c-erbB-2 levels and clinical factors and evaluate the use of c-erbB-2 levels in predicting response to treatment, and in identifying patients with recurrent disease.

Patients and methods: c-erbB-2 levels were determined in sera from 151 patients treated for benign and malignant breast disease, and from 20 healthy controls using a sandwich immunoassay. Serum samples were obtained pre-operatively after informed consent was obtained. The levels were compared with tissue HER-2 status, and serum levels of CA15-3, CA125 and CEA.

Results: c-erbB-2 levels according to stage of disease are summarized in Table 1. On applying the Pearson test, there was a significant positive correlation between disease stage and serum c-erbB-2 levels ($p < 0.005$). There was no correlation between tissue HER-2 status and serum levels.

Table 1. Serum levels according to stage of disease

Patient group	Control	Benign	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Patient #	20	21	16	36	62	12	4
Mean age	38.7	47.3	57.3	57.1	61.2	59.6	65.8
HER-2/neu (s)	10.7	10.9	10.08	11.4	11.4	11.0	58.0
	(0.5)	(0.4)	(0.5)	(0.5)	(0.4)	(0.79)	(46.97)
HER-2/neu (t)				1.1 (0.2)	1 (0.2)	0.7 (0.2)	0 (0)
CEA			1.2 (0.3)	2.2 (0.4)	2.0 (0.3)	1.9 (0.8)	3.0 (0.9)
CA15-3			20.7	20.1	19.3	29.0	195
			(3.3)	(2.0)	(1.5)	(8.4)	(0)
NPI			0.6 (0.1)	2.0 (0.1)	3.4 (0.9)	3.8 (0.3)	

Values expressed as mean (standard error of mean); NPI, Nottingham Prognostic Index.

Conclusion: We have shown that the HER-2 serum test is potentially useful in assessing disease stage at diagnosis. Its most important role may be as a predictor of response to treatment and as an indicator of recurrent disease.

O-12. Reading the prognosis of the individual by the exact NPI value

Mitchell M, Blamey RW . *Nottingham City Hospital*

The NPI has until now been used to group women to initially 3 and later 5 prognostic groups, with any two adjacent groups separated by 10-20% in their 10 year survival predictions. This is usually satisfactory for making therapeutic decisions.

However the prognosis is inversely related to the height of the NPI and it is possible to draw a graph through the survival figures for 8 NPI values at which are clustered enough patients.

From the graph the survival prediction for any individual (to one decimal point NPI value) may be read. This is particularly useful for calculating expected 10 year survivals and the median survivals for life expectancy for legal cases.

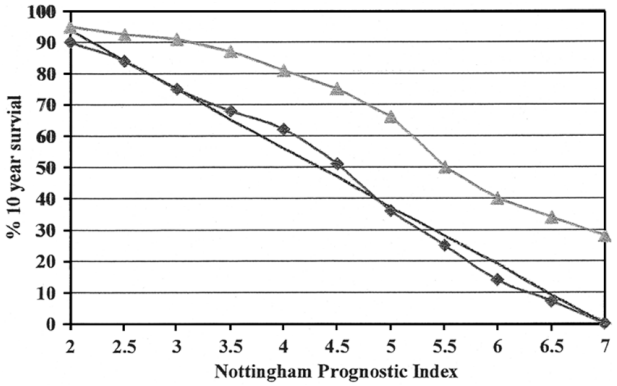

Fig. 1.

Fig. 1 shows lines based on 1980-86 (pre-adjuvant therapy) and 1990-96 (adjuvant local and systemic treatments used selectively).

O-13. The prognoses of tumours detected in the NHS BSP analysed by the Nottingham Prognostic Index (NPI)

Lawrence G, Bishop HM, Blamey RW, Pinder S, Wilson ARM. *West Midlands Cancer Intelligence Unit Birmingham and Nottingham City Hospital*

The prognosis of the turnOuTS detected at screening is overall better than for all those within a whole tumour set. It has been suggested that all small tumours do well, regardless of grade.

The tumours detected in the UK NHS BSP in 1992-3, with data combined from the BASO Breast Group annual audit in 2002 are compared with all cases (symptomatically presenting and screen detected) aged 50-64 diagnosed at NCH in 1990-1996 (Table 1). Comparison has been made using the Nottingham Prognostic Index (NPI), which combines the time dependent factors of size and LN stage.

As expected there are more cases in the GPG and less in the MPG and PPG in the screen detected set.

However once stratified by NPI screen detected tumours be-

Table 1

NPI group	n (%)		9 yr survival (%)	
	NHSBSP	NCH	NHSBSP	NCH
Overall	10390	772	89	77
Good (GPG)	5987 (58)	318 (41)	98	92
Mod (MPG)	3765 (36)	352 (46)	83	76
Poor (PPG)	638 (6)	102 (11)	45	41

have largely as expected by NPI (their slightly better survival within each NPI group correlating with their lower median size within each group).

O-14. Which women with screen detected breast cancer (SDBC) require chemotherapy? (new index predicting recurrence and mortality)

Prasad R, Byrne G, Wilson M, Barr L, Baildam AD, Morris J, Bundred NJ. *University Hospital of South Manchester*

Meta-analysis of symptomatic breast cancer trials recommends adjuvant chemotherapy for women under 70 years, at high risk of recurrence. Identification of women needing chemotherapy is required to avoid treatment morbidity in SDBC. To determine women with SDBC undergoing surgery, at high risk of recurrence, we produced a simple index based on tumour grade scored (1, 2 or 3), size (<1.5 cm = 1, 1.5–2.5 cm = 2, >2.5 cm = 3) and node status (negative = 1, <4 nodes = 2, ≥4 nodes = 3). Scores for each parameter were added producing a range from 3-9. Median follow-up was 70 months (range 21-103). Between 1990-1998, 962 SDBCs were diagnosed in one unit and overall survival was 96.3%. Regardless of grade and node status only 10/587 (1.7%) of tumours <1.5 cm had recurred. Overall 90% of SDBCs had scores 3-6 with 5 year 10 months survival of 98.7%, but this fell to 53.3% in SDBCs with score 9. Index scores identified women (scores 7–9) at high risk of recurrence ($p^* < 0.001$) and mortality ($p^* < 0.001$).

SDBC index score	Women n (%)	5 years 10 months	
		Recurrence n (%)	Mortality (cancer-specific) n (%)
3	166 (17.3%)	1 (0.6%)	nil
4	292 (30.4%)	10 (3.4%)	1 (0.3%)
5	250 (26%)	16 (6.4%)	2 (0.8%)
6	156 (16.2%)	23 (14.7%)	8 (5.1%)
7	45 (4.7%)	12 (26.7%)	10 (22.2%)
8	38 (4%)	18 (47.4%)	8 (21.1%)
9	15 (1.6%)	14 (93.3%)	7 (46.7%)
p*		<0.001	<0.001

*Chi-square test for trend.

Conclusion: This index can identify 10% of SDBCs at high risk of recurrence, who will benefit from chemotherapy.

O-15. Tables for the improvement in survival from adjuvant systemic therapies expected in the individual

Blamey RW, Mitchell M, Morgan DAL. *Nottingham City Hospital*

The EBCTCG overviews of adjuvant therapy provide figures of relative risk reduction (RRR). Applied to the survival chance of the individual, shown by the Nottingham Prognostic Index (NPI) the absolute improvement expected from therapies for that individual, are shown.

A. Women 50+, % survival

NPI group	Observed 1980-86	Expected	
	No Adj	Tam 5 yr (ER+) RRR 27%	CMF RRR 11%
E	84	89	86
G	63	73	67
MI	59	70	64
MII	43	59	49
P	15	39	24

B. Women under 50, % survival

NPI Group	Observed 1980-86	Expected		
	No Adj	Ov, abl, 31% RRR	CMF 27% RRR	ER+ Goserelin
E	90	93	93	93
G	80	86	85	85
MI	64	75	74	74
MII	46	63	61	61
P	14	41	37	37

The baseline figure ('observed 1980-86') was the survival before the introduction of adjuvant systemic therapies. The 'Expected' figures are the effects on these from the relative risk reductions (RRR) demonstrated in the EBCTCG overviews for each therapy.

O-16. Current practices in breast conservation surgery: results of a questionnaire

Young OE, Valassiadou K, Dixon JM. *Western General Hospital Edinburgh*

Aims: To obtain data relating to the variations in practice amongst breast surgeons regarding breast conservation surgery.

Methods: Questionnaires were sent to 280 breast surgeons in the UK.

Results: 127 Surgeons replied -all of whom were consultants individually treating 50 cancers annually.

61 % always take full thickness of breast tissue for wide excisions. 94% always orientate the specimen for the pathologist. 60% rarely use specimen x-ray (or palpable lesIons whereas 91% always take specimen x-rays for impalpable lesions. Cavity shavings were always or usually taken by 18.3% and bed biopsies by 13.4%. In 93% of units, the pathologists report the clearance margins.

With regard to clearance margins for invasive cancer, 7% were happy if there was no disease at the margin. 24% thought 1 mm was sufficient, 17% wanted 2 mm or more, 42% required 5 mm and 6% wanted 10 mm. There was wide variation in the practice of re-excision.

30% thought that the radiotherapist would not change the radiation dose if the margins were close, and 60% thought an Increased dose would be given and 10% did not know. 50% of Burgeons wanted a wider margin in the presence of an extensive in situ component. 39% wished wider margins for younger women.

In DCIS 17% were happy with 1 mm, 20% for 2 mm, 40%

for 5 mm and 20% for 10 mm or more. These figures differ from those in invasive cancer.

Conclusion: There is a wide variation in practice amongst breast surgeons with no consistent policy. Whist this may reflect a lack of evidence, it is of great concern.

O-17. Factors predisposing to cavity margin positivity and return to theatre following breast-conservation surgery for breast cancer

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Introduction: Incomplete excision is an important factor leading to local recurrence following breast conservation therapy (BCT). The aim of this study was to examine factors associated with cavity/margin positivity and return to theatre rates.

Methods: 303 breast cancers treated by breast conservation were; evaluated with a mean follow-up of34 months (median 38).

Results: A total of 73 (24.1%) patients had positive cavity margin. Large tumor size ($p < 0.001$) and tumor type ($p = 0.043$) were the significant predictors of cavity margin positivity both by univariate and multivariate analysis. The optimal cut-off value of tumor size: for cavity margin positivity was found to be 22.5 mm by using Receiver Operating Characteristics (ROC) curve. Cavity margin i positivity for invasive ductal carcinoma, invasive lobular carcinoma and DCIS was found as 51/250 (20.4%), 14/33 (42.8%), and 8/20 (40%) respectively. As a result of cavity margin (CM) status in relation to initial margin (1M) status, 13 (4.3%) of patients who were 1M negative and CM positive returned for further surgery. 60(19.8 %) of patients who were 1M positive and CM negative avoided the l need of further excision, 7 recurrences developed in cavity margin' negative patients (4[2.4%] in the IM(-)/CM(-) subgroup and 3 [6%] in the IM(+)/CM(-) subgroup). The 1M positive and CM positive I subgroup had 8 (28.6%) failed final margin after reexcision requiring further surgery.

Conclusion: Patients with large tumors undergoing BCT have a higher chance of residual tumor at the cavity margin. Negative CM may avoid the need for further surgery in the majority of 1M positive patients.

O-18. Breast-conserving surgery: selection criteria and local recurrence - Nottingham 1979 - 2002

Asgeirsson KS, Nasr R, Morgan DAL, Pinder SE, Ellis IO, Blamey RW, Macmillan RD. *Nottingham City Hospital*

Nottingham Breast Unit was one of the first to offer wide local excision (WLE) with post-operative radiotherapy and publish selection criteria and local recurrence rates (LRR). The first published series (1979-1986) reported the results of tumour excision with no pathological margin assessment. The second series (1988-1992) reported the results of wide local excision with a 5 mm minimum pathological excision margin (assessed by radial blocks) with certain exclusion criteria. The current analysis (1995-1997) reports the effect of adding circumferential shaves to margin assessment.

Series	WLE rate	N	Age (med)	NPI (med)	Re-X rate	LRR per annum	FU
1979-1986	17.1%	263	42	4.15	0%	2.2%	16
1988-1992	46.5%	275	53	3.84	10%	1.0%	10
1995-1991	40.5%	340	55	3.74	17.1%	0.4%	5
2001-2002	47.0%	470	56	3.50	16.9%	–	–

LRR's have decreased to very low levels with the introduction of detailed margin assessment. Re-excision (Re-X) rates have increased with circumferential shaves. Increasingly, selection criteria determine that the prognosis of women successfully treated by WLE is good.

O-19. Geographical miss in the planning of breast radiotherapy using an open MRI scanner

Whipp E, Hartley-Davies R, Carroll J, Greenwood R, Wells T, McKenzie A, Appleby H, Goddard P, Wakeley C, Cornes P, Devrell C, Shere M, Halliwell M. *Bristol Hospitals*

Good radiotherapy requires accurate targeting. In the UK, most conservative breast cancer radiotherapy is planned without benefit of modern three-dimensional radiotherapy imaging, CT having difficulties both in scanning the patient in the required position and in demonstrating the primary site and nodes without surgical clips.

MRI gives exquisite soft tissue definition in multiple planes, without using contrast. The primary site, nodes, surgical cavities and organs at risk are easily identified. The Open MRI configuration allows scanning in the treatment position. Distortion is corrected automatically using data derived from in-house phantom studies.

Using the most commonly used conventional midline and mid-axillary field margins, a Clinical Target Volume (CTV) of 1.5 cm surrounding the tumour cavity was chosen, and the degree of miss was calculated in 528 post-WLE cases. 57% of all cases would have received less than half the prescribed dose to part of this CTV. 47% cases receive 50% or less dose to the lower axillary nodes. Excluding pericardial fat, 73% patients had myocardium treated.

Plans were amended using this MR data. Local recurrence rates will be presented, and targeted boosts discussed. The apparent effectiveness of poorly targeted radiotherapy raises interesting speculation.

O-20. Omission of radiotherapy from breast conserving surgery in excellent prognosis (EPG) patients

Rampaul RS, Pinder SE, Morgan DAL, Macmillan RD, Mitchell M, Blamey RW. *Nottingham City Hospital*

Patients meeting the criteria for entry into the BASO II trial for small, node negative, excellent prognosis breast cancer (EPG) were analysed in this paper whether entering the trial or not. All patients were treated at NCH from 1984-2000. No tamoxifen was given. 387 patients were identified. Of these, 285 received RT (Median F/up = 122 months) and 102 had no RT (Median F/up = 104 months). The local recurrence rate per annum was 0.6% for those with no RT compared with 1.5% with RT.

Table 1

		EPG pts	LR rate (overall)	% PA
1984-1988	Median F/up	No RT	25.7%	1.77%
	14.5 yrs	RT	12.5%	0.86%
1988-1995	Median F/up	No RT	11%	2%
	5.5 yrs	RT	0.14%	0.03%
1995-2000	Median F/up	No RT	0.56%	0.17%
	3.2 yrs	RT	0%	0%

The effect of margin analysis (since 1988) and detailed margin assessment with circumferential specimen shaves(1995-2000) was further examined (Table 1).

O-21. Radiotherapy is necessary to improve survival after breast conserving surgery in elderly women

Absar M, Prasad R, Wicks P, Burke M, Byrne G, Bundred NJ. *South Manchester University Hospital*

Elderly women are less likely to be offered XRT after breast conserving surgery (BCS). To determine the effect of radiotherapy after BCS on survival, we studied women over 65 years who were treated in our unit between 1976-2000.

Treatment of breast cancer over 65 years of age was prospectively recorded (2396 women) of whom 29% underwent BCS. Frequency of postoperative XRT use, oestrogen receptor status, recurrence and overall survival were studied. Log rank analysis of recurrence and survival were done.

Out of 690 women, 198 (29%) had XRT. Use of XRT after BCS increased from 18% (29/162) in 1981–1985 to 64% (65/102) in 1996-2000 ($p < 0.001$). XRT use decreased with increasing age ($p < 0.001$). Failure to give XRT led to an increased recurrence and mortality ($p < 0.001$). Breast cancer mortality after XRT was 13% (26/198) compared with 29.4% (145/492) in the patients not receiving XRT. Breast cancer specific mortality did not differ in ER positive tumours whereas in ER negative tumours it was 23% for those receiving XRT versus 43.4% in those not receiving radiotherapy ($p < 0.005$).

Status	All tumours			T_1–T_2 N_0–N_1 tumours		
	n	Recurrence (5 yr)	Cancer specific mortality (5 yr)	n	Recurrence (5 yr)	Cancer specific mortality (5 yr)
XRT	198	45 (23%)	26 (13%)	140	35 (25%)	13 (9.28%)
No XRT	492	258 (52%)	145 (29%)	333	130 (39%)	79 (23.8%)

Failure to give DXT after BCS (regardless of co-morbidity) affects survival from breast cancer particularly in ER negative tumours.

O-22. A comparison of different methods of assessing cosmetic outcome following breast-conserving surgery

Charfare H, MacLatchie E, Bradley M, Eadie C, Burnet K, Chapman D, Byrtus A, George WD, Wishart GC, Purushotham AD. *Addenbrookes Hospital Cambridge and Western Infirmary Glasgow*

Methods to assess cosmesis following breast-conserving surgery are varied and assumed to yield similar results. The aim of this study was to compare three different methods of cosmetic assessment following breast-conserving surgery.

One hundred and ten patients undergoing breast-conserving surgery had 3 view digital photographs taken for assessment of cosmesis at one year post-surgery. Subjective analysis was performed by panel assessment and objective assessment by the methods of breast retraction assessment (BRA) and nipple deviation (ND).

The overall cosmetic outcome was fair to excellent in 99.1 % patients using BRA, 70% using ND and 89% using panel assessment. Inter-observer variation using kappa statistic for the panel assessment was 0.47 with a 95% confidence interval (0.43, 0.52), indicating moderate agreement. The kappa statistic for agreement between the three methods used for assessing cosmesis was -0.23 with 95% confidence interval of (-0.35, -0.12) indicating poor agreement.

The majority of patients undergoing breast-conserving surgery demonstrated satisfactory cosmetic results by the methods used above. However, there was poor concordance between the three methods used. These methods might be complementary to each other and therefore these observations merit further investigation.

O-23. Local flaps in breast conservation surgery, cosmesis and patient satisfaction

Hrabovsky M, Panchalingam L, Ingram S, Reid C, Heys SD, Chaturvedi S. *Aberdeen University Medical School*

Aim: The aim of this study was to determine whether adequate tumour clearance and reduction in mastectomy rates is achievable using local flaps for reconstruction after wide local excision for large breast tumours by an oncoplastic surgeon.

Patients and methods: A variety of procedures (n = 78), paranchymal flaps; dermo-cutaneous flaps and wide excision with mastopexy were done over 2 year period. Margin clearance, patient satisfaction and cosmetic results (universal rating scale) were evaluated. The change in mastectomy rates over this period was, compared to a similar period prior to commencement of oncoplastic procedures, was examined. The results were analysed using SPSS.

Results: The average margin clearance was 11 mm (ranging 4 to 23 mm). Average tumour size was 3.2 cm (2.2 to 5.6 cm). 377 mastectomies were carried out between March 1999 and February 2001 in comparison with 266 from March 2001 to February 2003. The immediate reconstruction rate increased from 9% to 17% in the two respective periods. Patient satisfaction forms were sent to 49 patients who underwent surgery at least 6 months previously. 41 patients responded. Three assessors (doctor, breast nurse, lay person) independently assessed the patients. Mean patient satisfaction was 8.8/10 for cosmesis and the median was 9/10. Satisfaction with information provided by breast nurses and surgeon was 9.2/10 with a median of 9. Cosmetic results as assessed by the panel was 'excellent to highly satisfactory' in 63%, 'satisfactory' in 29.8% with only 7.2% being 'below average'.

Conclusion: Local flaps used after breast conservation surgery achieve adequate tumour clearance and acceptable cosmetic results.'

O-24. Lymph flow in irradiated breast after breast conservation surgery

Perbeck L, Celebioglu F, Danielsson R, Boné B, Svensson L. *Huddinge University Hospital Stockholm Sweden*

It is not known whether lymph flow is altered longterm after radiotherapy following breast conservative surgery. The lymph flow was measured in 23 patients (mean age 58 years, range 44-75 years at the time of the measurements), 2-5 years after radiotherapy (50 Gy) following breast conservative surgery. None of the patients showed any persistant redness of the skin. The lymph flow in the subcutaneous layer was measured by the elimination of Technetium from the upper medial quadrant of the breast. The skin circulation was measured by laser Doppler fluxmetry (LDF) and also the skin temperature at the corresponding sites. The results were compared with the contralateral breast. The lymph flow measured by the elimination of the Technetium expressed as half-lites was 1554 (438) minutes (median, interqualites range) in the operated, irradiated breast and 796 (1218) minutes, in the non-operated, non-irradiated breast. The lymph flow was thus 2.3 times higher in the operated irradiated breast compared with the non-operated, non-irradiated breast ($p = 0.005$). No difference was observed in skin circulation measured by LDF 6.9 (3.9) volt in the operated, irradiated breast compared with 7.6 (2.5) volt in the non-operated, non-irradiated breast. Corresponding skin temperature values were 32.0°C and 32.0°C, respectively.

Conclusion: The results indicate that there is an increase in lymph flow in an operated, irradiated breast. If this increase in lymph flow exceeds the possibility for the tissue to eliminate lymph fluid, there is a risk to develop a lymphoedema. Whether this increase in lymph transportation is due to the irradiation or to the combination of irradiation and surgery is not known.

O-25. Protocol-based referral (PBR) to breast units - improving the patient journey from GP to specialist

Buhagiar KA, Donald JB, Anderson EDC. *Western General Hospital Edinburgh*

Managing the increased demand on specialist breast units and meeting national targets for rapid access to specialist appointments I. remains a major challenge. To develop the efficiency and effectiveness of referral from general practice of breast units, a PBR system was introduced to Edinburgh Breast Unit and the breast unit at St. Johns Hospital, Livingston. The system incorporates locally modified breast referral guidelines in conjunction with a breast referral proforma that can be sent electronically via email. An audit of 600 consecutive new General Practitioner (GP) referrals was conducted to assess the impact of the system on access to breast clinics, inclusion, of clinical information and effectiveness of referral guidelines. Thirty-six percent of referrals utilised the proforma during the audit period.

Use of the proforma was associated with more rapid receipt In breast units compared with letter-style referrals (0 vs 2 days (median), $p < 0.05$, Mann-Whitney U-test), enabling faster breast clinic appointment allocation. Proforma referrals were found to provide more complete clinical information. Of particular interest, 93% of proforma referrals indicated urgency compared with only 42% of letter-style referrals. In a comparison of risk assessment, 88% of cancers were designated urgent by breast specialists compared with 81% by GPs, while the probability of a cancer diagnosis in the urgent category was 0.12 and 0.18 for specialists and GPs respectively (p = NS). These results suggest that with appropriate use of referral guidelines, GPs are as effective at deciding the urgency of referral as breast specialists, who prioritise referrals based on review of the GP letter. We conclude that PBR to breast units improves the patient from GP to specialist by expediting clinic appointment allocation, providing more complete information to breast specialists and encouraging appropriate use of referral guidelines. Following a further period of implementation within primary care, a second audit will be conducted.

O-26. Delay in diagnosis of breast cancer

Barber MD, Jack W, Dixon JM. *Western General Hospital Edinburgh*

Delay in diagnosis of breast cancer has important clinical and medico-legal implications. This study assessed the frequency, causes and potential implications of delay in diagnosis of breast cancer in a specialist breast unit. From the period 1988-1999 inclusive, the notes of patients who had an interval between attendance at a new patient clinic and diagnosis of invasive breast cancer of over 2 months were reviewed. Potential causes of delay were identified and the consequence of delay assessed. Characteristics were compared with those of all 641 cancers diagnosed over a 2 year period between 1999 and 2001.

Cancer was diagnosed in 5283 patients during the period reviewed and potential delay in diagnosis was suggested in 72 women (1.4%). Patients with a potential delay in diagnosis were younger (median 49 versus 61 years, $p < 0.0001$) and had smaller tumours at diagnosis (17.0 vs 20.0 mm, $p = 0.01$) compared with the control group but had no difference in node positivity or requirement for mastectomy. Common causes of delay included failure of clinical signs to impress, failure to adequately image palpable masses, failure to perform FNA or core biopsy, misinterpretation of mammograms and acquisition of benign cytology from a malignant lesion. In patients with a delay, those who were able to undergo conservatIon therapy were delayed for a significantly shorter time (128 vs 263 days, $p = 0.0055$).

A longer delay in the diagnosis of breast cancer was associated with a reduced chance of being treated by conservation therapy. All patients with a palpable mass require triple assessment to minimise chance of delay.

O-27. Features of screen detected cancers following arbitration of disparate double reading opinions

Cornford E, Evans A, James J, Burrell H, Pinder S, Wilson R. *Nottingham City Hospital*

The purpose of this study was to compare the features of screen detected cancer detected following arbitration of disparate dou-

ble reading opinions with screen detected cancers diagnosed by single reading.

All 148 cancers detected by screening in 2000/01 when films were single read were compared to 27 cancers detected in 2001/2 following arbitration of disparate reading opinions.

Invasive cancers detected following arbitration were less likely to be over 20 mm in size, $p = 0.01$. There were non-significant trends for arbitration cancers to be lower grade (42% vs 29%, 47% vs 49%, and 11% vs 22% for grade 1,2 and 3 respectively) and have a lower Nottingham Prognostic Index (74% vs 54% in good prognostic group) than invasive cancers r detected by single reading. The proportion and grade of DCIS detected were similar. Cancers detected following arbitration were more likely to manifest as parenchymal distortion than cancers detected by single reading (44% vs 6%, $p < 0.001$).

The features of screen detected cancer detected following arbitration of disparate double reading opinions suggests they may be more important in improving the effectiveness of mammographic screening than their number might suggest.

O-28. An assessment of the current investigation and management of localised asymmetrical nodularity of the breast and suggestions for how it might be enhanced in future

Somner JEA, Dixon JM. *Western General Hospital Edinburgh*

Aims: A review of cancers in the Edinburgh Breast Unit demonstrated that between 9 and 12% of cancers each year had nodularity as the main clinical finding. However, there are no uniformly agreed guidelines for the assessment and management of localised asymmetrical nodularity of the breast. The aim of this study was to establish what current practice is, how it might be improved and to gain further details of what the radiological and surgical characteristics of the cancers involved are.

Methods: 350 questionnaires were sent out, of these 279 were returned (reply rate of 79.7%). 90% of the 264 complete questionnaires were returned by surgeons who treat more than 100 cases per annum. The questionnaire comprised ten questions designed to examine how respondents would investigate cases of definite localised asymmetrical nodularity found on examination in both 32 year old and 45 year old women. It also explored how management would proceed given normal ultrasound (US) and mammographic findings. Finally it looked at respondents' perception of the sensitivity of these techniques for detection of breast cancer. Further research involved a case study of 120 patients from a regional breast unit who presented with areas of localised asymmetrical nodularity which, although cancerous, were not revealed by either mammography or ultrasound scanning.

Results: When a 32 year old presents in this way 98.9% of respondents would investigate with US, 69.7% with Fine Needle Aspiration (FNA), 38.6% with Core Biopsy and 11.7% with Mammography. While in 42 year olds only 21.2% of respondents would use US alone, 27.3% Mammography alone, 82.6% a combination of the two, 65.9% FNA and 43.6% Core Biopsy. In the event of a negative ultrasound in the 32 year old 58.4% of respondents requested FNA, 34.7% Core Biopsy, 23.7% 'none of the above' and 1.5% an Open Biopsy. In 45 year old women with negative ultrasound scans and Mammograms 58.8% requested FNA, 45% Core Biopsy, 16.4% 'none of the above' and 5.7% Open Biopsy. There was no consensus on the level of sensitivity of these techniques in either 32 or 45 year olds, however there was a trend to be Jess confident in ultrasound alone and more confident in the sensitivity of a combination of the two modalities. The case study is currently under review.

Conclusion: There is considerable variability in approaches to localised asymmetrical nodularity. Guidelines based on best evidence may be required to optimise management.

O-29. Addition of fine needle aspiration cytology (FNAC) to core biopsy improves the pre-operative diagnosis of screen-detected breast lesions

Jah A, Wright D, Pittam MR, Ravichandran D. *Luton and Dunstable Hospital*

Aim: Within the last five years there has been a considerable shift in favour of core biopsy with some breast screenIng units discontinuing FNAC for assessment of breast lesions. This study aims to assess the value of FNAC as an adjunct to core biopsy (CB) in the pre-operative diagnosis of screen detected breast lesions.

Methods: Breast screening records of the patients assessed during the a two-year period (1999-2001) were studied. Only those patients who had both FNAC and CB and subsequently had a surgical excision were included for the study. The results of FNAC and CB were compared against the results of surgical histology in 207 patients.

Results:

Histology	Total	Non-diagnostic CB Diagnostic FNAC	Non-diagnostic FNAC Diagnostic CB
Benign	57	5 (8.7%)	5 (8.7%)
Malignant	150	29 (19.3%)	47 (31.3%)

Both CB and FNA missed 8 (14.1%) benign and 13 (8.7%) malignant lesions. Sensitivity and specificity of CB for detecting malignancy was 72% and 87.7% respectively but when combined with FNAC it improved to 80.9% and 95.7% respectively.

Conclusion: FNAC is complementary to core biopsy and improves the pre-operative diagnostic yield in the assessment of screen-detected abnormalities of the breast.

O-30. Needle biopsy in the breast clinic: core biopsy, fine needle aspiration cytology or both?

Thrush S, Kunasingam K, Russell G, Bentley PG. *Kent and Sussex Hospital Tunbridge Wells*

Tissue biopsy is a basic component of the triple assessment in the diagnosis of 0 patients presenting with a breast lump. The aim of this study was to assess whether the combination of core biopsy (CB) and fine needle aspiration cytology (FNAC) was better than either alone in the diagnosis of palpable breast

cancer. Importance of operator experience on sensitivity was also examined.

625 symptomatic breast cancer patients presenting to an NHS Breast Unit and 152 to an experienced consultant surgeon (>10 years as a breast specialist) in his private practice (PP) were examined. All patients underwent both an FNAC and CB. In the NHS group the sensitivity of FNAC was 74.2% and CB of 79.4%. The conjunction of both tests produced a sensitivity of 89.1%. In the group seen in pp the sensitivity of FNAC was 86.6% and 92.8% for CB. The combination produced a sensitivity of 95.9%.

These results demonstrate that the combination of both techniques is superior to either used individually. The combination of the tests did reduce the effect of experience but not to an insignificant level.

We recommend the use of both FNAC and CB in the assessment of symptomatic breast lumps when performed without imaging guidance. Regular audit and training should be performed to ensure an acceptable level of sensitivity.

O-31. Is touch imprint cytology the way forward for one-stop clinics in symptomatic breast cancer?

Klevesath M, Munthali L, Bannon R, Godwin R, Coveney E. *West Suffolk Hospital Bury St Edmonds*

Touch imprint cytology of core needle biopsy is a simple method of providing a same day tissue diagnosis in patients with breast lumps. This study examined the potential value in a one-stop clinic setting of touch imprint cytology in predicting malignancy on final histology in patients presenting with symptomatic breast cancer.

143 consecutive patients with clinically palpable and radiologically suspicious lesions underwent needle core biopsy under ultrasound guidance. For touch imprint cytology, the core was smeared between two slides prior to placement in formalin. Air dried imprints were stained with Diff-Quik. Imprint cytology cellularity was deemed adequate if six or more ductal cell groups were identified. The core biopsy and imprint cytology slides were reported independently. Imprint slides categorised as carcinoma (C5) or suspicious (C4) were considered positive while lesions classified as atypical (C3) or benign (C2) were scored as negative. There were 104 cancers with corresponding cores and imprint cytologies available for analysis. There were no false positives, and only two cases produced cytology deemed inadequate for diagnosis (CI). Of the remaining 102 cases, 101 were scored as positive (90 C5's, 11 C4's). This gives an overall sensitivity of 97% in predicting a malignancy on final histology.

Touch imprint cytology of core needle biopsies is an accurate method of providing an immediate diagnosis of malignancy in patients presenting with symptomatic breast cancer. Routine use of this procedure in a one-stop clinic setting may help allay short term anxiety and expedite therapeutic management.

O-32. Stereotactic breast biopsy: advanced breast biopsy instrumentation (ABBI) versus mammotome™

Weber WP, Langer I, Zuber M, Oertli D, Marti WR. *University Hospital Basel & Regional Hospital Olten Switzerland*

Open biopsy under general anaesthesia following wire localization for non-palpable suspicious radio-opaque breast lesions is nowadays replaced by stereotactic biopsy techniques performed under local anaesthesia on an outpatient basis. We assessed the Mammotome™-system (Dec 99-Mar 03) and compared the results with a historical series of ABBI-procedures (Apr 97-Au 99 performed by the same investigator team [1].

Results (n = total number)	ABBI	Mammotome
Non-palpable suspicious lesions	144 (100%)	75 (100%)
Successfully localized and excised	135 (94%)	72 (96%)
Breast too small/lesion to close to chest wall	4 (2.8%)	0
Suspected lesion not evident on image	3 (2.1%)	1 (1.3%)
Biopsy refused/Discontinuation because of pain	2 (1.4%)	1 (1.3%)
Technical problems	0	1 (1.3%)
Average procedure time (minutes)	92 (50-180)	51 (30-105)

Histology	ABBI	Mammotome
Benign	104 (77%)	55 (76%)
Malign (Invasive, In situ, Invasive + In situ)	31 (23%)	17 (24%)
In situ-component missed	2 (7%)	3 (18%)
Invasive component missed	0	2 (12%)
Average follow-up (months)	12 (1-29)	24 (2.6-37.5)

One invasive lobular carcinoma was sonographically detected 3 months after false negative ABBI arid one DClS 3 months after a Mammotome™
Sensitivity/specifity: 97/99% ABBI; 94/98% Mammotome™

Conclusions: ABBI and Mammotome TM are both reliable diagnostic tools. The ABBI procedure achieves a larger specimen resulting in a more detailed histological diagnosis but provokes a larger tissue loss, which makes the following therapeutic excision more difficult. Therefore the ABBI is superseded by the Mammotome™ in our departments.

References

[1] Marti, W.R. et al. Eur J Surg, 2001;167:15-18.

O-33. Cytological examination of nipple discharges - 20 years experience at Newcastle upon Tyne

Mohammed P, Thilak L, Griffith CDM, Wadhera V. *Royal Victoria Hospital Newcastle upon Tyne*

Background and objectives: The accuracy and effectiveness of the cytological examination of nipple discharges in the diagnosis of breast cancer is still being evaluated. This study was undertaken to assess this practice at a single institution over a 20-year period.

Materials and methods: The results of all patients who had cytological examination of nipple discharge(s) were retrieved from laboratory records for the period May 1983 to April 2003. These were classified as inadequate/acellular, inflammatory/benign, atypical, suspicious and malignant. The clinical, radiological and histological findings of the atypical, suspicious and malignant groups were analysed after examination of laboratory reports and case notes.

Results: Over the study period 1082 nipple discharges were examined in 888 patients. An inadequate/acellular specimen was reported for 393 (36.3%), inflammatory/benign 604 (55.8%), atypical 17 (1.6%), suspicious 64 (5.9%) and malignant 4 (0.4%). Twenty (20) cases of cancer were diagnosed -2 cases were in patients with a report of 'atypical' cells, 12 with a 'suspicious' report while 4 cases had frankly malignant cytologies. Histology confirmed in-situ disease in 9 cases and invasive in the remainder. An associated mass or thickening was recorded in 5 cases. Radiology was regarded as malignant in 9 and indeterminate in 1. Seven patients with nipple discharge had no clinical or radiological evidence of cancer at presentation.

Conclusion: Although the diagnosis of carcinoma of the breast can be made by cytological examination of nipple discharges, the yield is low. Patient selection and more efficient methods of retrieving ductal cells will probably improve the efficiency and accuracy of this cheap, quick and easily available examination.

O-34. Anastrozole maintains a beneficial efficacy and side effect profile: updated results from the ATAC ('Arimidex', Tamoxifen, alone or in combination) trial

Tobias JS *on behalf of the ATAC Trialists Group. Middlesex Hospital London*

We present the first efficacy update results of the ATAC trial (median follow-up 47 months for disease-free survival [DFS]) and updated safety analysis performed in line with normal regulatory requirements (median duration of treatment 36.9 months). 'Arimidex' (anastrozole [A], n = 3125) continued to be superior to tamoxifen (T, n = 3116) for all major efficacy endpoints in the adjuvant treatment of postmenopausal women with early breast cancer (BC). At the efficacy update, the number of first events was 413 and 472 for A vs T. The table shows updated hazard ratios 95% confidence intervals (CIs) and p-values for DFS and time to a recurrence (TTR: time to earliest local or distant recurrence, new primary BC or BC- related death) (A vs T) in the overall population and the hormone receptor positive (HR+ve) population.

Efficacy update endpoints	Hazard ratio 95% CI	p-value
DFS (overall population)	0.86 (0.76-0.99)	0.030
DFS (HR+ve)	0.82 (0.70-0.96)	0.014
TTR (overall population)	0.83 (0.71-0.96)	0.015
TTR (HR+ve)	0.18 (0.65-0.93)	0.007

The updated safety analysis also confirmed the findings of the first analysis in that endometrial cancer ($p = 0.007$), vaginal bleeding and discharge ($p < 0.001$ for both), cerebrovascular events ($p < 0.001$), venous thromboembolic events ($p < 0.001$) and hot flushes ($p < 0.001$) were lower on. A, while fractures and musculoskeletal disorders ($p < 0.001$ for both) were still higher on A, showing that the safety profile of A remains consistent. With increased follow-up, A continues to show superior efficacy and numerous tolerability benefits compared with T; efficacy benefits were most apparent in the clinically relevant HR+ve population. These updated results suggest that the benefits of A in postmenopausal women are likely to be maintained in the long term.

O-35. Survival analysis from a phase III trial of fulvestrant versus anastrozole

Vergote I *on behalf of the Trial 0020 investigators. University Hospitals Leuven Belgium*

Fulvestrant ('Faslodex') is an Oestrogen Receptor (ER) Down-regulator with a unique node of action, which lacks the agonist effects associated with tamoxifen. Fulvestrant (250 mg via intramuscular injection) is I approved in the USA for the treatment of postmenopausal women with metastatic breast cancer who have progressed on prior antioestrogen therapy.

Results from a multi centre, randomised, open-label, phase III study demonstrated fulvestrant to be as effective as the highly selective third-generation aromatase inhibitor anastrozole ('Arimidex') with respect to the primary endpoint median time to progression (5.5 months vs. 5.1 months, respectively; hazard ratio [HR]: 0.98; 95% confidence interval [CI] 0.80, 1.21; $p = 0.84$) after a median follow-up of 14.4 months. Time to death (TTD) was not previously analysed as the data were immature (<75% patients died). This new analysis of TTD was performed after a median follow-up of 24.5 months, when 167 patients (75.2%) in the fulvestrant group and 173 patients (75.5%) in the anastrozole group had died. For the analysis of TTD, treatments were compared using a Cox proportional hazards regression model. An upper confidence limit for the TTD HR of <1.25 may be considered to indicate non-inferiority of fulvestrant relative to anastrozole. Median TTD was 26.5 months in the fulvestrant group and 24.3 months in the anastrozole group. Statistical analysis showed that fulvestrant was not significantly different from anastrozole in tenus of TTD (HR: 0.97; 95% CI 0.78, 1.21.; $p = 0.82$) and that since the upper CI was <1.25, fulvestrant may be considered non-inferior to anastrozole.

In conclusion, overall survival is not significantly different for fulvestrant compared with anastrozole, further supporting fulvestrant as a choice for postmenopausal women with advanced breast cancer progressing on anti oestrogen therapy.

O-36. GEFITINIB ('Iressa', ZD1839) has activity in patients with oestrogen receptor (ER)-negative breast cancer ER-positive breast cancer that has acquired resistance to tamoxifen: results from a phase II study

Gutteridge E, Cheung KL, Owers R, Koehler M, Hamilton L, Gee J, Nicholson RI, Robertson JFR. *Nottingham City Hospital*

Control of cell proliferation in acquired resistance may be through alternative signalling mechanisms such as the epidermal growth factor receptor (EGFR) pathway. This trial investigated in patients with tamoxifen (T AM)-resistant tumours and ER-negative breast cancer, the efficacy and safety of the oral EGFR-TKI (EGFR-tyrosine kinase inhibitor) gefitinib ('Iressa', ZD1839) 500 mg/day.

For 33 patients the median age (range) was 61 (32-85) years. Metastases included local regional disease and distant

metastases. At 6 months, using UICC criteria, gefitinib showed antitumour activity in both groups. Of the ER-positive patients (n = 9), 1 patient had a partial response (PR) and 5 had stable disease (SD). Of the ER-negative patients (n = 18), 1 had a PR 1 had SD and 16 patients had progressive disease. Gefitinib was generally well tolerated, with generally mild (grade 1/2) side effects.

Biopsies were assessed for EGFR cerbB2 and activated cerbB2 using HScore analysis. In ER-positive tumours (n = 2), EGFR, cerbB2 and activated cerbB2 were co-expressed. This agrees with data from preclinical models, which indicate that acquired resistance to TAM might be partly mediated through increased EGFR signalling. For ER-negative tumours (n = 9) expressing EGFR, only those not co-expressing cerbB2 showed clinical benefit.

In conclusion, gefitinib showed antitumour activity and was generally well tolerated in patients with acquired resistance to TAM.

'Iressa' is a trademark of the AstraZeneca group of companies.

O-37. Tamoxifen (TMX) followed by an aromatase inhibitor (AI) in early breast cancer. A pooled analysis of two consecutive trials

Boccardo F, Rubagotti A, Amoroso D, Mesiti M, Caroti C, Farris A, Paladina G *on behalf of GROCTA 04 and ITA study investigators*

Between September 92 and October 02, 806 postmenopausal ER +ve patients have been entered into two prospective trials comparing the value of 5 years of TMX (20 mg/d) or of 2-3 years of TMX (same) followed by 3-2 years of either aminoglutethimide (AG: 250 mg/d) or Anastrozole (ADZ: 1 mg/d). 380 patients were entered in the study with low dose AG (GROCTA 04-B trial) and 426 in the study with ADZ (ITA trial).

Patients characteristics. TMX group (n = 408): median age = 65 years (43-77); N0 = 57 (14%), N + 1-3 = 208 (51%), N + ≥4 = 143 (35%); prior RT = 174 (43%), prior adjuvant CT = 190 (47%); median time on TMX at randomisation = 35 months (23-51). AI group (n = 398): median age = 64 years (38-78); N0 = 60 (15%), N + 1-3 = 217 (54%), N + ≥4 = 121 (31%); prior RT = 172 (43%), prior adjuvant CT = 170 (43%); median time on TMX at randomisation: 35 months (23-55).

Results (median follow-up time = 36 months, range 3-108 months)

	GROCTA 4B	ITA	All patients
Reduction in the hazard of relapse	0.90 (0.63-131) p = 0.6	0.36 (0.17-0.75) p = 0.006	0.73 (0.63-1.01) p = 0.06
Reduction in the hazard of death	0.42 (0.22-0.79) p = 0.005	0.18 (0.02-1.57) p = 0.07	0.38 (0.21-0.70) p = 0.001

Switching patients on TMX to treatment with an AI appears to decrease their risk of relapse and death. ADZ appears to be more effective than low dose AG and better tolerated. An increased risk of breast cancer unrelated death and a different pattern of relapse is confirmed for the women continued on TMX.

O-38. Atypical hyperplasia and risk of breast cancer

Scott N, Rampaul RS, Pinder SE, Blamey RW, Macmillan RD, Ellis IO. *Nottingham City Hospital*

Risk of developing cancer in patients with previous histology demonstrating an 'at risk' lesion, either atypical ductal or lobular hyperplasia (ADH, ALH), is poorly understood.

63 patients between 1981-2002 have been diagnosed at Nottingham City Hospital Breast Unit (ALH = 35, ADH = 28). All patients were followed-up by regular clinical examination and mammography. Median follow-up is 73 months (range 0.3-252 months) and median age at presentation was 50 years (range 32-88 yrs). 48% (n = 27) were detected following recall from the NHSBSP and 52% (n = 29) were incidental findings on biopsy for benign symptomatic lesions. (6 pts were excluded after diagnosis revised on pathology review).

8 women developed cancer (2.1% per annum, mean age 52 yrs, median time to cancer [TTC] = 8.1 yrs). 6 cancers arose at site of biopsy and 2 in contra-lateral breast. 4 presented under age 50. Only 1 woman had a high-risk family history (FH). Table 1 shows details of the cancers.

Table 1

No.	Grade	Size (mm)	Ipsilateral	S-D	NPI	Biopsy	TTC (yrs)
1	1	13	Yes	Yes	4.26	ALH	6.3
2	1	27	Yes	No	2.54	ALH	4.9
3	2	15	Yes	No	5.30	ADH	15.5
4	2	35	Yes	Yes	3.70	ADH	8.1
5	2	13	Yes	Yes	3.26	ALH	11.1
6	2	15	No	Yes	3.30	ADH	10.5
7	1	9	No	No	3.18	ALH	4.8
8	1	28	Yes	No	3.56	ADH	6.9

Women with atypical hyperplasia require long-term follow-up.

O-39. Screen detected lobular carcinoma in situ of the breast - a new disease?

Hogben MK, Kissin MW, de Vries CS, Jackson P, Kissin C. *Royal Surrey County Hospital Guildford*

Background: LCIS is classically an incidental finding on breast biopsy with no positive mammographic features. However screening has identified a small number of cases of pure LCIS. Little is written about this in the medical literature. Does it behave like the incidentally found LCIS or not?

Aims: To review cases of screen detected LCIS within the NHS Breast screening programme since its inception.

Methods: After MREC approval whilst awaiting for PIAG clearance a pilot study of pure screen detected LCIS were reviewed from 3 screening centres in the South Eastern (East) region - The Jarvis, Worthing & South West London, The Quality Assurance offices identified LCIS cases from each centre. Mammograms & pathology were reviewed and described, and recurrence/survival data obtained.

Results: 33 cases of screen detected LCIS were identified in these 3 centres since 1988. 23/33 (70%) presented with calcifications on mammography, 8/33 (24%) with a mass lesion and 2/33 (6%) with distortion. Initial biopsy often diagnosed lesion

as DCIS. Calcification was present within the LCIS in most of the lesions.

Of 17 patients in which follow up was available to date 5 (29.4) went on to get an invasive cancer at a median time of 60 months∼ 4 of these were unilateral and 1 was contralateral.

Conclusions: Screen detected LCIS is a rare but important lesion and better understanding of it would help the multidisciplinary Team provide improved patient care. Our results suggest that screen detected LCIS has a higher incidence of further disease than incidentally found LCIS. This pilot study justifies the larger national study envisaged.

O-40. Can imaging predict the presence of invasive cancer in women thought to have ductal carcinoma in situ at screening?

Johnston V, Rubin C, Royle GT. *Royal South Hants Hospital Southampton*

A proportion of women thought to have pure DCIS on mammography and pre-operative diagnostic core biopsy have invasive cancer at definitive surgery. The surgical treatment of DCIS and invasive cancer differ. It would be useful if there were an investigation that could accurately predict invasion pre-operatively.

A retrospective analysis of 82 cases of screen detected DCIS was undertaken.

Micro-invasion was present in 6 (7.3%) and 22 (26.8%) had invasion. In 19 (67.9%), invasion had been suspected prospectively on imaging. Retrospective review of the assessment images increased this to 21 (75%). However invasion was also suspected prospectively in 9 (16.6%) cases with pure DCIS on final histology (false positives). The sensitivity and specificity for prospective prediction of invasion were 68% and 83% respectively. This rose to 75% and 84% respectively for retrospective prediction of invasion. The sensitivity and specificity for core biopsy diagnosis of invasion were 40% and 98% respectively.

The imaging features of the true positive invasive carcinomas in DCIS were compared with the false positive and false negative cases to identify features predictive for invasion. Invasive tumours were found in 50% of cases with linear, 41% with variable microcalcification and only 12% with punctate microcalcification. The presence of invasion was suggested by the presence of a mass on mammography or ultrasound, an asymmetric or developing density or distortion but there were no clear cut imaging features.

O-41. Screen detected DCIS in the Trent region: comparisons in treatment and outcome over time

Reed JA, Sibbering M, Murphy A. *Derby City Hospital & East Midlands Quality Assurance (QA) Reference Centre*

The QA service has undertaken a retrospective audit of screen detected cases of DCIS (with or without microinvasion) comparing treatment modalities. recurrence free survival and overall survival rates. Two consecutive cohorts of patients diagnosed in the Trent region were compared. Patient case notes were audited, results were electronically recorded and Kaplan-Meier survival analysis performed using SPSS.

Time period	1988-93 (n = 301)	1994-97 (n = 319)
Pre-op diagnosis	59 (19.6%)	142 (44.5%)
Final operation type:		
Mastectomy	134 (44%)	126 (40.%)
Wide local excision	123 (41%)	134 (43%)
Excision alone	44 (15%)	59 (17%)
Tamoxifen	123 (41%)	128 (40%)
Radiotherapy	27 (9%)	25 (8%)
5 yr LRR:		
Mastectomy	3 (1%)	3 (2.5%)
Wide local excision	12 (12%)	21 (12%)
Excision alone	10 (20%)	7 (12%)

The number of lesions graded increased from 47% to 75% between the 2 cohorts with a corresponding decrease in the proportion designated high grade from 81% to 52%. Margins were clear in 264 (88%) and 292 cases (91.5%) over the early and later cohorts respectively. The overall local recurrence free survival rate was identical for both periods with 92% at 5 years. Around half of all local recurrences were invasive (12/25, 1988-93 and 17/31 1994-97). Significant differences in local recurrence rates by operation type were observed. Conclusion: the local recurrence rates after treatment of DCIS in the first 10 years of the NHSBSP are relatively high. This may be due to lower pre-op diagnosis rates, less aggressive surgery, less stringent post-op, histological assessment and less use of adjuvant therapies than employed in current practice.

O-42. Ductal carcinoma in situ of the breast treated by wide local excision in Nottingham

Macmillan RD, Pampaul R, Valassiadou P, Evans AJ, James J, Pinder SE. *Nottingham City Hospital*

Since 1989 the Nottingham Breast Unit has offered wide local excision (WLE) for localised ductal carcinoma in situ (DCIS) with no adjuvant treatment, provided a histological excision margin of 10 mm is achieved. This experience has been analysed.

Between 1989 and 2001, 229 patients underwent WLE for DCIS. 69% of these DCIS cases were screen detected. 35% had undergone a diagnostic localisation marker biopsy 72 patients (31%) required a second therapeutic operation and 35 (15%) were converted to mastectomy for involved margins. Median follow-up is 4.1 years. (mean = 4.9 years, range 0.2-13 years). 19% of lesions were of low grade histologically, 20% were of intermediate and 61 % of high nuclear grade.

29 local recurrences have been observed (3.6% per annum), 15 invasive recurrences, in 194 patients treated by WLE. Local recurrences were significantly and independently associated with patient age, size of DCIS and margin width. A 'low' and 'high'-risk group was identified. For women over age 50 with a margin width of at least 10 mm and DCIS size less than 25 mm (130 patients), the rate of local recurrence was 2.3% per annum. For women who were either under age 50 or had a margin of less than 10 mm or had lesions larger 25 mm (53 cases), the rate of local recurrence was 6.9% per annum.

In this group of patients, with relatively short median follow

up, a group can nevertheless be identified who have a high risk of local recurrence and for whom more extensive surgery may be appropriate.

O-43. Hormone receptor status in ductal carcinoma in situ (DCIS) - implications for therapy

Barnes N, Boland G, Davenport A, Knox WF, Bundred NJ. *South Manchester University Hospital*

The recent NSABSP-24 results indicate that adjuvant tamoxifen therapy is of benefit only in oestrogen receptor (ER) positive DCIS. ER status will therefore need to be determined for all cases of DCIS.

The ER arid progesterone receptor (PR) status on all women diagnosed with DCIS since mid 2001 has been prospectively collected. ER and PR status were assessed by immunohistochemistry. Tumour grade and size were also assessed, using H&E microscopy.

Pre 2001, 190 cases, and post 2001, 103 cases were analysed. After 2001, 76% of cases were ER positive and 58% were PR positive. PR positivity was associated with ER positivity ($p = 0.0001$ Fisher's exact test). A strong negative correlation was seen between increasing tumour grade, ER ($p = 0.0008$ Chi-square linear trend), and PR positivity ($p = 0.0076$ Chi-square linear trend). A negative relationship between ER positivity and increasing tumour size was also, noted ($p = 0.09$ Chi-square linear trend); Comedo necrosis was associated with, ER negativity ($p = 0.04$ Chi-square) and a lower ER percentage expression level ($74 \pm 39\%$ versus $93 \pm 15\%$ $p = 0.001$ Mann Whitney U test). Oestrogen receptor positivity increased from 66% to 76% in 2001/2.

	Grade 1		Grade 2		Grade 3	
	Pre 2001	2001/2	Pre 2001	2001/2	Pre 2001	2001/2
ER+	17	10	39	23	70	45
ER−	41	0	10	1	50	25
PR+	–	6	–	19	–	32

Over 95% of grade 1 and grade 2 lesions are ER positive. Oestrogen receptor status needs to be determined in DCIS before commencing tamoxifen therapy.

O-44. Effect of a RAS farnesyl transferase inhibitor (FTI) on HER2 positive tumours and DCIS

Warnberg F, White D, Anderson E, Knox F, Clarke RB, Bundred NJ. *Christie Hospital Manchester*

Ductal carcinoma in situ of the breast (DCIS) often expresses the HER-2 oncogene. Therefore, inhibition of HER2 dependent ras-signalling may be an efficient therapy. Our aim was to study the effect of a ras-FTI on HER2-positive tumour growth and DCIS *in vivo*

Cultured cancer cells were injected and allowed to form tumours in nude mice or, in separate experiments, xenografts from 12 women with widespread DCIS undergoing mastectomy were implanted. Mice were gavaged twice daily with a ras-FTI, R115777 (50 mg/kg, and 100 mg/kg) or vehicle. Tumour growth was measured twice weekly whereas DCIS xenografts were harvested after 7 and 14 days of treatment. Proliferation (Ki67 by immunohistochemistry) and apoptosis (Tunel and H&E) were determined in all tissue samples. Growth of MCF7/HER18 tumours was inhibited by R115777 50 mg/kg and 100 mg/kg by 80.8% (56-99%; $p = 0.00$ by Mann-Whitney U test) and 95.9% (68-110%; $p = 0.002$) and SKOV3 tumours by 60.1% (39-92%; $p = 0.04$) and 20.4% (-25-70%; $p = 0.4$) respectively. The cell turnover index (CTI = proliferation/apoptosis) was reduced by 20.9% and 38.3% ($p = 0.0009$ and $p < 0.0001$) in MCF7/HER18 and by 46.2% and 35.4% ($p = 0.004$ and 0.05) in SKOV3 tumours. Apoptosis was significantly increased in the DCIS xenografts compared to controls after 7 and 14, days of treatment (32.8%; $p = 0.02$ and 20.9%; $p = 0.007$) resulting in a reduction of the CTI by 55.6% ($p < 0.0001$) and 22.4% ($p = 0.03$) respectively.

Inhibition of farnesyl transferase inhibits growth and reduces the CTI in HER2-positive tumours and in DCIS. Ras-inhibition is a novel promising treatment for breast cancer.

O-45. Protein kinase C alpha expression in normal breast, DCIS and invasive ductal carcinoma

Ainsworth P, Winstanley J, Pearson JM, Bishop HM, Garrod DR. *Royal Bolton Hospital*

PKC-α is a serine/threonine kinase involved in cell signal transduction. It activates alteration in cell differentiation and proliferation. MCF-7 breast cancer cell lines stably transfected with PKC-α show a more aggressive phenotype and tumorigenicity in nude mice. The purpose of this study was to determine if PKC-α is altered in expression or localisation in normal breast, ductal carcinoma in situ or invasive ductal carcinoma.

We obtained 50 paraffin blocks of DCIS of which 14 had associated invasive ductal carcinoma and 25 had areas of adjacent normal epithelium. The sections were stained immunohistochemically for PKC-α expression. Staining was scored by 2 Independent observers. Each case was scored from Level 1 (weak) to Level 4 (strong) for the relative staining in normal breast, DCIS and IDC.

Staining occurred in the cytoplasm. Results are tabulated:

Description	Number of cases	Average staining score	Standard deviation
Normal breast	25	3.75	0.44
DCIS	50	2.82	0.73
Invasive ductal carcinoma	14	2.27	0.65

The results suggest a progressive reduction in staining from the normal breast to invasive ductal carcinoma. The staining pattern was heterogeneous In the cytoplasm of DCIS and IDC but homogeneous in the cytoplasm of normal breast ductal epithelium. Interestingly staining was focally increased in the cytoplasm of cells with abnormal or mitotic nuclei in DCIS and IDC. PKC-α activity is altered in dividing or abnormal cells but overall expression is reduced in invasive ductal carcinoma. This raises the possibility of alteration in intracellular localisation of PKC-α.

O-46. Isotope localisation and sentinel lymph node biopsy

Frayn E, Stepp K, El Gammal M, Paterson AG, Christensen D. *Royal Cornwall Hospital Treliske*

Introduction: Since June 1998 we have been using pre-operative isotope injection to localise impalpable breast lesions rather than the traditional wire-localisation method. By injecting a higher dose of isotope sentinel lymphnode (SLN) biopsy can be performed concomitantly with the localisation biopsy.

Methods: Between June 1998 and June 2002 two hundred and eighty patients underwent isotope localisation with 6 to 30 MBq of albumin bound ^{99m}Technetium using either ultrasound or stereotactic mammography. Of these, 88 patients underwent simultaneous SLN biopsy.

Results: 279 lesions were correctly identified, one lesion was missed. Histology was malignant in 184 patients and benign in 96. Surgical margins were complete (2 mm and wider) in 110 patients. Of the 88 patients undergoing simultaneous SLN biopsy 19 had metastatic nodes despite an average tumour size of 14 mm. A further 54 patients underwent lymphnode surgery at a second operation and of these 8 were found to have lymphnode metastases (overall 22% of impalpable cancers were shown to have lymphnode metastases).

Conclusion: We have found isotope localisation to be a reliable and easy method for excision of impalpable breast lesions permitting simultaneous SLN biopsy in those with invasive cancers.

O-47. A prospective randomized trial of radio-guided lesion localization (ROLL) versus wire-guided surgery for impalpable breast lesions

Rampaul RS, Bagnall M, Burrell H, Wilson ARM, Pinder SE, Evans AJ, Macmillan RD. *Nottingham City Hospital*

The use of radioisotopes for occult lesion localisation has recently been assessed by several breast units. We present the results of the first randomised trial comparing ROLL with standard wire placement.

Both procedures were performed under stereotaxis or ultrasound. Correct positioning of the wire tip or isotope (with omnipaque) was confirmed with check mammography. Analysis of results included accuracy, duration and degree of difficulty (1-10), lesion concentricity, rate of immediate re-excision and second therapeutic operation. QOL questionnaires were administered to patients following each procedure.

95 patients have been entered, 48 randomized to ROLL and 47 to wire guidance. Of the 48 who underwent ROLL, 2 had a failed technique. Accurate marking was 96% for ROLL and 90% for Wire (NS). The difficulty of radiologically localizing with isotope (subjective score: 2.8/10 versus 4.3/10 for wire) and the degree of surgical difficulty (2.9/10 vs 4.0/10) was significantly less for ROLL than for wire ($p < 0.01$). Procedural pain was less for ROLL (2.7/10 versus 3.6/10) ($p = 0.009$).

There was no significant difference in operation time for either group, mean specimen weight, intra-operative re-excision or second therapeutic operation. ROLL appears to be easier to perform for both radiologists and surgeons and has similar success rates. Patients prefer ROLL as is associated with less pain.

O-48. Non-axillary regional nodal recurrence after breast cancer surgery

Newton T, Boland GP, Gurrala SCR, Sarvepalli R, Prathap P, Lionaki A, Harland RNL. *Wrightington, Wigan and Leigh Hospitals Lancashire*

Background: None-axillary nodal involvement (interpectoral and internal mammary) is reported in up to 15% of women with breast cancer and may be sentinel nodes. Routine Interpectoral node excision at axillary clearance (ANC) has been advocated.

Aims: To determine the frequency of non-axillary nodal recurrence and factors associated with survival.

Methods: A cohort of 494 women undergoing breast surgery with a level III ANC between 1992 and 1995 were followed-up prospectively for a median of 7 years and 62 loco-regional recurrences (42 local and 20 regional nodal) recorded.

Results: The median time to regional recurrence (n = 20) was 928 days (IQR 550-1314 days) and did not differ between recurrence sites ($p = 0.14$). Factors predictive of survival after recurrence were absence of distal disease ($p < 0.001$), low NPI group ($p = 0.02$), ER tumour positivity ($p = 0.05$) and absence of lymphovascular invasion ($p = 0.05$).

Number of axillary nodes involved	XRT	Site of regional nodal recurrence		
		Axilla	Interpectoral	Int. Mammary
0	Yes	2	0	1
	No	2	0	1
1 to 3	Yes	3	0	0
	No	1	0	0
≥4	Yes	4	0	0
	No	3	2	1

Conclusions: Non-axillary regional nodal recurrences occurred in only 1% of women. Since women most at risk (4 or more axillary nodes involved) now receive adjuvant radiotherapy to chest wall to reduce local recurrence, involvement of these nodes is unlikely to impact on survival.

O-49. Mammaglobin and indicator of metastatic disease in patients with breast cancer

Thorne AL, Amar S, Yiangou C, Thorne AW, Jeffery M, Crane-Robinson C, Perry PM. *Queen Alexandra Hospital Portsmouth*

Introduction: We have detected the genetic marker mammaglobin (MOB) in 87% of breast tumours. It has been shown to be better than routine histology for detection of micrometastases in axillary lymph nodes (ALN). We wonder if this expression is reflected in peripheral blood and bone marrow and its presence correlates with the Nottingham Prognostic Index (NPI).

Methods: Tumour, ALN, venous blood and sternal bone marrow were investigated in 133 consecutive patients. RNA was extracted from 101 patients and RT PCR assays were performed for expression of MOB.

Results: MOB expression identified nodal micrometastases in 30 patients with histologically negative lymph nodes. As shown in the table NPI scores correlate with MOB expression in bone marrow and ALN, the latter reaching statistical significance ($P = 0.0022$, unpaired t test).

NPI	MGB expression in tumour	MGB expression in blood	MGB expression in bone marrow	MGB expression in lymph nodes
<3.4	32	21 (38%)	7 (21%)	17 (53%)
3.4-5.4	44	18 (41%)	13 (30%)	32 (73%)
>5.4	12	4 (33%)	4 (33%)	10 (83%)

Conclusion: Mammaglobin had been successfully identified in blood, bone marrow and ALN in breast cancer patients. Mammaglobin expression has been detected in some patients with otherwise favourable prognosis. Long term follow-up of these patients is needed to see if they are at increased risk of systemic recurrence and to assess the prognostic significance of MGB expression.

O-50. Bone metatases from breast carcinoma: histopathological - radiological correlations and prognostic features

James JJ, Evans AJ, Pinder SE, Gutteridge E, Cheung KL, Chan S, Robertson JFR. *Nottingham City Hospital*

The aim of this study was to identify factors that may be associated with the development of none metastases in patients with metastatic breast carcinoma and to see is any of these factors had a bearing on subsequent survival.

492 patients presented to the Nottingham City Hospital with metastatic I breast carcinoma between July 1997 and December 2001 267 patients had bone metastases at presentation with metastatic disease. 91 patients in this group had bone as their only site of metastatic disease. Sites of first presentation of metastatic disease were prospectively recorded, as were histological features of the primary tumour (tumour type, histological grade and oestrogen receptor (ER) status). The radiological features of the bone metastases, the metastases free interval and serological tumour marker levels at presentation with metastases were all recorded.

There was a significant association between the development of bone metastases and lower grade tumours ($p = 0.019$) and ER positive tumours ($p < 0.0001$). A multivariate analysIs found that metastases free interval, additional sites of metastatic disease other than bone, ER status, and serological tumour marker levels all independently predicted survival from time of presentatIon with bone metastases.

O-51. Detection of a common amplication of 7Q in docetaxel resistant breast cancer cell lines by comparative genomic hybridisation

McDonald SL, Moir SE, Stevenson DAJ, Heys SD, Schofield AC. *University of Aberdeen Medical School*

Docetaxel is one of the most effective chemotherapeutic agents used to treat advanced breast cancer. Unfortunately, many patients develop resistance to treatment and the resistance pathways are largely unknown. To investigate the genetic changes involved in resistance, we have created docetaxel resistant cell lines as an in vitro model of resistant tumours. In order to do this, MCF-7 (oestrogen receptor positive) and MDA-MB-231 (oestrogen receptor negative) human breast cancer cell lines were exposed to increasing concentrations of docetaxel for a period of 50 weeks. This resulted in new sub-lines, which were able to with-stand 24 h exposure to 30 μM docetaxel. MTT assay was used to confirm that the new sub-lines were less sensitive to docetaxel than their parental cell lines. Comparative Genomic Hybridisation was then carried out on the parental and resistant cell lines. The MCF-7 docetaxel resistant cell lines showed an amplification of 7q, 17q and a deletion of 6p. The MDA docetaxel resistant cell line showed amplification of 7q, 9q and deletion of 12q. The amplification of 7q is therefore a common event between the cell lines. Western analysis revealed that the multi drug transporter, P-glycoprotein (which is contained on 7q 21) is over expressed between the two cell lines. However, this is not the only gene involved in the resistance. Bacterial artificial chromosomes will be used to characterise the amplification of 7q more accurately in order to identify additional genes involved in resistance to docetaxel.

O-52. Molecular changes involved in docetaxel resistance in breast cancer cells

Brown I, Moir SE, Heys SD, Schofield AC. *University of Aberdeen Medical School*

Docetaxel is the most effective single agent regimen in advanced breast cancer therapy. However, up to 50% of patients can be resistant to this expensive drug. There are limited data on molecular factors involved in resistance to docetaxel and we sought to determine, therefore, the molecular changes in breast cancer cell lines which had been made resistant to docetaxel in order to further understand the mechanisms of resistance to this drug. Breast carcinoma cell lines, MCF-7, were made resistant to docetaxel by continual exposure to increasing amounts of the drug over a period of time. We looked at the levels of expression of genes and proteins expected to be involved in the pathways implicated in the mechanism of action of docetaxel (apoptosis, cell cycle control and tubulins). Gene expression and protein expression were analysed by cDNA microarrays, RT-PCR and western analysis. Cancer pathway specific microarrays indicated several changes in the resistant cell lines including up regulation of surviving and downregulation of p27 and bax. Bax and p27 downregulation have been confirmed with both western analysis and RT-PCR. P27 protein has also been shown to be downregulated in another resistant cell line (MDA-MB231) although it appears to have an increase in gene expression. The MCF-7 resistant cells have also shown to overexpress bcl-2 and β-tubulin III, and the drug transporter P-glycoprotein. Docetaxel normally upregulates p27 leading to apoptosis. Reduced expression of p27 (cell cycle regulator) is not well documented in drug resistance, in fact increased expression is normally associated with resistance, although it has been shown to be a poor prognostic indicator in many turnOUTS. Reduced expression of the protein in two different resistant cell lines even though the mRNA was increased in one of them suggests that it may be an important mechanism in docetaxel resistance. We have previously shown that bcl-2 overexpression is a poor predictor of response to chemotherapy and it is known that bcl-2 expression is upregulated in response

to docetaxel treatment, but this is the first time it has been shown to be upregulated in a docetaxel resistant cell line. It appears likely that there may be multiple mechanisms involved in resistance to docetaxel. We will be studying these changes further to determine whether they are involved in resistance or caused by resistance.

O-53. To evaluate the in vitro effect of transtuzumab alone and in combination with hormone therapy using the 'life and death assay'

Early SA, Curran C, Salman R, Given HF. *University Hospital Galway Ireland*

Transtuzumab is the first biologic modifier with significant activity in advanced breast cancer patients amplifying the HER2 gene. Transtuzumab has shown efficacy and ability to extend survival in HER-2-positive metastaic breast cancer patients. Our aim was to simulate the effect of transtuzumab in vitro and to determine the effectiveness of transtuzumab in combination with other standard hormonal therapies.

Breast cancer cell lines ZR-75-1 and MCF-7 were cultured. Tamoxifen Anastrozole, Transtuzumab, were added alone and In combination at 18, 42 and 66 hours. Proliferation and apoptosis indices were detected simultaneously in the same sample using the 'Life and Death', Phoenix Flow Assay, which results in a triple staining image. Analysis of variance test and post hoc comparisons were made using the Newman Kules protected T-test.

Significant difference was noted between the number of apoptotic cells observed in the normal, and drug treated cells in both MCF-7 and ZR-75-1 ($p < 0.0001$). Post-hoc analysis revealed that there was a statistically significant difference between control samples and study samples. Transtuzumab had a significant effect on proliferation in ZR-75-1 alone and in combination with hormonal therapies. The effect being more marked when used with anastrozole ($p < 0.001$).

These findings demonstrate transtuzumab when used alone and in combination with hormonal therapies, has an antiproliferative effect on both cell lines and a marked proapoptotic effect on ZR 751. Our findings would suggest that transtuzumab may have a role to play in patients with newly diagnosed breast cancer. We have also shown that the life and death assay is a reliable way of measuring apoptosis and proliferation.

O-54. Neoadjuvant letrozole: the Edinburgh experience

Jackson J, Renshaw L, Cameron DA, Miller WR, Dixon JM. *Western General Hospital Edinburgh*

The randomised neoadjuvant trial of letrozole versus tamoxifen reported a clinical response rate of 55% (85/154) for patIents randomised to letrozole and a relationship between response and ER level.

83 postmenopausal patients with large operable or locally advanced ER rich breast cancers have been treated with 3 months of letrozole and response assessed clinically and volume changes over the 3 month study assessed by clinical measurement and ultrasound -65 patients responded - overall response rate 78%, a significantly better response rate than In the 024 study, $p = 0.0004$. Response rate did not differ significantly between ER categories but percentage reduction in volume did (table).

ER score Allred	No. of pts.	No. of responders	% response	Median reduction in tumour volume	
				Clin	USS
8	60	48	80	76+	67+
6 + 7	23	17	74	63	48

+ $p < 0.05$

Letrozole is confirmed as being a highly effective agent at producing tumour shrinkage in postmenopausal women with ER rich breast cancers.

O-55. PTEN mutation and HER2 overexpression may predict response to CCI779, an MTOR inhibitor

Sharma R, Pinder SE, Ellis IO, Paish C, Chan SY. *Nottingham City Hospital*

CCI-779 blocks the mTOR (mammalian Target of Rapamycin) signal transduction pathway. It causes cells to arrest in the G1 phase of the cell cycle thus inhibiting the cell cycle. mTOR Dnase is downstream of phosphatidyl inositol 3-kinase and Akt signalling pathway and can be up regulated due to PTEN gene mutation. HER2 over expression can have a similar effect. A randomised 2 trial CCI-779 was set up for patients with metastatic breast cancer who have failed on prior chemotherapy with a taxane or an anthracycline containing regimen. A response rate of 10% to 20% has been reported. Tumour tissue from 32 patients in the trial was studied using immunohistochemical techniques for PTEN, Akt, ER and HER2 over expression. Results are available on 28 patients. 4/28 cases had mutated PTEN. 3/28 showed HER2 over expression. Chi squared tests showed a correlation with PTEN mutation HER2 over expression and best response (PTEN mutation vs best response: $p = 0.133$; HER2 over expression vs best response: $p = 0.043$; (PTEN mutation vs HER2 over expression: $p = 0.006$). These findings suggest PTEN mutation and HER2 over expression may predict, response to CCI-779. Further studies in this area is indicated.

O-56. ZD6464, an orally available inhibitor of vascular endothelial growth factor signalling, inhibits angiogenesis and tumour growth

Wedge SR. *AstraZeneca Macclesfield*

In order to grow and metastasize, tumours must develop a blood supply; inhibition of tumour vascular development has therefore been identified as a clinical approach with great potential in the treatment of solid tumours. Vascular endothelial growth factor (VEGF) is thought to be crucial for new blood vessel formation (angiogenesis) and maintenance and therefore represents an important therapeutic target.

ZD6474 is a novel inhibitor of VEGF receptor tyrosine kinase, that also has activity against epidermal growth fac-

tor receptor (EGFR) tyrosine kinase. This compound inhibits physiological and pathological angiogenesis in vivo. Chronic once-daily oral administration of ZD6474 has been shown to result in dose-dependent inhibition of tumour growth in it range of histologically-distinct human xenograft models (breast, lung, prostate, colon, ovary, and vulva). This broad-spectrum activity is consistent with inhibition of VEGF signalling and distinct from therapeutic approaches that directly target tumour cells. ZD6474 also demonstrates excellent activity in orthotopically implanted tumour models (eg renal and pancreatic tumours).

Phase I clinical evaluation of once-daily oral ZD6474 has now been completed. Adverse events were generally mild, and anti-VEGF activity has been suggested by a delay in dermal wound angiogenesis. In addition, preliminary observations of tumour regression have been documented. Clinical evaluation of ZD6474 continues in a series of Phase II studies.

O-57. Mammaglobin expression and serum tumour markers CA15.3 CA 27.29, CA 125 and CEA, in patients with breast cancer

Thorne AL, Amar S, Yiangou C, Thorne AW, Coombs E, Jeffery M, Crane-Robinson C, Perry PM. *Queen Alexandra Hospital Portsmouth*

Introduction: Both the genetic marker mammaglobin (MOB), which; is expressed in peripheral venous blood and bone marrow, and serum markers CA 15.3. CA 27.29, CA 125 and CEA have been used to detect metastatic disease in breast cancer (BC). Is MGB expression a reflection of abnormal serum markers?

Methods: Tumour, axillary lymph nodes (LN), peripheral venous blood (PB) and bone marrow (BM) were collected. RNA was extracted and nested RT PCR assays were performed for expression of MGB. Serum tumour marker levels were taken every 6 months.

Results: 101 patients with proven early BC were recruited. Of the 82 patients who had their serum markers measured, 24 (29%) patients had abnormal tumour-markers. In this group of patients with abnormal markers, 19 had MOB expression in PB, BM and/or LN. Of the 58 patients with normal markers, 35 had MOB expression in PB, BM and/or LN.

Conclusion: Those patients with abnormal markers have a poor prognosis and most of those patients had MGB expression indicating metastatic disease. However, in those patients with normal tumour markers we have found 60% of patients had micrometastatic disease as indicated by MGB express outside the tumour. It seems that serum tumour markers may not be as sensitive as MOB expression. Clinical follow-up of these patients is ongoing.

O-58. Development and partial characterisation of an in vitro model of Tamoxifen-resistant breast cancer

Parkes AT, Ponchel F, Burdall SE, Speirs V. *University of Leeds*

Tamoxifen (TAM) is routinely used to treat estrogen receptor (ER)- positive breast cancer. Although initially responsive, many patients eventually relapse. Despite intensive research the mechanisms by which this occurs have yet to be identified. The aim of this study was to develop an in vitro cell model of TAM resistance through the continuous treatment of the TAM-sensitive breast cancer cell line (wtMCF-7) with 0.1 μM 4-Hydroxy-Tamoxifen (4-HT) over 28 months. This model has been used as a means to assess changes in mRNA expression levels of components of the ER signalling pathway as resistance developed over time, using Real-Time PCR. ER subtypes -α, -β, and -βcx and a number of their associated co-regulator proteins were investigated. Cell response to TAM was assessed on a monthly basis by the MTT assay and RNA extracted for Real-Time PCR analysis. Initially, cells grown in 4-HT were inhibited by 50%. By month 5 the inhibitory effects were lost, and full resistance developed by month 8. In the continued presence of TAM, resistant cells (MCF-7rs) lost the ability to proliferate in response to 0.1 nM estradiol (E2), however when 4-HT was removed the agonistic effect of E2 was restored. Marked differences in cell growth were apparent with MCF-7rs, growth being approximately 30% less than wtMCF-7. ER-α, -β and PR expression was seen in wtMCF-7 and in MCF-7rs cells, indicating a functional ER-signalling pathway. Real-Time PCR results suggest a decrease in expression of ER-α (30%), -β and -βcx (60%) from M0-M6. The co-activator AIB-1 was highly expressed by all cells, with a suggestion of a biphasic response. Up-regulation of the co-regulators SRC-1 and REA was also seen in the initial stages of development of resistance. Further evidence of altered ERs and co-regulator expression in the later stages of resistance is underway. Our in vitro model provides a valuable resource to facilitate the understanding of the mechanisms involved in Tamoxifen resistant breast cancer.

O-59. Oestrogen receptor expression in primary and recurrent breast tumours: a comparison between ER alpha and ER beta

Hennessy E, Salman R, Uhlmann V, Curran C, Adegbola T, Connolly E, Given HF. *University College Hospital Galway Ireland*

Introduction: Breast cancer and its treatment by hormone therapy has been associated with two nuclear oestrogen receptors, ER alpha and ER beta. To date ER alpha is the more established receptor and is commonly used as a predictive marker for breast cancer. In addition, the decision to administer endocrine therapy in the form of the anti-oestrogen drug, Tamoxifen, is influenced by the presence/absence of ER alpha.

Methods: As yet, studies have primarily focused on ER beta at the molecular, i.e. mRNA, rather than the protein level. We studied the protein expression of ER beta by immunohistochemistry using a specific monoclonal antibody (ER beta-14C8, Abcam) on a group of 51 archival primary breast tumours and their matching local recurrences. Within the group the average patient age was 52.6 years (range 32-80). 47% of patients had a family history of breast cancer. Of the tumours 56.8% were ductal and 19.6% were lobular. The average size of the primary tumours was 2.1 cm (range: 0.5-4.5 cm).

Results: ER alpha and ER beta stained positive in 40% and 81% of the primary tumours and in 13.5% and 89% of the

local recurrences, respectively. 27% of primary tumours and 13.5% of local recurrences were positive for both ER alpha and ER beta. There was more than 80% concordance between the primary and the recurrence in ER alpha negativity and ER beta positivity.

Conclusion: Overall, ER beta expression was associated with negative axillary node status, 85% of patients had been on Tamoxifen regardless of their ER status. In conclusion. we determined that receptor status and anti-oestrogen therapy did not have a major influence over local recurrence in the long term.

O-60. Oestrogen receptor expression in breast cancer: can we better predict ER status and response to adjuvant hormone treatment

Cooke FJ, McCann AH, Chung WY, Gallagher E, Balfe P, McAlister K, Kennedy M, Dervan P, Kerin MJ. *Mater Misericordiae Hospital Dublin Ireland*

Aims: ER status is an important prognostic marker and predictor of response to tamoxifen in breast cancer. Not all ER positive tumours are tamoxifen sensitive. Discovery of ERβ and the concept of epigenetic transcriptional inactivation of ER gene expression has major clinical significance in predicting tamoxifen sensitivity/resistance.

Methods: Methylation-specific PCR (MSP) was carried out on bisulphite modified breast DNA using primers designed to the promoter regions of ERα. (ERαA) and ERβ3 genes.

Results: We performed MSP analysis on 85 cases, 74 cancers and 11 benign cases. We report ERα IHC data on 71 of 74 cancers (96%) and ERβ IHC data on 40 of 74 cancers (54%). There is concordance of 61% (43 of 71) between MSP profiles and IHC for ERα. and 65% concordance for ERβ (26 of 40). We have identified two distinct groups within the cohort. Thirty-one of 74 cancers (42%) displayed a fully methylated profile for ERα and a fully unmethylated profile for ERα and 21 of 74 cancers (28%) showed I partial methylation for both ERα and ERβ.

Conclusions: These observations have important clinical implications in predicting responsiveness to adjuvant tamoxifen and we have identified a sub-group of patients with potential tamoxifen independent/resistant disease.

O-61. Oestrogen receptor beta expression in normal benign and malignant breast and mammary cell lines

Shaaban AM, O'Neill PA, Foster CS. *University of Liverpool & Clatterbridge Cancer Research Trust*

The development of specific antibodies to ERα and more recently to ERβ allows the study of their genes at the protein level.

We have assembled a cohort of benign lesions with different histological risk including 42 normal breasts, 43 hyperplasia of usual type (HUT), 23 ductal carcinoma in situ (DCIS) and 139 invasive breast carcinoma. Paraffin embedded sections were stained with monoclonal anti-ERα and ERβ1 antibodies. We also studied the expression of both proteins in MCF7, ZR-75, T47D, ERα+ and MDAMB231, HUMA121 ERα- breast cancer cell lines using immunohistochemistry and Western blotting.

The expression of ERβ1 significantly decreased from normal breast (94.33%) through HUT (76.66%) and DCIS (78.33%) to invasive cancer (60.00%, $p = 0.002$, and 0.01 respectively). However, there was no significant difference in ERβ expression between HUT and DCIS. Thirty (71.4%) normal breasts, 33 (76.7%) HUT and 83 (59.7%) invasive cancers showed concurrent expression of ERα and ERβ. A proportion (33.8%) of ERα- invasive tumours was ERβ+. The ratio of ERβ:ERα decreased with neoplastic progression. All benign and malignant mammary cell lines including the ERα- cell lines expressed the ERβ protein. The highest level of expression occurred in T47D. Our data show an unequivocal decrease in ERβ expression with neoplastic progression and suggest that the role of ERα and ERβ- driven pathways and/or their interaction change during breast tumourigenesis.

O-62. Oestrogen receptor beta (ERβ1) mRNA and protein expression in Tamoxifen treated breast cancer

O'Neill PA, Shaaban AB, Foster CS. *University of Liverpool & Clatterbridge Cancer Research Trust*

We studied expression of ERα and ERβ1 proteins in 167 patients with invasive breast cancers treated with adjuvant endocrine therapy. We used a previously validated PPG5/10 monoclonal antibody to detect full length, wild type ERβ1. The results were compared with mRNA expression of the same genes by RT-PCR.

For ERα protein expression was closely associated with RNA expression detected by RT-PCR ($p < 0.001$), but this was not the case for ERβ1. Associations were seen between expression of both receptors by RT-PCR ($p < 0.001$) and between ERβ RT-PCR and ERα IHC ($p < 0.027$), but not between the ERα and ERβ1 proteins detected by IHC. It is therefore possible that translational or post-translational control plays a significant part in ERβ1 expression. There was no significant association between ERβ1 IHC status and PgR status, tumour stage or grade, axillary nodal status, presence of lymphovascular invasion, size of tumour or proliferation. In those cases that were negative for ERα by RT-PCR, ERβ1 RT-PCR positive cases had a significantly worse relapse free survival ($p = 0.015$). By contrast in the ERα RT-PCR positive cases, there was a trend for ERβ1 RT-PCR positive cases to have a better survival ($p = 0.084$). No such relationship was seen at the protein level.

O-63. Unlocking the secrets of ER*β*

Speirs V, Murphy CE, Parker MD, Parkes AT, Burdall SE, Lansdown MRJ, Carder PJ, Hanby AM. *Leeds Teaching Hospitals & University of Leeds*

Estrogen receptor (ER) α remains the only reliable biological prognostic marker in breast cancer. A sister molecule, ERJ3 has been described, but while ERa predicts a favourable disease outcome, data on ERβ has been contradictory with correlation with both good and poor prognostic outcome.

The goal of our research is to understand the role of ERβ in breast cancer.

Immunohistochemical analysis of ERβ by our group on 512 breast biopsies (including normal, pre-invasive, invasive and metastatic lesions) showed loss of ERβ expression in 21% of cases during the transition from normal/pre-invasive lesions to invasive cancers, but constitutive expression in metastases. We hypothesised that loss of ERβ may be due to promoter hypermethylation. To address this, two ERβ-cell lines (SKBr3 and MDA-MB-435) were pulsed with the DNA methyltransferase inhibitors 5-aza-cytidine (2.5-5 μM) or 5-aza-2'-deoxycytidine (0.25-0.5 μM) on alternative days. RNA was extracted on day 6. ERβ mRNA expression was restored in treated cells, providing experimental evidence that silencing of ERβ in breast carcinomas could be due to promoter hypermethylation. This is currently being pursued further using methylation-specific PCR in a cohort of ERβ- clinical breast cancers. Loss of expression of ERβ may be one of the hallmarks associated with breast carcinogenesis, and appears to be a reversible process involving methylation. However, expression of ERβ in 15 metastases from a range of sites (liver, lung, bone, brain and skin) was unexpected. Speculatively, its retention in metastases may represent an adaptive response by the host to prevent further tumour spread.

Given the recognised importance of ERα in breast carcinogenesis, the clues we have so far with regard to the biology of ERβ create an imperative for us to unlock its secrets.

O-64. A flow cytometric method for androgen receptor (AR) expression and its relationship to age, serum androgen levels, oestrogen receptor alpha (ERα) and epidermal growth factor (EGFR) receptor expression in primary operable breast cancer

Aspinall SR, Stamp S, Shenton BK, Shrimanker J, Bliss RD, Griffiths AB, Griffith CDM, Lennard TWJ. *University of Newcastle*

A method for the determination of AR expression by flow cytometry is described below. Androgen receptor expression has been correlated with age, serum androgen levels, grade, lymph node status, oestrogen receptor alpha expression and epidermal growth factor expression. Serum androgen levels were measured using ELISA kits (DRG Diagnostics). AR antibody AR441 (DAKO) was titrated against an AR+ve cell lines LNCap and AR-ve cell line DU145. Frozen tumour specimens were thawed, disaggregated through wire mesh and incubated with biotinylated primary antibody. Streptavidin phycoerythrin was used as a secOndary antibody. Analysis was performed on a Becton Dickinson FACScan using LYSYS II software. Antigen expression was determined in molecules of equivalent fluorochrome with reference to RCP50 beads (Spherotec) using Tallycal software. AR was present on 86% of the 63 breast tumours analyzed. AR expression increased with increasing Bloom Richardson grade (ANOYA $p = 0.05$). There was no association with the presence of lymph node metastases. AR was co-expressed with ERα ($p < 0.0001$) and EGFR ($p = 0.05$). AR expression increased with patient age ($p = 0.02$). Serum androgen levels fell with increasing patient age. A trend towards increasing serum DHEAS ($p = 0.09$) and androstenedione ($p = 0.18$) levels with decreasing tumour AR expression was observed.

These results provide evidence for negative autoregulation of AR expression *in vivo* and 'crosstalk' between AR and EGFR pathways in breast cancer.

O-65. Anastrozole demonstrates clinical and biological effectiveness in erbB2 ER positive breast cancers

Jackson J, Hills M, Renshaw L, Cameron DA, Anderson TJ, Miller WR, Dowsett M, Dixon JM. *Western General Hospital Edinburgh & Royal Marsden Hospital London*

22 postmenopausal women with large operable or locally advanced 1 with oestrogen receptor (ER) rich breast cancers were randomised to receive 1 mg or 10 mg of anastrozole for 3 months following which they had surgery. The age range of women was from 56 to 92 ER levels were Allred score 5 (1 patient), 6 (3 patients), 7 (10 patients), 8 (8 patients). Responders continued on anastrozole post surgery for 5 years. Median follow up: 44 months.

All patients had erbB2 assessed in their initial biopsy using the HercepTest. Response was assessed by clinical examination (pre) and ultrasound according to standard criteria (CR/PR complete or partial response, SD stable disease). Proliferation before and after 3 months (post) was assessed by Ki67. Progesterone receptor (PgR) was assessed before and after treatment.

ErbB2	No	Clinical		Ultrasound		Median Ki67		Fall in
		CR/PR	SD	CR/PR	SD	Pre	Post	PgR
0/1+	16	15	1	10	6	23.5	5+	13/13*
3+	6	6	0	5	1	22.5	7.5∼	3/4*

*5 patients PgR 0 on first biopsy. ∼$p = 0.017$, +$p < 0.0001$.

Response did not differ in relation to erbB2 statu. All 0/1+ and all 3+ patients had a reduction in proliferation. These are the first data demonstrating the clinical and biological effectiveness of anastrozole in erbB2 positive ER positive breast cancers.

O-66. Trilostane blocks actions of oestrogens through two pathways

Barker S, Glover HR, Malouitre SDM, Puddefoot JR, Vinson GP. *Queen Mary College London*

Selective estrogen receptor modulators (SERMs) have been developed new therapeutic agents for the treatment of breast cancer. These take advantage of specific effects on oestrogen receptor (ER) conformation that arise when a given ligand binds within the ligand binding pocket. We have studied the actions of trilostane (Modrenal), a newly licensed treatment for advanced breast cancer, on both ER alpha and beta. Our data suggest that the effects of trilostane on ER alpha occur via an allosteric mechanism which changes ER conformation leading to reduced binding to a consensus oestrogen response element (ERE) and can thereby block the proliferation of MCF-7 breast cancer cells.

We have further studied more detailed components of the cell proliferation pathway looking at expression of key genes. Expression of mRNA for both the proto-oncogene *c*-myc and anti-apoptotic protein bcl-2, were reduced by trilostane treatment. In addition, we have shown that trilostane can inhibit the activation of an AP1 (activating protein-1) reporter system. These data indicate that trilostane can block cell proliferation mediated through both ERE and AP1-dependent pathways.

O-67. Role of routine preoperative lymphoscintigraphy prior to sentinel node biopsy for breast cancer

Goyal A, Mansel RE. *UWCM Cardiff on behalf of the ALMANAC Study Group*

Background: Whether SLN visualisation on a preoperative lymphoscintigram adds diagnostic accuracy to offset the additional time and cost required is not clear.

Methods: In the ALMANAC audit phase, 31 surgeons in 17 centres throughout the UK operated on 842 breast cancer patients. SLN was identified using the combined technique followed by standard axillary dissection. Lymphoscintigraphy was performed around 3 hours after peritumoural injection with ^{99m}Tc albumin colloid.

Results:

Results of preoperative lymphoscintigraphy

SLN identified on lymphoscintigram	No. of patients (n = 820)	%
No drainage	228	27.8
Axillary only	520	63.4
1M only*	15	1.8
Axillary + 1M/Axillary + 1M + other	48	5.9
Axillary + other/other only	9	1.1

*1M-internal Mammary.

Results of SLN biopsy

Drainage on lympho-scintigram	Successful localisation of SLN SLN at operation			False-negative rate	Operative time (min)	No. of SLNs removed
	All	BMI < 30	BMI > 30		mean (SD)	mean (SD)
Yes	583/592 (98.5%)	302/303 (99.7%)	58/63 (92.1%)	6.12%	18.6 (10.8)	2.3 (1.3)
No	205/228 (89.9%)	106/112 (94.6%)	37/46 (80.4%)	6.98%	17.3 (10.8)	1.9 (1.2)
p-value	< 0.001			NS	NS	<0.001

SLN identification on lymphoscintigram by tumour location with the breast

Location of tumour	SLN identified on lymphoscintigram		p-value
	Yes	No	
Upper outer quadrant	178/272 (65.4%)	94/272 (34.6%)	0.028
Upper inner quadrant	63/95 (66.3%)	32/95 (33.7%)	
Lower outer quadrant	48/59 (81.4%)	11/59 (18.6%)	
Lower inner quadrant	36/43 (83.7%)	7/43 (16.3%)	
Central	8/13 (61.5%)	5/13 (38.5%)	

Conclusions: SLN visualisation on preoperative lymphoscintigraphy increases the success rate of localisation. The advantage is maintained in women with BMI > 30. It helps to define unpredictable areas of lymphatic drainage such as the 1M chain. It did not decrease the false-negative rate or the mean operative time. Tumours located in the lower half of the breast had a higher chance of SLN visualisation on the lymphoscintigram.

O-68. Factors influencing successful sentinel node identification in a multicentre study

Kissin M, Dixon JM *on behalf of the ALMANAC Study Group*

Aims: In the audit phase of the ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) study 31 surgeons from units throughout the UK contributed 842 patients. Localisation of sentinel node was with both blue dye and radioisotope. There were 33 failed localizations (3.9%). Factors influencing failure to localize a sentinel node have been analysed.

Results: The time interval between injection of the radioisotope to the axillary incision was not significantly related to successful sentinel node localisation. Age, an important factor identified by some groups, was also not a significant factor related to success of sentinel node biopsy; neither was size or grade of the tumour. Site of the tumour which was recorded in 521 patients did influence failure to localize sentinel nodes, failure being more common in inner tumours (12/154 failures, rate 22%) compared with other locations failure (8/367 failures, rate 2.2%) p = 0.008. There was also a significant correlation between successful localization of a sentinel node and body mass index with the highest failure rate being in women with a body mass index over 30, p < 0.0001. The presence of nodes on a pre-op scan significantly predicted for success-scan outcome known in 799, successful localization in 541/550 positive scans, 98.3% versus 226/249 negative scans, 90.8%, p < 0.0001.

Conclusions: These data demonstrate that in a large multicentre study, sentinel node mapping success is influenced by tumour location, body mass index and visualization of nodes on a pre-op scintigram.

O-69. Sentinel lymph node biopsy in breast cancer patients

Schlichting E, Kåresen R, Westerheim O, Sauer T, Babovic A. *Ulleval University Hospital Oslo Norway*

From April 2000 sentinel node (SN) biopsy has become the standard procedure in our hospital and all surgery, except a few with severe cardiopulmonary problems and dementia, has been done as day care surgery. 643 patients with clinically localized breast cancer <3 cm) without palpable axillary lymph nodes and age <80 year underwent SN biopsy. Patients with DCIS III have been included for the last 15 months. The average age was 57 year. Based on preoperative lymphoscintigraphy, SN biopsy was performed guided by a gammaprobe and peritumoral patent blue dye injection. Preoperative lymphoscintigraphy disclosed a SN in 66% of the patients and SN was preoperatively identified in 90% of all patients (stable for several years). Based on imprint and frozen sections 20% of the patients had metastases to SN, while histological examination revealed metastases to 23%. The sensitivity was 58% and 77% respectively for imprint and frozen sections, no false positives and 3.3% false negatives. False negative imprints were due to suboptimal sampling and 68% were micrometastases (<2 mm). Rapid immunocytochemistry of imprint and frozen sections were tested, but did not add

any information. Two skip lesions are registered. We will now focus on improving the imaging technique.

O-70. The usefulness of scintimammography (99m-Tc-Sestamibi) in the diagnosis of axillary lymph node metastases in breast cancer

Jönsson P-E, Pawlowski R, Heddson B, Chebil G, Scheike M, Dahlström J. *Helsingborg Hospital Sweden*

Scintimammography (SCM) with 99m-Tc-sestamibi has been shown not only to be taken up in primary breast cancer but also in axillary lymphnode metastases. The method was prospectively evaluated in a well defined group of primary breast cancer patients.

89 patients, age 32-77 yrs, median 51, with a cytologic verified primary breast cancer and a tumor size of >20 mm on mammogram were included. All had a clinical evaluation of the axillary node status. The SCM was performed by injection of 99m-Tc sestamibi (Cardiolite) 700 Mbq in a vein on the foot.

After 10 minutes we registered a supine anterior image and prone lateral images using a specially constructed breast mattress. Surgery was performed by partial or mastectomy with axillary clearance or sentinel node biopsy. Tumor size, histologic type, grade and number of axillary lymphnodes involved were analysed. Blinded and unblinded interpretations of the SCM images will be given. Unblinded reading of the images i.e. the clinical situation had an overall sensitivity (sn) of 47% and a specificity (sp) of 93% in 89 patients. The prevalens was 52%. The positive predictive value (pv+) was 88% and the negative (pv-) 52%. In 25 patients with tumor size of >30 mm the prevalens was 60%, the sn 80%, the sp 90%, which gave a pv+ of 92% and a py- of 20%. An extensive analysis in relation to other factors including clinically evaluation and pathological node status will be given.

The diagnostic outcome of SCM in the evaluation of axillary lymphnode metastases is low and related to the tumor volume. The method cannot be recommended for this purpose.

O-71. Diagnosis of axillary nodal metastases by ultrasound guided core biopsy in primary operable breast cancer

Cornford EJ, Damera A, Evans AJ, Wilson ARM, Burrell HC, James JJ, Pinder SE, Ellis IO, Lee A, Macmillan RD. *Nottingham City Hospital*

The purpose of this study was to examine the utility of ultrasound guided core biopsy of abnormal axillary nodes in patients presenting with operable breast cancer.

Methods: 166 patients presenting with suspected primary operable breast cancer had their ipsilateral axilla scanned. Nodes identified were classified based on their shape and cortical morphology. Abnormal nodes underwent US guided core biopsy/FNA. These results were correlated with subsequent axillary surgery.

Results: Nodes were identified in 103 of 166 axillae scanned. 54 (52%) fitted the criteria for biopsy. 48 cores (26 malignant, 20 benign node,2 normal) and 6 FNA (1 suspicious, 1 benign, 4 inadequate) were done. On subsequentdefinitive histological examination 64 of 166 (39%) had axillary metastases. Of the 64 patients with involved nodes at surgery, preoperative ultrasound identified nodes in 46 patients (72%), of which 35 (55%) fitted the criteria for biopsy and 27 (42%) of these were diagnosed preoperatively by ultrasound guided biopsy.

Conclusions: Ultrasound can identify abnormal nodes in patients presenting with primary operable breast cancer. 65% of these nodes are malignant and this can often be confirmed with ultrasound guided core biopsy. Ultrasound guided core biopsy is more sensitive in identifying metastases in patients with extensive nodal involvement.

O-72. Anatomy of the lymphatic vessels of the upper limb: a prospective study of patients undergoing axillary lymph node clearance for breast cancer

O'Mahony S, Barber R, Ballinger J, Rose S, Chilvers A, Peters AM, Purushotham AD. *Addenbrookes Hospital Cambridge*

The anatomy of the upper limb lymphatic vessels is poorly understood. It is hypothesised that patients may possess or develop certain anatomical features that may protect against breast cancer-related lymphoedema (BCRL). The aim of this study was to develop a high-resolution method of imaging upper limb lymphatic vessels and to prospectively study alteration in lymphatic vessel anatomy in a cohort of patients undergoing axillary clearance for breast cancer.

A total of 12 healthy volunteers underwent two lymphoscintigrams on the same upper limb to compare subcutaneous and intradermal injection and ^{99m}Tc-nanocolloid with ^{99m}Tc-Human Immunoglobulin (^{99m}Tc-HIG) High resolution images were produced with intradermal injection of ^{99m}Tc-HIG and this method was further used to study lymphatic vessel anatomy in 20 patients undergoing axillary lymph node clearance for breast cancer. Each patient underwent dynamic lymphoscintigraphy of the ipsilateral arm pre-operatively and 2-3 months post-operatively.

Initial results of pre-operative images of lymphatic anatomy show 3 distinct patterns: a) a single lymphatic channel travelling the length of the upper limb; b) a single channel in the forearm which then divides into multiple channels around the elbow re-grouping to form one channel in the upper arm; c) multiple channels throughout the length of the upper limb. Post-operative alterations in anatomy, the opening of 'collateral' channels or the loss of appearance of some channels were recorded.

Long-term follow-up of patients is required in order to correlate pre- and post-operative anatomical features with the development of BCRL in order to identify patients at risk of developing BCRL.

O-73. Survey of management of the axilla in breast cancer by specialist breast surgeons

Gaston M, Dixon JM. *Western General Hospital Edinburgh*

Aims: To survey management of the axilla by specialist breast-surgeons in the UK.

Methods: Questionnaire returned by 328 surgeons.

Results: Of the 328, 323 (85%) were consultants All but 15 treated more than 50 cases of breast cancer per year. 87% did general on call emergency surgery. 87 (27%) treated all patients with invasive breast cancer by axillary clearance (AxCL) alone, 18 (5%) only used sampling (AxNS), 133 (41%) used both AxNCl and AxNS, 35 (10%) AxNCl and sentinel node biopsy (SNB) and 55 (17%) AxNCl, + AXNS and SNB. 9% cleared to level I and sometimes to level II, 42% always cleared the axilla to level II and 49% to level III. 5% always divide pectoralis minor and 7% usually do when performing AxNCl. 11% try and preserve multiple intercostals nerves (ICN) during AxNCl, 46% try to preserve 1 ICN and 43% routinely divide all ICNs. Success at preserving nerves varies significantly between surgeons who try to preserve ICNs. Sampling is by four node sample (70%) or level one dissection (30%). 54% only perform SNB in trials, whereas 13% use it within and out with trials and 33% perform it out with trials only. A variety of techniques are used for SNB out with trials. 82% inject around the tumour, 12% intradermally and 6% into the subareolar region. For sentinel node biopsy to become routine surgeons reported they needed long term results from randomised trials, greater funding for the technique, better access to nuclear medicine and improved programs for training.

Conclusions: There is no consistent practice of managing the axilla in the UK and this is of concern. SNB is being used out with trials using a variety of techniques. A consensus view on axillary management is urgently required.

O-74. Long-term regional recurrence and survival for axillary node sampling for breast cancer

Rampaul RS, Pinder SE, Morgan DAL, Ellis IO, Blamey RW, Macmillan RD. *Nottingham City Hospital*

Axillary node sampling (ANS) with selective radiotherapy (RT) to the axilla for node positive disease aims to avoid axillary node clearance (ANt) for all clinically node negative patients. Regional recurrence (RR) and survival (OS) by nodal status has been analysed in this study to assess the long-term outcome of this protocol.

Between January 1991 and December 1994, 852 patients with primary operable breast cancer underwent ANS. Stage 1 (node negative) patients received no further treatment to the axilla; Stage 2 (1-3 nodes positive) and Stage 3 (>3 positive) patients were treated by RT to the axilla.

At a median follow-up of 7.5 years, 41 RR's have occurred (0.66% annum, 95% free of RR). Stage 3 patients had a higher rate of RR than Stage 2 or Stage 1 ($p < 0.001$). For Stage 2 patients, those with 3 nodes positive had a higher rate of RR compared to those with 1 or 2 positive nodes ($p < 0.05$).

When OS was analysed by number of nodes positive (0,1,2,3), outcome is distributed evenly as expected (89%, 84%, 75%, 65% survival), suggesting that under-staging is not a significant problem for ANS.

ANS and selective RT results in low RR.

O-75. Salvage axillary node clearance in metastatic breast carcinoma

Sharif MA, Harland RNL. *Wrightington, Wigan and Leigh Hospital Lancashire*

Introduction: Axillary recurrence is rare but poses a challenging clinical problem. The aim of this study was to assess the long-term results of salvage axillary clearance. Method: The clinical notes of all patients undergoing axillary clearance for recurrent disease within the axilla between December 1992 and June 2000 were reviewed retrospectively to analyse the efficacy of local control and long-term clinical outcome. Eighteen patients (all females) with a median age of 54 years (range 32 to 80) in whom salvage level III axillary node clearance was attempted were identified. In seventeen patients clearance without gross residual disease was achieved. In one patient complete removal of macroscopic disease was not possible. All patients had further systemic treatment. Median follow up after salvage surgery was 28 months.

Result: Initial control of regional disease was achieved in 17/18 patients (94%), None of the 17 patients developed further axillary recurrence. The overall actuarial survival at 10 years was 50% with most patients dying from metastatic disease.

Conclusions: Our experience showed that aggressive salvage axillary surgery gives excellent local control of recurrent disease and should be attempted even when operability is doubtful.

O-76. Axillary vein changes contribute to breast cancer-related lymphodema - a prospective study

Pain SJ, Purushotham AD. *Addenbrookes Hospital Cambridge*

Lymphoedema remains a common and poorly understood complication of breast cancer treatment, with a multi-factorial aetiology. This study aims to prospectively evaluate the effect of axillary clearance on the axillary vein, and to investigate the relationship with subsequent development of lymphoedema.

Women were studied prior to breast cancer surgery which included a Level 11 or III axillary clearance, and 3 and 12 months thereafter. Circumferential arm measurements were taken at 4 cm intervals, and arm volume calculated by pre-programmed calculator. Doppler ultrasound was used to assess axillary venous flow pattern, wall movement and anatomy.

A total of 70 women were studied. Arm swelling (>10% relative volume increase of all or part of the arm) was observed in 15.7% of women at 3 months and 11.4% at 12 months. In this group, significant alterations to venous flow patterns were observed compared with those without arm swelling ($p = 0.03$) and with pre-operative measurements for the group as a whole ($p = 0.02$). Veil wall movement following surgery was significantly reduced compared with pre-operative measurement ($p = 0.0001$) and with the contralateral arm ($p = 0.007$), but did not correlate with arm swelling. Obvious alterations in venous anatomy (stenosis or complete occlusion) were seen in 4 women at 3 months (2 of whom had >10% volume increase) and 6 women at 12 months (1 with >10% volume increase).

Axillary clearance can cause altered flow within the axillary vein, which is associated with an increased risk of developing

breast cancer-related lymphoedema. Alterations to venous wall movement occur early and in the absence of arm swelling, but may be an indicator for future development of oedema.

O-77. Breast cancer prognostication: Adjuvant! versus NPI

Hughes-Davies L, Thomas SK, Wilson CB, Caldas C, Wishart GC. *Addenbrookes Hospital Cambridge*

Introduction: Since the publication of Overview II in 1992, the idea of constant proportional benefit from adjuvant therapies is widely accepted. In order to estimate the absolute benefit for an individual patient, accurate prognostication is essential. We have compared the Nottingham Prognostic Index (NPI) with an alternative prognostication system (Adjuvant!) [1], recently developed using a grade-adjusted TNM approach, to assess the impact on prescription of adjuvant systemic therapy.

Method: A mock MDM was held using Adjuvant! to review 104 consecutive anonymised patients who had been discussed at our MDM in 2002. A new treatment plan (Adjuvant!) was compared to the original NPI-based treatment plan.

Results and discussion: Substantial differences in prognostication between the two systems were found. In 102 of 104 patients, the Adjuvant! program gave a better prognosis than the NPI ($p < 10^{-6}$). On average, Adjuvant!'s estimate of death was a third less than the NPI (RR 0.65 $\pm$ 0.15) The effect of Adjuvant! on our MDM decision making was striking. 10 of 104 patients previously recommended chemotherapy would not have been offered chemotherapy at all. For another 14 patients, benefits were so marginal that the decision would have been left to the patient rather than the MDM making a strong recommendation. Assuming that half of these patients would have decided against chemotherapy, we estimate that about 17 patients would have been spared chemotherapy using Adjuvant! for prognostication rather than the NPI, reducing our unit's overall chemotherapy use by nearly 40%.

[1] Ravdin, P. et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 2001, Feb 15;19(4):980-991.

O-78. Primary operable invasive breast cancer: lympho-vascular invasion

Pinder SE, Blamey RW, Evans AJ, Lee AHS, Ellis IO, Macmillan RD, Robertson JFR, Elston CW. *Nottingham City Hospital*

Early lymphatic spread can be determined by the histological evaluation of lympho-vascular invasion (LVI) in well-fixed histological material. This was assessed on haematoxylin and eosin-stained sections at the periphery of 3667 primary operable invasive breast cancers in women presenting to the Nottingham Breast Unit. LVI was- categorised as definite, probable or absent. Lymph node status was determined by an axillary sampling surgical procedure and each node carefully examined histologically. Long term follow-up and tumour and patient characteristics were recorded.

60% of all the invasive carcinomas showed no LVI, 14% probable LVI and 27% were classed as LVI positive. However 43% of patients with LN+ disease showed definite LVI compared with only 17% of 2309 LN-cancers ($p < 0.0001$).

In lymph node negative breast cancer the 10-year overall survival was 67% in LVI+ disease and 79% for LVI- (absent or probable) tumours ($p < 0.001$). Multivariate analysis in LN- cancers with histological grade, invasive tumour size and LVI entered, showed that LVI retained independent prognostic significance. Beta co-efficients for grade, size and LVI were 6.9, 10.0 and 3.1 respectively.

In conclusion, these data show that LVI adds prognostic discrimination in lymph node negative invasive breast cancer.

O-79. Improved prognosis for breast cancer across prognostic spectrum

Blamey RW, Mitchell M, Elston CW. *Nottingham City Hospital*

The Nottingham Prognostic Index (NPI) was originally derived from multivariate analysis of prognostic factors. It recognised three groups with significantly differing survivals and was prospectively validated, intra- and inter-centre and internationally in series totalling over 20,000 cases. Later analysis divided patients into 5 groups.

Mortality from breast cancer in the UK has fallen since the 1980s. Earlier detection is partly responsible for this (from raising the percentages lying in the best prognostic groups and by detection of DCIS).

Prognosis has also greatly improved within each prognostic group and there is greatly improved overall survival (from 55–75%). Considerable relative risk reductions apply across the prognostic range but are larger in the better prognostic groups.

	Breast cancer specific 10-year % survival			
NPI	$\leq$	1980-86	1990-96	Reduction in risk of death
Excellent	2.4	88	95	0.58
Good	3.4	72	90	0.64
Moderate I	4.4	61	79	0.46
Moderate II	6.4	42	71	0.50
Poor	6.4	14	44	0.34
V. poor	7.0	12	33	0.24
All cases		55	77	0.49

Since the improvement is after stratification into prognostic groups, the risk reductions demonstrated here have been brought about by therapeutic management.

O-80. Detection of isolated tumour cells in bone marrow is a prognostic factor in breast cancer

Widswang G, Borgen E, Kåresen R, Kvalheim G, Nesland JM, Qvist H, Schlichting E, Sauer T, Janbu J, Harbitz T, Naume B. *Ullevaal University Hospital, The Norwegian Radium Hospital, Baerun Hospital and Aker University Hospital Oslo Norway*

Purpose: The aim of this study was to disclose the clinical impact of detecting isolated tumour cells (1TC) in bone marrow (EM) in breast cancer patients at operation and three years after primary treatment.

Material and methods: BM-aspirates were collected at primary surgery in 817 patients and in 356 of these a second aspiration was obtained three years later. Tumour cells in BM were detected by immunocytochemistry using anticytokeratin antibodies (AE1/AE3). Analyses of the primary tumour included histopathologic grading, vascular invasion and immunohistochemical expression of cerbB2, cathepsinD, p53 and ER/PgR receptors. These analyses were compared to clinical outcome. Median follow-up was 49 months in the 817-group and 66 months in the 356-patient group.

Results: Of all patients (62.5% NO, 60.7% T1), ITC was detected at surgery in 13.2%. The detection rate rose with increasing T -and N-status. Systemic relapse and death of breast cancer occurred in 31.7% and 26.9% of the BM + versus 13.7% and 10.9% of the BM+ patients, respectively ($p < 0.001$). ITC in BM did not predict local relapse. Analysing N+ and NO patients separately, ITC in BM was associated with poor prognosis among the N + and in subgroups of the NO patients. Analysing BM three years after diagnosis in 356 relapse free patients, ITC was detected in 14.9%. Positive BM at this time predicted reduced clinical outcome ($p < 0.001$), with positivity at both examinations predicting the worst outcome.

Conclusion: ITC in BM predicts independently reduced disease free and breast cancer specific survival when detected at diagnosis and after end of treatment. In multivariate analysis, ITC in BM is an independent predictor of outcome and combination of prognostic factors can classify subgroups of both N+ and NO into excellent and high-risk prognosis groups.

O-81. Array CGH identifies genes commonly applied in breast carcinoma

Witton CJ, Ruffalo T, Cooke TG, King W, Bartlett JMS. *Royal Infirmary Glasgow & Vysis Inc, Ill, USA*

Breast cancer, the most common cancer in the UK, is a complex disease characterised by multiple genetic alterations. Emerging data suggests that, alterations in different genetic pathways affect patient response to treatment and survival. To test this hypothesis we have used molecular cytogenetic chips to identify differing genetic patterns in a cohort of breast tumours.

Frozen breast carcinoma tissue was collected from 69 patients treated in Glasgow between 1984-1995 with. complete clinical and demographical data. Ethical approval was obtained from North Glasgow University Hospitals Ethics Committee.

DNA was extracted from tumour sections and amplified by DOP-PCR. Sample and male reference DNAs were labelled by random priming with Cy-3 and Cy-5 tagged nucleotides respectively. DNA was hybridized to micro arrays with 287 clones (Amplionc 300). Copy number changes were detected using the Vysis Genosenor™. Control hybridisations using DOPed male/female DNA where performed. Individual hybridisation ratios and 95% confidence intervals for 'normal' DNA content were calculated independently for each locus. In breast tumours loci with hybridisation ratios above these 95% confidence intervals were scored as 'Amplified' whilst those below were scored as 'Deleted'.

The most commonly amplified genes (>30% of tumours) were NRAS, GLI, 4QTEL11, RAF1, GARP, CCND1, JAG1, D6S414, INSR, C84C11/T3, U11829, AKT2, 5QTEL70. Specific 'hot spots' relating to previously identified amplification rich regions (11q, 17q, 20q) were also identified. Regions of frequent deletion were also identified (4p, 17p).

We have shown that using CGH combined with DNA micro arrays we can refine previous CGH data to localise specific gene alterations within amplified regions. The clinical significance of the different patterns of molecular alterations within amplicons and of other genetic alterations is currently being investigated.

O-82. A survey of breast cancer patients' views on entry into multiple clinical studies

Burnet K, Benson J, Earl H, Thornton H, Cox K, Purushotham AD. *Addenbrookes Hospital, University of Leicester & University of Nottingham*

Throughout their treatment, patients with breast cancer are likely to be asked to join a number of clinical studies. Concerns have been expressed about entry of individual patients into multiple studies. This survey was undertaken to understand the patient's perception of entry into several clinical studies.

A total of ninety-six patients who had previously undergone surgery for breast cancer from January to June 2000 were sent an anonymous questionnaire 6-12 months after completion of their treatment for breast cancer. In all, 84% of the questionnaires were returned and 62% were eligible for analysis. Of these, 64% believed that there should not be limit on the number of clinical studies offered to any patient. Furthermore, 75% of all patients would have considered entering more than one study if adequate explanation and written information were provided. Most patients felt that their participation in a clinical study was worthwhile. None of the patients surveyed regretted their decision to take part in a study.

About two thirds of the patients who returned questionnaires believed there should not be a maximum number of studies offered to them. This survey shows that the majority of patients are keen to participate in more than one clinical study, provided they are given sufficient explanation.

O-83. Biological sub-studies in clinical trials - UK patients are willing to donate biological material

Johnson L, Bliss J, Johnson S, Yarnold J. *Institute for Cancer Research & Royal Marsden Hospital Sutton for the Trial Management Groups and Trial Steering Committees for START and TACT*

With the establishment of NTRAC, the UK is well placed to become an international leader in setting up a national cancer tissue resource to conduct biological research. Following Alder Hey however, there has been much debate about ethical issues and patient consent, and a lack of clear guidance on acceptability of blanket patient consent for future research.

Since 1999, the ICR-CTSU has carried out 2 major national breast cancer clinical trials where biological material was collected. Within the START (Standardisation of Radiotherapy) Trial, 27 out of 35 centres opted to take part in a sub-study

to collect patients' blood samples for DNA testing. 3585 patients from 27 participating centres agreed to take part in the main START Trial between January 1999 and October 2002, of whom 2849 (79.5%) also donated a blood sample for future research.

Within the TACT (Taxotere as Adjuvant Chemotherapy) Trial, all UK patients were asked to donate breast tumour tissue for future research. Between February 2001 and February 2003, 3507 patients consented to take art in TACT, of whom 3445 (98.2% agreed to donate tissue.

	No UK centres taking part (as % of those taking part in main study)	No patients consenting (as % of those from participating centres)
START (blood samples)	27/35 (77%)	2849/3585 (79.5%)
TACT (paraffin blocks)	102/102 (100%)	3445/3507 (98.2%)

Conclusion: Alder Hey has had little impact on the willingness of patients to donate biological material for research purposes, with the overwhelming majority of patients in clinical trials consenting to this type of research. Any impact made by Alder Hey is likely to be due to concerns of pathologists over releasing material, and/or professional anxieties over ethical and legal issues.

O-84. Survey of patient opinion on the retrospective use of their tissues for research

Mullinger K, Blamey RW. *Nottingham City Hospital*

Translational research in breast cancer and many diseases is threatened if legislation is introduced which forbids the retrospective use of tissues and data without obtaining permission from the patients. Whilst in future permission may be obtained prospectively at the time of diagnosis, it will require a number of years of follow-up before any clinical correlations are available.

This survey sought opinion on the retrospective use of tissues from the people most involved, i.e. the patients.

The survey was carried out in the Primary Breast Cancer Follow-up Clinic over a three-month period. Patients attend this clinic who were treated as long ago as the 1970s to recently.

Questionnaires were handed out and returned to the clinic nurses. They were accompanied by a short explanatory letter stating that they were under no obligation to return the questionnaire.

Results: (1) 'The use of my tissues and data for research without my permission.' I approve 468; I disapprove 15.

(2) 'If I was the closest living relative of a patient who had died of breast cancer.' I would approve 394; disapprove 44, of the use of their tissues and data for research.

The patients were asked if they wished their views to be reported to the Secretary of State: 236 did.

Conclusion: It is clear that the overwhelming proportion (97%) of patients treated for breast cancer support the retrospective use of their tissues and data for research and do not believe that their permission is required. Many felt strongly enough to wish their replies to be communicated to the Secretary of State.

O-85. Development of a consent form for use of surgical tissue in breast cancer research

Murphy C, Hepper J, Lansdown M, Hanby A. *United Leeds Teaching Hospitals*

Introduction: Public awareness and attitudes towards research utilising human tissue has shifted considerably in recent years and patients now expect full consultation and are required to give informed consent to the use and/or retention of any tissue. We describe the steps taken within the Leeds Breast Unit to address this issue by developing a consent form that allows us to obtain tissue samples for research.

Methods: We circulated an initial draft consent form widely within the Breast Unit. We obtained approval from LREC to proceed and thel1 presented the form to a focus group. The objective of the focus group was to explore the local population's attitudes to a new consent form we were considering using. The views of the focus group, Breast Unit staff, members of the research group, LREC and the Plain English Campaign were taken into account in drawing up the final version. Patients were approached in pre-assessment clinic by a research nurse and asked to sign the form.

Results: Through the focus group we have realised that knowledge and understanding amongst the public of what actually happens to tissue removed at surgery and what the work of a Pathologist entails is very limited. There was however general approval of our form from patients and interest in finding out more about the research in progress. To date 80 patients have been asked to sign the consent form. 100% of the patients have agreed.

Conclusions: We have introduced a consent form that is acceptable and understandable to patients. We are able to use reserve breast tissue removed at operation in research. The form has been awarded a crystal mark from the Campaign for Plain English. We have also succeeded in engaging Breast Unit staff and increasing their understanding of the' research that takes place in the Unit.

O-86. Brain metastases from breast cancer: identification of a high risk group

Evans A, James J, Cornford E, Chan S, Burrell H, Pinder S, Gutteridge E, Robertson J, Hornbuckle J, Cheung KL. *Nottingham City Hospital*

The aims of this study are to document the type, frequency, temporal occurrence and survival of women with brain metastases from breast cancer and to attempt to identify a subgroup of women at high risk of brain metastases who may benefit from pre-emptive: medical intervention. The radiological reports of all women presenting with metastases aged, under 70 who had subsequently died were examined. Correlations were sought between the frequency of brain metastases and age at metastatic presentation, tumour grade, histological type and oestrogen receptor (ER) status. Of 219 patients, 49 (22%) developed brain metastases. The development of brain metastases was related to young age ($p = 0.0002$) with 43% of women under 40 developing brain metastases. Brain metastases were commoner in women whose tumours were ER negative

Abstract O-88 – Table

Group		Recurrence			Mortality		
		Symptomatic (n)	Screening (n)	P value*	Symptomatic (n)	Screening (n)	P value
Size (cm)	<1.5	44 (18.6%)	17 (2.9%)	<0.001	14 (5.9%)	1 (0.2%)	<0.001
	1.5 - 2.5	72 (23.4%)	43 (14.2%)	0.011	62 (20.1%)	18 (5.9%)	<0.001
	> 2.5	41 (41%)	34 (47.2%)	0.3	45 (45%)	17 (23.6%)	0.072
Tumour grade	I	16 (8.6%)	9 (3.5%)	0.038	10 (5.4%)	1 (0.4%)	0.014
	II	58 (21.1%)	18 (4.6%)	<0.001	41 (14.9%)	9 (2.3%)	<0.001
	III	83 (44.9%)	67 (21.1%)	<0.001	70 (37.8%)	26 (8.2%)	<0.001
Node status	Neg	72 (16.6%)	47 (7%)	<0.001	42 (9.7%)	8 (1.2%)	<0.001
	Pos	85 (40.1%)	45 (21.5%)	0.005	79 (37.3%)	26 (12.4%)	<0.001

Cov's proportional hazards regression.

(38%) compared to women with ER positive disease (14%) ($p = 0.0003$). By combining age and ER status it is possible to identify a group of women (age under 50 and ER negative) with a 53% risk of developing brain metastases. 68% of this group had either stable disease or disease response at other sites at the time of brain metastases presentation. In conclusion it is possible to identify a subgroup of women at high risk of brain metastases who may benefit from pre-emptive medical intervention.

O-87. Impact of earlier diagnosis and changes in treatment on survival improvement in women with breast cancer

Twelves CJ, Thomson CS, Brewster DH, Dewar JA. *Beatson Oncology Centre Glasgow & Ninewells Hospital & Medical School Dundee*

We investigated changes in survival, and their causes, in women with early breast cancer diagnosed in Scotland between 1987 and 1993. The Scottish Cancer Registry identified 1617 and 2077 such women, without metastases at diagnosis who underwent surgery as part of their primary treatment, diagnosed in 1987 and 1993, respectively. There was a statistically significant 11% improvement in 8-year survival between 1987 and 1993. Survival improved across almost all clinical, treatment and health-care delivery/deprivation categories; improvement was not limited to those women diagnosed through the screening programme. In a multivariate model, improved survival appeared to be explained largely by screening and clinical prognostic factors. Deprivation also had an adverse effect on survival; however, the geographical variation in survival observed for women diagnosed in 1987 was not apparent by 1993. We conclude that survival has increased partly as a consequence of screening and earlier diagnosis, but also due to improvements in the organisation and delivery of care.

O-88. Comparison of survival of screen detected breast cancers (SDBC) with symptomatic ones of same age (50-65 years) in one unit

Prasad R, Bryne G, Knox WF, Wilson M, Barr L, Zeiton A, Baildam AD, Morris J, Bundred NJ. *University Hospital of South Manchester*

Controversy exists about the survival benefits of breast cancer screening but SDBC now constitute 60% of cancers women aged 50-65 years. The aim of this study was to compare SDBC and symptomatic breast cancer survival in women aged 50-65 years. From 1990-98, in one unit, 1607 breast cancers (962 SDBC and 645 symptomatic) were treated in the age group 50-65 years. Clinico-pathological data was compared for risk of recurrence and cancer specific mortality in each of the sub-groups. Median follow-up was 70 months (range 21-103). Smaller turnouts ($p < 0.001$) and higher node negativity ($p < 0.001$) occurred in SDBCs, but tumour grade did not differ.

Conclusion: SDBCs (size <2.5 cm) have a better survival than symptomatic cancers irrespective of grade or node status.

O-89. The effect of screening on mortality

Blamey RW, Mitchell M, Evans AJ. *Nottingham City Hospital*

Screening has its effect by detecting tumours with better prognostic tumours. The overall effect on the whole tumour set (screen detected and symptomatic) from January 1990 to December 1996 at presentation and the expected effect of this on survival can be calculated:

	1980–86			1990–96	
	% in grp	(% 10 yr surv)	Observed 10 yr n surviving	% in grp	Expected 10 yr n surviving
E	12	(84)	10	19	16
G	19	(63)	12	23	14
MI	30	(59)	18	29	17
MII	24	(43)	10	16	7
P	15	(15)	2	12	2
Overall			52		56

Distribution to prognostic groups in women aged <50 has not changed.

With 11% more tumours in the screened age group in the best 2 prognostic groups and 11% less in the poorest 2, the calculated effect on survival is +4% absolute (relative reduction of 8%).

We estimate the high rate of detection of DCIS by screening reduces mortality by 8%.

Our estimate of the effect of screening on mortality is an absolute reduction of 12% (relative risk reduction of 24%).

O-90. A contemporary analysis of early lymphoedema following axillary clearance for breast cancer

Hawkes MM, Little GS, Brown DC, Thompson AM, Wood RAB. *Ninewells Hospital Dundee*

Lymphoedema is a significant complication of axillary clearance for breast cancer, causing physical and psychological problems for patients. The reported incidence of lymphoedema ranges between 9 and 60%. The aim of this study was to ascertain the current incidence of early, symptomatic lymphoedema within Tayside and to determine predisposing factors. Retrospective data retrieved from Tayside Cancer Audit Database identified 185 cases undergoing surgery for breast cancer from Jan 2001-Jan 2002. The 22 patients who developed lymphoedema within 2 years had all undergone axillary clearance.

	Lymphoedema		No Lymphoedema	
Cases	22		124	
Node Nos.	7-27	Mean 15	3-35	Mean 15
Node	11	50%	59	47%
Positivity seroma	13	59%	64	50%

The incidence of early lymphoedema was found to be 15%. Number of nodes, nodal positivity and seroma formation were not significantly associated with lymphoedema.

This study provides contemporary evidence for the morbidity of axillary clearance and supports the development of Sentinel Lymph Node Biopsy as a low morbidity alternative.

O-91. Is physical function a more appropriate measure than volume excess in assessment of breast cancer-related lymphoedema?

Pain SJ, Vowler SL, Purushotham AD. *Addenbrookes Hospital Cambridge*

Lymphoedema remains a common complication of breast cancer treatment, and has been shown to increase the psychological morbidity associated with a diagnosis of breast cancer. The aim of this study is to objectively measure impairment of arm function in women with breast cancer-related lymphoedema (BCRL), and investigate possible association between this, arm volume excess, and psychological morbidity.

A total of 48 patients with a history of BCRL were studied. Arm volume was calculated from circumferential measurements at 4cm intervals up the arm. Physical function was assessed by a timed task of manual dexterity which involved removing a number of nuts from fixed bolts and then replacing them, for which normative data is available. Psychological morbidity was quantified with the SF-36 questionnaire.

Manual dexterity was significantly impaired in the affected arm ($p = 0.003$) compared with the unaffected contralateral arm, independent of dominant or non-dominant arm involvement, but was not associated with arm volume excess. Psychological morbidity was significantly impaired in the domains of 'physical function' and 'bodily pain' when compared with population controls. Degree of impairment in the 'physica function' domain correlated significantly with the manual dexterity score.

Impairment of manual dexterity appears to have a greater impact than arm volume excess on the overall psychological morbidity associated with BCRL, suggesting that greater emphasis should be placed upon arm function in the assessment, treatment targeting, and monitoring of patients with this condition.

O-92. Investigation of lympho-venous communications in the upper limb

O'Mahony S, Ballinger J, Barber R, Rose S, Peters AM, Purushotham AD. *Addenbrookes Hospital Cambridge*

Breast cancer-related lymphoedema (BCRL) occurs in only a proportion of patients who undergo treatment to the axilla for primary breast cancer. It is hypothesised that a protective mechanism against the development of BCRL exists in the form of lympho-venous communications (LVCs) in the upper limb, which allow protein-rich lymph to bypass the axilla. The presence or function of LVCs has never been satisfactorily proven.

Red blood cells are too large to cross the vascular endothelium and have no access to blood via lymphatic drainage and therefore well suited to the study of LVCs. Differently radiolabelled red blood cells were injected into the interstitium of the dorsum of the hands of 4 healthy volunteers. Dynamic lymphoscintigraphy to confirm their entry into lymphatic vessels and bilateral venous blood sampling to measure their presence in local venous blood, corrected for systemic re-circulation, was carried out.

Red cells injected into the dermis, but not into the subcutis, gained direct access to lymphatic vessels, as was demonstrated by axillary lymph node imaging. However, no labelled red cells were detected in the circulation up to 3 hours after injection, demonstrating that there are no LVCs in the normal upper limb. This observation requires further investigation in patients undergoing axillary lymph node surgery for primary breast cancer and patients with BCRL.

O-93. Evaluation of cosmesis after breast reconstruction

Shokrollahi K, Daltrey I, Rayter Z, Winters ZE. *Bristol Royal Infirmary*

The cosmesis following immediate breast reconstruction (IBR) may be influenced by the type of reconstruction, use of radiotherapy (RT) and duration of follow-up. There is little published data on long-term cosmesis, dependent on RT and choice of technique. Variation in assessment of cosmesis and lack of standardisation precludes comparative audit or research to define the best treatment option.

A questionnaire was sent to 325 consultant breast surgeons to evaluate the types of reconstruction offered, the timing and types of reconstruction in relation to RT, whether cosmetic outcome was assessed and how this was undertaken. A Universal Scoring System (USS) was proposed and its general acceptance evaluated.

Of the 81 respondents, 61 (75%) performed IBR, with 46% (28/61) performing less than 20, and a similar number, 20-50 reconstructions per year. Subpectoral implants were performed

by 87% of surgeons and offered prior to RT in 38% (21/53) of cases. Most surgeons offered a Latissimus Dorsi (LD) and implant/expander reconstruction, and considered this prior to RT in 53% (35/66). Fewer surgeons offered an autogenous LD and favoured this option in the event of RT in 54% (15/28). TRAM flaps were performed by 59% of surgeons, and considered prior to possible RT in 47% (14/30). This suggests no clear preference for an autogenous breast reconstruction versus an implant-based procedure in the likelihood of RT. Formal cosmetic assessment was highly variable with only half of surgeons evaluating the breast in all or most patients and 31% (19/61) similarly assessing the donor site. Importantly, 47% and 59% of surgeons rarely assessed the breast or donor site. An interest in formalizing cosmetic assessment was expressed by 79% (48/61) and 71% wished to be involved in such a process. Of those who expressed an opinion, 90% favoured USS.

There is marked variation between breast units in the types of reconstruction offered, the timing relative to RT, and the cosmetic evaluation undertaken after surgery. The 25% response rate to this questionnaire potentially reflects the lack of importance given to this aspect of IBR and illustrates the difficulty of achieving a consensus with regard to cosmetic assessment, suggesting the need for a universal system for cosmetic evaluation.

O-94. Breast conserving surgery (BCS) and immediate reconstruction with latissimus dorsi flap (IRLDF)

Bruzas S, Mudenas A, Luksyte A, Meskauskas R. *Oncology Institute of Vilnius University*

Introduction: BCS has more than 30 years history in the treatment of breast cancer (BC). Two main problems in BCS still exist: local recurrence rate (which is usually greater compared with mastectomy and occur even in small tumors) and cosmesis. It is not easy to coordinate good radicalism with good cosmesis. For this purpose the value of IRLDF after BCS was evaluated.

Material and methods: From 1997 until 01.2003, 50 patients with BC were operated by using the combined method: wide excision of cancer (quadrantectomy) with axillary lymph node clearance and IRLDF. Distribution of tumor size was from 1.5 cm to 5 cm, median patient age 43.5 years, node-positive were 24 (48%), 15 (30%) patients received preoperative chemotherapy, 32 (64%) had got adjuvant radiochemotherapy, 15 only adjuvant radiotherapy. Most tumors were in the upper lateral quadrant - 45 (90%). Median duration of operation - 2 hours.

Results: No cases of local recurrences in the breast. 3 patients have further disease dissemination and 3 patients died of metastases. The cosmesis of operated breast is good. In 8 cases a lift of the operated breast happened, in 2 clear bulk in axilla.

Conclusions: For final interference (especially for local relapses) it is not long enough follow up time. However, our conclusions are:

1. It is possible to perform BCS together with IRLDF in big tumor cases (4-5 cm) and to reach similar radicalism as in mastectomy.

2. BCS with IRLDF minimizes the possibility of local relapse in the breast.

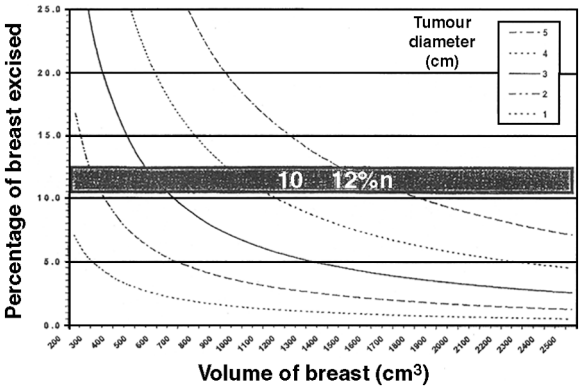
3. IRLDF after BCS allowed preserving good breast cosmesis despite the tumor size.

O-95. Pre-operative prediction of cosmesis and patient satisfaction after breast conserving surgery

Phipp LH, Hurd KB, Wilson ARM, Evans AJE, Macmillan RD. *Nottingham City Hospital*

Many factors affect cosmesis after breast conserving surgery. One of the most influential is the percentage of breast volume excised. Previous studies have shown that excising more than 10-12% of the breast volume is more likely to be associated with poor cosmesis and decreased patient satisfaction.

We have designed an at-a-glance chart (the Phipp chart) for pre-operatively estimating the percentage of breast volume that will be removed for any given tumour size, if the mammographic breast projection and base width are known. The chart is based on the assumption that the excision biopsy is spherical and clearance margins are 10 mm around the cancer.



The chart is being validated in the Nottingham Breast Unit and is a simple and useful adjunct to the pre-operative decision process.

O-96. Size of invasive breast cancer and risk of local recurrence after breast-conserving surgery

Asgeirsson KS, McCully SJ, Pinder SE, Macmillan RD. *Nottingham City Hospital*

Risk of local recurrence is one important factor that determines a woman's suitability for breast-conserving surgery. With the evolution of oncoplastic surgery, tumours of a size that traditionally require mastectomy may be treated by breast-conservation and partial breast reconstruction. This article reviews the evidence relating to tumour size as a risk factor for local recurrence to assess whether this change in practice is appropriate.

A literature review through Medline and Pubmed was performed. All pathological studies analysing tumour size as a predictor of multifocality and all randomised trials and large case series of breast-conservation including tumours larger than 2 cm were reviewed and critically interpreted.

Pathological studies report consistent evidence that tumour

size is not predictive of multifocality. Randomised trials and clinical series of breast-conservation report conflicting evidence relating to tumour size as a risk factor for local recurrence, although most studies report no association. Evidence relating to cancers over 3 cm is limited: There is little evidence to justify the use of tumour size alone as an exclusion criterion for breast-conserving surgery. A registration study of patients with cancers larger than 3 cm treated by breast-conservation with or without partial breast reconstruction is proposed.

O-97. Breast conserving surgery and partial breast reconstruction - a review

Asgeirsson KS, McCully SJ, Macmillan RD. *Nottingham City Hospital*

Breast-conserving surgery is firmly established as a good and safe option for women with early breast cancer. Perceived cosmetic outcome can have an impact on a woman's suitability for breast-conserving surgery.

This review examines the role of partial breast reconstruction as a means of enhancing cosmesis and expanding the indications for breast-conserving surgery.

A literature review through Medline and Pubmed was performed. Recent advances in partial breast reconstructive techniques suggest that the role of breast-conserving surgery may be expanded to include larger cancers in addition to improving the cosmetic outcome for smaller ones. To date, detailed studies are small and outcome measures varied.

Breast surgeons should be aware of the range of surgical techniques that may enhance the aesthetic results of breast-conserving surgery as well as expand the indications for its use. A registration study is proposed to improve our understanding of the safety and outcome of partial breast reconstruction.

O-98. Nurse led follow up for women post breast cancer treatment

Noblet M, Keeling F, Baildam A, Bundred N. *South Manchester University Hospitals*

Background: Despite the lack of evidence that new or recurrent breast disease is identified at follow-up surgical clinics, women who have received primary treatment for breast cancer continue to be clinically managed in this way.

A randomised study was undertaken to compare the outcomes of traditional surgeon-led versus nurse-led follow-up clinics in a large UK breast centre.

Aims: The study aims were to quantify:

- detection rates of recurrent/new breast disease and/or psychological morbidity
- user satisfaction

and to undertake a cost benefit analysis

A secondary aim was to explore job satisfaction of the nurses running the follow-up clinics and to quantify their development of advanced nursing practice.

Methodology: Approximately 600 study volunteers were randomised to surgeon or nurse-led follow-up clinics over an 18-month period. Two consultant breast surgeon teams and two breast care nursing teams provided the follow-up care. In addition to clinical data collection, pre and post-consultation questionnaires (including HAD and Spielberger State and Trate) were completed by study volunteers and reflective diaries were maintained by the breast cancer nurses.

Results: Results indicated that nurses were acceptable to women in the follow up setting. They detected reoccurrence and new disease in the same way as medics. Women were no more anxious prior to or after seeing the nurse. Both breast care nurses reported improved job satisfaction and through their diaries demonstrated the acquisition of new competencies. Analysis of satisfaction questionnaires in still in progress.

O-99. Eighteen months experience of a breast nurse practitioner performing clinical examinations, ultrasound guided cyst aspirations and core biopsies in the breast clinic

Cubbison RN, Cliff A, Gardiner L, Donaldson LA, Ashton MA. *Diana Princess of Wales Hospital Grimsby*

In 2002, we introduced a Breast Nurse Practitioner to examine patients in the clinic, aware that the Nursing and Midwifery Council has supported nurses undertaking extended roles. The assessment of training and competence must be made by individual Trusts. We wrote the policies, limitations, training required and how each role would be assessed.

Aim: To report the benefits of a Breast Nurse Practitioner working i in the breast clinic over 18 months.

Results: She has examined 780 new and 520 follow up patients, performed 127 cyst aspirations and 115 core biopsies all under VIS control. The CB was evaluated at the M D M and the hard copy ultrasound images reviewed. Comparing the first six months of 2001 with 2002, we saw 8% more new and 9% more follow up patients, routine appointment waiting time reduced from 5.5 weeks to 3.5 weeks and the average length of clinic reduced from $4^3/_4$ hours to 4 hours.

	Total number	0-9 mm	10-14 mm	15-19 mm	20-29 mm	>29 mm
Cysts aspirated	127	4	10	42	47	24
Core biopsies	115	15	24	29	27	20
B1		1	0	1	1	0
B2		11	17	18	10	11
B3		1	2	1	0	0
B4		0	1	0	1	0
B5		2	4	9	15	9

Conclusion: A Breast Nurse Practitioner can independently and accurately clinically assess new patients. With an ultrasonographer she can achieve a high accuracy in cyst aspiration and core biopsy under U/S control. This is to the patients' benefit and is an excellent example of cross boundary working to improve the breast service.

O-100. The rates of growth of breast cancers

Blamey RW, Brooks M, Burrell H, Pinder S, Mitchell M. *Nottingham City Hospital*

The diagnostic rate at prevalent screening, the natural rate of symptomatic presentation and the diameter of screen detected

and symptomatic tumours have been used to calculate the diameter doubling time during the observable phase of breast cancers.

For each grade these are approximately grade I 5 years, grade II 2 years and grade III around 3 months. These are in line with mammographic observations and the relative rates fit with the ratios of mitotic rates for each grade.

If growth was by volume doubling throughout this would mean grade I tumours took from before birth years from inception to presentation.

We have previously (Connor [1]) shown that mitoses are concentrated. in the outer 2 mm shell. We suggest that growth is by volume doubling and from 4 mm by doubling. This is growth according to the Gompertzian equation, seen in experimental tumours.

Based on calculations of the growth rates from this, grade I tumours take approximately 12 years from inception to symptomatic presentation, grade II 5 years and grade III 3 less than 1 year.

This observation casts doubt on the claims of therapeutic (tamoxifen) 'prevention' of breast cancers and explains the predominance of grade III tumours presenting in young women.

References

[1] Connor AJM, Pinder SE, Elston CW, Bell JA, Wencyk P, Robertson JRF, Blamey RW, Nicholson RI, Ellis IO. Intratumoural heterogeneity of proliferation in invasive breast carcinoma evaluated with MIB1 antibody. The Breast, 1997;6:171-176.

O-101. The origin of DCIS? Discussion paper

Blamey R W, Lakhani S. *Nottingham City Hospital & Royal Marsden Hospital*

We suggest that DCIS is a risk lesion which has an increased chance of acquiring a mutation giving an invasive tumour, rather than as an inevitable or obligate precursor of invasive cancer.

DCIS is unicentric and monoclonal. Even though not invasive it may be extensive, occupying a whole lobe or small, occupying a terminal duct lobular unit. Despite their infiltrative nature invasive carcinomas do not occupy whole lobes.

As a monoclonal lesion DCIS must originate from a mutation in a single cell, It appears no more likely to be underlain by a germline mutation than does invasive cancer. Mutations only occur during cell division and one of the highest rates of cell division occurs in the developing breast.

We postulate that a mutation occurs in a precursor cell during breast development and that because all cells in the lobe or lobule arising from that cell are from then unstable, this explains the lobular/lobal distribution of DCIS. DCIS is the later developing morphological expression of this instability.

Supporting evidence will be presented including research from Lakhani's laboratory showing LoH changes in normal breast and in breasts with carcinoma, from tissues without morphological abnormality; these have been seen restricted to one part of the breast.

O-102. Asymptomatic, contralateral breast disease in patients presenting to a rapid access breast clinic

Davies M, Horocks LE, Holland PA, Gateley CA. *Royal Gwent Hospital Newport Gwent*

Introduction: The purpose of this study was to determine the incidence and nature of asymptomatic contralateral breast disease in patients presenting to a rapid access breast clinic.

Methods: Patients diagnosed with breast disease contralateral to the presenting side were identified from the BASO database.

Results: 4673 new patients were seen in the two-year period. Sixty-three (1.4%) patients were identified. A total of 117 extra radiological investigations and 50 needle biopsies were performed. In 29 patients disease was identified radiologically. Nine breast cancers were diagnosed in total (*Table 1*).

Table 1. Asymptomatic contra-lateral diseases

Invasive carcinoma	7
Ductal carcinoma in situ	2
Benign breast cyst	21
Fibroadenoma	17
Sclerosing papilloma	1
Fibrocystic disease	15

Patients were age-matched with a control cohort randomly selected from the database (*Table 2*). The control cohort contained three times as many patients as the case cohort.

Table 2. Age distribution of pathology identified

Age	Case Number		B:M*	Control Number		B:M*
	Benign	Malignant		Benign	Malignant	
15-40	11	0	–	33	0	–
41-50	25	1	25:1	73	4	18.3:1
51-60	10	0	–	28	2	14:1
61-70	6	2	3:1	24	1	24:1.
>70	2	6	0.3:1	15	9	1.7:1

*B:M, Benign to malignant ratio.

Conclusion: The significant amount of contralateral disease identified generates a considerable amount of extra work. This has implications on the resources required to run such clinics. There is a much greater risk of a contralateral breast cancer in women presenting over the age of 60, when compared to cancer risk in the whole clinic cohort.

O-103. Contralateral core biopsy at the time of mastectomy - is it worthwhile?

Hogben MK, Kissin MW, Jackson P. *Royal Surrey County Hospital Guildford*

Background: One of the main risk factors for breast cancer is previous breast cancer (BC) in the other breast. Contralateral core biopsy at the time of mastectomy to find this is controversial. Previous research has suggested it may be useful in cases of invasive lobular carcinoma.

Aims: To identify the number and type of contralateral biopsies (CCB) in patients having mastectomy for early BC during a period 1995-2000.

Methods: The total cohort of mastectomy patients in this period was identified, as was the number of contralateral core biopsies. Abnormal biopsies were reviewed and related to known prognostic factors (lymph node status, multifocality and histological type).

Results: 879 mastectomies were performed in this period of which 398 had contralateral biopsies at the time of their surgery. 19/398, (4.8%) were positive, 3 (0.75%) with invasive disease, 5 (1.3%) with in situ disease and 11 (2.8%) with atypical hyperplasia.

The table below shows type of cancer producing positive core biopsies.

	No. -ve cores	No. +ve cores	%
Inv. Lobular	23	8	25.8 (11.8-14.6) $p < 0.001$
Inv. Ductal	102	5	4.71
IDC + DCIS	171	5	2.8
DCIS	77	1	1.3
Others	7	0	0
Totals	380	19	

Of patients with lymph node positivity 13/89 = 14.4% (7.9-23.4) $p < 0.0001$, had positive contralateral core biopsies, as did 7/74 = 9.5% (3.9-18.5) $p = 0.088$ of patients with multifocal disease.

Conclusions: This study confirms other studies that Invasive lobular cancer carries a very high risk of positive contralateral core biopsy and we feel should be offered routinely to these patients. The place for CCB in ductal carcinoma remains controversial, however, an incidence of 5% suggests it is worthwhile, particularly in node positive patients.

O-104. Does multifocal breast cancer predispose to contralteral disease?

Nasr R, Khan HN, Pinder S, Robertson JFR. *Nottingham City Hospital*

Aim: We aimed to assess whether multifocal breast cancer predisposes to development of either synchronous or metachronous contralateral breast cancer.

Patients and Methods: Patients were those diagnosed with invasive breast cancer at Nottingham City Hospital from January 1995 to December 2002. We compared the development of contralateral breast cancer in those with and without multifocal breast cancer on histological examination of the primary excised tumour using Kaplan Meier survival plots for univariate analyses and Cox regression to adjust for tumour grade, lymph node stage and size as potential confounding variables.

Results: 230 patients out of 1979 (11.6%) cases of breast cancers during the study period were noted to have multifocal breast cancer. Mean ages of the groups with and without multifocal disease were 59 (range 25-87) and 66 (range 27-102) respectively. 13 cases of multifocal disease developed contralateral breast cancer whilst only 25 patients without multifocal disease developed contralateral cancer during the study period. Hazards ratio for development of contralateral breast cancer in those with multifocal disease compared to those without was 16.1 (95% C.I. 4.9-53.1). Adjusting for tumour size, grade and stage, the adjusted hazards ratio was 14.8 (95% C.I. 4.3-51.3), which was strong and significant.

Conclusion: Multifocal disease is seen in 11.6% of breast cancers. It appears to increase the probability of developing contralateral breast cancer.

O-105. Paradoxical effects of dietary phytoestrogens on breast cancer cells in vitro

Limer JL, Burdall SE, Lane S, Hanby AM, Speirs V. *University of Leeds*

Breast cancer incidence rates are lower in Asian populations compared with Western nations, correlating with consumption of a phytoestrogens (PE). PEs structurally resemble 17β-estradiol and competitively bind to estrogen receptor (ER) -α and -β, with a greater affinity for ERβ. Despite their putative chemoprotective effects against breast cancer, the effect of dietary PEs on the proliferation of pre-existing mammary turnouts is ambiguous. The aim of this study was to assess the proliferative effects of the PEs genistein, daidzein and coumestrol in breast cancer cell lines of defined ER status and identify potential ER-mediated signalling pathways. The effect of PEs on primary cultures derived from human breast tumours was additionally investigated. Cell lines MCF-7 ($ER\alpha^+\beta^+$; $\alpha > \beta$), T47D ($ER\alpha^+\beta^+$; $\beta > \alpha$), and MDA-MB-231 ($ER\alpha^-\beta^-$) were incubated with 0.1-50 μM PEs ill the absence of exogenous estradiol, and growth assessed by MTT incorporation and DNA analysis. Genistein and coumestrol exhibited biphasic growth effects in MCF-7 and T47D. Physiological doses of 0.1-10 μM stimulated cell proliferation and S-phase activity, whilst concentrations in excess of 25 μM were inhibitory. Daidzein stimulated MCF-7 growth at all concentrations tested, whilst T47D was inhibited at 25 μM. Similar results were obtained with primary breast epithelial cultures established from four $ER\alpha^+PR^+$ breast tumours with PE doses of 0.1–10 μM exhibiting significant proliferative effects (up to 40% over controls. In contrast, the $ER\alpha^-\beta^-$ cell line MDA-MB-231 showed a dose-dependent growth inhibition with all 3 PEs. Using a reporter gene assay, proliferative effects of PEs correlated with enhanced transcriptional activity at an ERE, suggesting ER-dependent mechanisms. Our data indicate that consumption of dietary PEs may exacerbate the growth of ER^+ breast tumours. This may be a cause for concern for post-menopausal subjects using PEs as natural alternatives to HRT.

O-106. Serum enterolactone and risk of breast cancer in women with palpable cysts

Rubagotti A, Lunardi G, Guglielmini P, Parodi M, Murialdo R, Boccardo F. *University & National Cancer Research Institute Genoa Italy*

Low levels of lignans, namely of enterolactone, have been reported to be associated with a decreased risk of breast cancer in the general female population. We assessed retrospectively the relationship between enterolactone serum concentration and the occurrence of breast cancer in women with palpable cysts.

Criopreserved serum aliquots obtained from 383 women with palpable cysts at the time of their first cyst aspiration were processed for enterolactone measurements through a time-resolved fluoroimmunoassay.

After a median follow-up time of 6.5 years (range 0.5-12.9 years) 18 women were found to have developed an invasive breast cancer.

Median values of serum enterolactone were significantly lower in women who subsequently developed breast cancer: 8.5 nM/l vs 16.0 nM/l: p = 0.04. Odd ratios for breast cancer were: 0.36 (p = 0.03), 0.57 (p = 0.3), and 0.38 (p = 0.25) for 25th (8 nM/l), 50th (16 nW/l), and 75th (24 nM/l) percentile values respectively. The ROC analysis showed a satisfactory accuracy of enterolactone as breast cancer risk indicator (AUC = 0.64: p = 0.04).

Logistic regression analysis confirmed that enterolactone concentration had a strong protective effect on breast cancer risk.

These findings can have important clinical implications in the perspective of interventional diet-focused chemopreventive trials.

O-107. BRCA1 2841/5insA is a recurring mutation with a founder effect in Singapore Malay women with early onset breast/ovarian cancer

Sng J-H, Ali AB, Lee SC, Zahar D, Wong JEL, Cross G, Blake V, Sharif A, Iau PTC. *National University Hospital Singapore and Nottingham City Hospital*

Breast cancer is the most common cancer among women in Singapore with the Malay ethnic population showing the greatest increase in the incidence of breast cancer over the past 3 decades. *BRCA1* (OMIM 113705) is a high-penetrant cancer predisposition gene with the prevalence and nature of mutations in this gene appearing to be ethnic-specific. Knowledge of *BRCA1* gene mutations in Asian populations is still largely unknown and to date, *BRCA1* mutations in breast and/or ovarian patients have not been characterized in the Malay population.

In this study, the entire *BRCA1* coding region of 65 Singapore Malay patients with breast or ovarian cancer were successfully analysed using protein truncation test (PTT), polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP), followed by sequencing.

Ten alterations were identified: one frame-shift mutation, two missense mutations, three polymorphisms and four intronic alterations. Of interest, the germline BRCA1 frame-shift mutation, 2841/5insA, was detected in 7 of 65 (10.80%) probands with either early onset ($\leq$45 years at diagnosis) breast cancer or ovarian cancer.

These findings suggest that 2842/5insA is a recurrent mutation and could represent a founder mutation in this homogenous ethnic subpopulation.

This work is to be published in the Journal of Medical Genetics in the issue of September 2003.

O-108. BRCA1 testing in medullary breast cancer

Iau PTC, Marafie M, Ali A, Sng JH, Macmillan RD, Pinder S, Denley HE, Ellis IO, Wencyk P, Scott N, Cross G, Blamey RW. *National University Hospital Singapore and Nottingham City Hospital*

Recommended guidelines have limited BRCA1 mutation testing to individuals with a personal or family history of early onset breast and/or ovarian cancer, and those with multiple affected close relatives. Such large breast cancer families are rare in the general population, limiting the clinical application of the BRCA1 discovery. Previous reports have suggested an association between medullary breast cancer and BRCA1 mutation carriers.

To test the feasibility of using these rare histological subtypes as an alternative to epidemiological factors, DNA from 42 cases of medullary cancer unselected for family history were screened for BRCA1 point mutations and large exon rearrangements. Only 17% (7/42) of patients had a significant family history of breast cancer. All coding exons and adjacent intronic segments were analysed using a combination of single strand conformation polymorphism (SSCP) and protein transcription-translation (PTT) tests, with confirmation of mutations using direct sequencing. Long-range polymerase chain reactions (PCR) were carried out in samples in which no mutation were detected to exclude the presence of large exonic rearrangements.

Two deleterious mutations resulting in a premature stop codon, and one exon 13 duplication were found. All mutations were detected in patients with typical medullary cancer, who had family history of multiple breast and ovarian cancers. Our findings suggest that medullary breast cancers are not an indication for BRCA1 mutation screening in the absence of significant family risk factors.

O-109. Breast imaging findings in women with BRCA1 and 2 associated breast carcinoma

Hamilton L, Evans A, Wilson R, Scott N, Cornford E, Pinder S, Khan HN, Macmillan D. *Nottingham City Hospital*

The aim of the study was to document the mammographic and ultrasound findings of women with BRCA1 and 2 associated breast carcinoma. Family history clinic records showed 28 BRCA1 or 2 positive women who had 27 invasive cancers and 4 DCIS lesions with pre-operative imaging (29 mammograms, 22 ultrasounds). The age range was 26-62 yrs, mean 37 yrs. 2 mammograms were normal and 27 (93%) abnormal.

The commonest mammographic features seen were ill or well-defined mass 17 (63%) and microcalcifications 10 (37%). 37% of women had a dense mammographic pattern, 55% mixed and 7% fatty. Ultrasound was performed in 22 patients and 21 (95%) showed a mass. These were classified as benign in 24% indeterminate in 29% and malignant in 48%.

There is a trend for the mammographic appearances of the cancers of BRCA1 and 2 women to be different. Mammograms of BRCA1 women more frequently showed a mass (13 of 18 (72%) vs 5 of 11 (45%)), whilst mammograms of BRCA2

women more frequently showed microcalcification (8 of 11 (73%) vs 2 of 18 (11%) p = 0.001).

36% of the BRCA2 cancers were pure DCIS while none of the BRCA1 cancers were pure DCIS (p = 0.01).

45% of BRCA2 cancers were detected at mammographic screening compared to 15% of the BRCA1 cancers.

This data suggests the mammographic findings of BRCA1 and 2 associated carcinomas are different and that both are atypical compared with sporadic breast carcinoma. Furthermore, mammographic screening may be more effective in BRCA2 carriers.

O-110. The effect of weight loss on biomarkers of breast cancer risk - a pilot trial

Harvie MH, Mercer T, Alford D, Howell A. *South Manchester University Hospitals & Manchester Metropolitan University*

Weight gain over the premenopausal years is associated with risk of postmenopausal breast cancer. We determined the effects of a 6-month calorie restricted and exercise weight loss programme as compared with standard diet and exercise advice on a range of biomarkers of cancer risk amongst 72 premenopausal women (aged 35-45) with relatively large adult weight gains (>10 kg since the age of 20) and a family history of breast cancer (1 in 6 lifetime risk or greater).

Body weight, waist circumference and fasting insulin, glucose, sex hormone binding globulin (SHBG) and testosterone were determined at baseline and 6 months. After 6 months women in the intervention group had significantly lower body weight, waist circumference and fasting glucose, and tended to have lower levels of testosterone compared to the control group. There were no differences in SHBG or insulin between the groups.

Body size and biomarkers of breast cancer risk after a 6-month weight loss intervention

	Intervention (n = 37)	Control (n = 35)	p**
Weight - kg	73 (0.6)	76.7 (0.6)	0.000
Waist - cm	93.1 (1.0)	97.4 (1.0)	0.004
Fasting glucose - mmol/L	4.6 (0.05)	4.8 (0.06)	0.027
Testosterone - nmol/L	1.47 (0.07)	1.7 (0.08)	0.085
Insulin - pmol/L	36.9 (2.7)	36.8 (2.8)	0.714
SHBG - nmol/L	65.0 (2.8)	61.4 (3.0)	0.398

*Mean (SE) **ANCOVA adjusted for baseline levels.

The weight loss intervention achieved weight loss and some beneficial effects on biomarkers of breast cancer risk amongst women with a family history of breast cancer. We are currently examining the effects of the weight loss intervention on changes in other breast cancer biomarkers (i.e. salivary oestradiol, mammographic density and igf-1) over 12 months, as well as the effect of compliance and change in body fat on changes in SHBG and insulin within the groups.

O-111. High-density Lipoprotein cholesterol (HDL-C) as part of metabolic syndrome, influences postmenopausal breast cancer risk. A Norwegian Cohort Study including 38,823 women

Furberg A-S, Veierøed M, Wilsgaard T, Bernstein L, Thund I. *University of Tromsø, Oslo Norway and University of Southern California USA*

Background: The metabolic syndrome (obesity, glucose intolerance, dyslipidemia, hypertension) has a high and increasing prevalence that runs in parallel with an increase in breast cancer incidence worldwide. Serum androgens decrease HDL-C and have been positively associated with breast cancer risk. Thus, our aim was to assess the effect of HDL-C on the risk of breast cancer, especially in women with a positive energy balance (e.g. high body mass index, BMI).

Methods: In two population-based screening surveys during 1977-83 and 1985-88 serum HDL-C was assayed enzymatically among 38,823 women aged 20-54 at entry. Height, weight, blood pressure, serum lipids, fat and energy intake, physical activity, parity, OC, HT, alcohol and tobacco use were assessed. We used Cox proportional hazards model to estimate the effect of HDL-C on the risk of breast cancer and to adjust for potential confounding variables and performed stratified analyses to evaluate whether the effect was modified by other risk factors.

Results: In this large Norwegian cohort study during a median follow-up of 17.2 years, we identified 708 cases of invasive breast cancer. In multivariate analysis the risk of postmenopausal breast cancer decreased by each higher quartile of HDL-C. Among women with HDL-C above 1.65 mmol/l (upper quartile) vs. below 1.2 mmol/l (bottom quartile) a relative risk (RR) of 0.75 (95 percent confidence interval (95% CI), 0.58-0.97; P_{trend} = 0.01) was observed. When we divided the population into a normal weight (BMI < 25 kg/m^2) and an overweight (BMI ≥ 25 kg/m^2) group, the effect of HDL-C was confined to the heaviest subgroup with an observed 66% reduction in risk of postmenopausal breast cancer in women with HDL-C above 1.65 mmol/l vs. below 1.2 mmol/l (RR = 0.34; 95% CI, 0.19-0.59; P_{trend} < 0.001; $P_{interaction}$ = 0.006). Among women with an above median weight gain (>1.5 kg) between surveys and HDL-C assessed twice, a 51% reduction in postmenopausal breast cancer risk was observed for HDL-C above 1.65 mmol/l vs. below 1.20 mmol/l (RR = 0.49; 95% CI, 0.28-0.85; P_{trend} = 0.01).

Interpretation: Our study demonstrates that low HDL-C as part of the metabolic syndrome, is a potential marker of increased postmenopausal breast cancer risk that might facilitate the identification of high-risk, individuals and disease prevention in clinical practice.

O-112. Quantitative analysis of breast cancer tissue micro arrays in the assessment of HER-2 status

Rampaul RS, Pinder SE, Wencyk P, Paish C, Blamey RW, Robertson JFR, Ellis IO. *Nottingham City Hospital*

Use of the automated ACIS system on whole section slides has been shown to provide an accurate score of Her-2 expression. Use of this technology on tissue micro array sections has not

been examined previously. A tissue array construct of 900 cases of primary breast cancers was made. Sections from this micro array were stained for Her-2 expression using the DAKO HercepTest kit. Whole section slides from 250 cases of this series were also stained to compare for heterogenity. In tissue micro array slides, manual and ACIS (Chromavision Inc) system derived scores were obtained to assess variability between the two methods. FISH assays (Vysis Pathvision) were performed on all tissue array sections and on whole sections that scored 2+ on either manual or ACIS. Analysis of manual vs ACIS vs FISH in tissue array sections is ongoing. A high degree of correlation was seen between the whole section slides and corresponding micro array specimens [98%], demonstrating that heterogenity did not influence the reliability of tissue array biopsies in being representative of the tumour. For tissue array sections, 16% scored positive for Her-2 overexpression manually. ACIS had a 97% correlation with all cases. Variation in scores was limited to those that were 2+ by the manual method. FISH analysis showed amplification in 97% for 2+ by manual scoring and 88% for those by ACIS. Correlation between ACIS v TA or Matched whole sections was highly significant ($p < 0.001$, $r = 0.845$).

Use of an automated image analyser such as the ACIS system and tissue micro array technology can allow accurate high throughput analysis of Her-2 status.

O-113. HER2 overexpression is more prevlant in breast carcinoma of younger women and should be tested more regularly

Wong CS, Dew R, Cutress R, Theaker J, Bateman A, Eccles D, Rew D, Royle G. *Royal South Hants Hospital Southampton*

92 young women (age 19 to 35, median 32), identIfied on the Southampton Breast Unit Database as having diagnosed with breast II carcinoma between 1983 and 2001, were found to have more grade III and ER negative tumours (70% and 60% respectively), compared with the 101 older women (age 55 to 65, median 60) identified on the same database from 1985 to September 1988 (40% and 27%, $p < 0.0001$ for both).

We also studied the HER2 expression and found that it was more prevalent in the younger women, 25% in those aged 35 and under compared with 14% in those aged 55 to 65 ($p = 0.0535$). However, this was only after fluorescent in situ hybridisation was performed to determine gene amplification in those scored +2 on immunohistochemistry (IHC), IHC alone demonstrating no difference between the two groups ($p = 0.5067$).

The HER2 overexpression was associated with axillary nodal status ($p = 0.0069$) and inversely with ER ($p = 0.0085$). Since the presence of axillary nodes with metastases indicate the possibility of systemic disease, and ER is a marker of response to endocrine therapy, this has implications for systemic adjuvant therapy in these young women who generally have a poorer prognosis. Furthermore, HER2 itself has been reported as being a marker of resistance to chemotherapy and endocrine therapy, rendering standard adjuvant treatments less effective.

We therefore propose that testing for HER2 expression status, by IHC and FISH, should be performed more frequently in young women with breast cancer, to suggest modifications in systemic adjuvant therapy, including possibly the earlier use of Herceptin.

O-114. Evaluation of EGFR levels in primary breast cancer does not provide independent prognostic information

Rampaul RS, Pinder SE, Wencyk P, Bell J, Nicholson RI, Gullick WJ, Blamey RW, Robertson JFR, Ellis IO. *Nottingham City Hospital*

EGFR has been studied as a marker of poor prognosis in several studies. However, the data is inconclusive as some studies show an independent significance and others do not. Most of these studies suffer from small study size, short follow up and influence of adjuvant therapy. We have examined the expression and prognostic value of EGFR in a large set of primary breast cancers ($n = 254$) with long term follow-up and no adjuvant therapy.

254 patients (median f/up = 186) presenting to NCH (1975-1979) were analysed. Surgical management was either mastectomy or WLE and node sampling +/- RT. No adjuvant therapy was given.

EGFR status was determined using IHC (E30 antibody) on paraffin embedded tissue and scoring was semi-quantitative (0-1 = negative and 2,3 = positive). 32% ($n = 82$) were positive for EGFR, Univariate analyses showed a significant relationship between EGFR and LN status ($p = 0.05$), ER ($p < 0.001$) and grade ($p < 0.001$). In Cox regression analysis only LN positive disease had a worsened OS ($p = 0.05$). Multivariate analysis (MVA) showed size, grade and LN status but not EGFR to be of prognostic significance. MVA on subgroups by nodal status showed EGFR significant for OS ($P < 0.08$) but not DFI for LN positive disease. This effect was not present following Bonferonni correction ($P < 0.09$).

Our data demonstrates that EGFR does not possess sufficient prognostic power to be of independent significant when compared to standard histopathologic factors. Nonetheless, it may still possess a role as a predictive marker for selecting patients for novel EGFR-directed therapies.

O-115. Clinical outcome and human epithelial growth factor receptor (HER) 1-4 status in 79 invasive breast carcinomas with bromodeoxyuridine evaluated proliferation indices

Tovey SM, Witton CJ, Stanton PD, Reeves JR, Cooke TG, Bartlett JMS. *Glasgow Royal Infirmary*

79 women with invasive breast cancer had *in vivo* labelling with 5-bromo-2 prime-deoxyuridine (BrdU) to determine the labelling index (BLI), the length of S phase (Ts) and the potential doubling time of the tumour (Tpot). 10 year survival data on these patients demonstrates a significant correlation between high BLI values and breast cancer related death. However this was not substantiated when controlled for known prognostic factors such as grade, nodal status and size using Cox regression analysis. There was no significant correlation between Tpot values and outcome suggesting that addition of a

dynamic measurement to the labelling index does not improve prognostic information.

The HER family comprises four receptors (HER 1-4) which heterodimerise following ligand binding to activate intracellular signal transduction pathways. It has been well established that overexpression of HER 1 and 2 is associated with a poor prognosis in breast cancer. We wished to explore any relationship between HER 1-4 status and proliferation indices. Using immunohistochemistry we established the HER 1-4 status on 55 of the BrdU labelled carcinomas. Tumours found to be positive for HER 1, 2 or 3 had significantly ($p = 0.036$) higher labelling indices, with HER1 (EGFR) also showing significantly higher indices when considered independently ($p = 0.02$). HER 4 positivity however significantly correlates ($p = 0.01$) with low BLI values in line with previous evidence demonstrating an association of this receptor with good prognosis tumours.

In conclusion we have not demonstrated an ability for BrdU proliferation indices to provide any additional prognostic information about an individual tumour. However the clear link shown between BLI values and HER status does support the hypothesis that HER 1, 2, 3 have a role in driving tumour proliferation whilst HER 4 is involved in an antiproliferative or protective role.

O-116. HER-4 expression reduces cell proliferation and blocks the negative effect of HER-2 on ER expression in ductal carcinoma in situ (DCIS) of the breast

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Background: Although over-expression of the HER-2 receptor leads to increased proliferative drive and poor prognosis breast cancer, HER-4 expression is associated with favourable prognostic features. The aim of this study was to determine if HER-4 expression abrogates the effect of HER-2 on oestrogen receptor (ER) status and cell proliferation.

Methods: HER-2 and 4, ER and Ki67 (a nuclear marker of epithelial cell proliferation) expression were determined by immuno-histochemistry on paraffin sections of 71 patients with DCIS and expression assessed by light microscopy. HER-2/4 expression was scored 0 (absent) to 3 (maximum) by staining intensity. The Ki67 score was the % of nuclei labelled. Nuclear staining $>5\%$ was considered ER positive.

Results: Positive staining for HER-2 (44/71, 62%) and HER-4 (45/71, 63%) was associated with a higher ($p = 0.02$*) and a lower (<0.001*) cell proliferation rate than HER-2 and HER-4 negative tumours respectively. HER-4 positive tumours showed greater ER positivity compared to HER-2 positive tumours ($p < 0.005$*).

Variable		HER-2 neg HER-4	HER-2 pos neg HER-4	HER-2 neg pos HER-4	HER-2 pos pos HER-4	p value pos
Ki67	n (% of total)	10 (15%)	15 (21%)	14 (20%	30 (44%)	<0.001**
	Median (IQR)	14 (3-29)	31 (19-37)	6 (2-13)	9 (6-14)	
ER	n pos (%)	2 (82%)	5 (33%)	11 (79%)	20 (65%)	0.005*
	n neg (%)	9 (18%)	10 (67%)	3 (21%)	11 (35%)	

**Kruskall-Wallis *Chi-squared.

Conclusion: HER-4 expression reduces DCIS cell proliferation increases ER expression and blocks the negative effect, of HER-2 on ER expression. Further study of the effect of HER-4 expression on DCIS local recurrence is warranted.

O-117. Effect of Herceptin on gene expression in HER2 positive breast cancer cell line

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Her2/neu, an epidermal growth factor receptor mediates cell growth, differentiation and survival. Over expression of Her2/neu occurs in up to in 30% of breast cancers and its associated with a high risk of relapse and death.

Herceptin is an anti-Her2neu monoclonal antibody that inhibits that particular receptor and it has been a valuable addition to the standard therapy demonstrating a survival benefit. Development of resistance to Herceptin treatment is common but not well understood. Insulin-like growth factor I receptor (IGF-IR), another member of the tyrosine kinase family, has been discussed with increased risk of several cancers. However, resistance to Herceptin might not be merely dependent on the lack of efficacy in inhibiting Her2/neu but might be associated with IGF-IR over expression.

We investigated the anti-proliferative effect of Herceptin on a breast cancer model system using microarray assay. We also evaluated the effect of Herceptin on mRNA expression of IGF-IR.

A Her2/neu positive cell line (SKBR3) was cultured with and without Herceptin. mRNA was extracted and analysed in a cell-cycle specific cDNA microarray. Expression of the IGF-IR gene was determined by applying solution phase RT-PCR and RNA in situ hybridisation.

In situ hybridisation and RT-PCR showed similar expression patterns for IGF-IR with and without Herceptin. Herceptin has an anti-proliferative effect on the Her2neu cell line.

Microarray technology is a useful tool to check the anti-proliferative effect of Herceptin on Her2/neu positive breast cancer cells. The association between IGF-IR and resistance to Herceptin need to be further evaluated.

O-118. Insulin-like growth factor binding protein 3 (IGFBP-3) as a therapeutic target in epidermal growth factor (EGF) and HER2 related breast cancer - implications for its mechanism of action

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Insulin-like Growth Factors (IGF's) promote cellular proliferation and survival. The actions of IGFs are modulated by high affinity binding proteins (IGFBPs), of which IGFBP-3 predominates in serum. IGFBP-3 can effect breast epithelial cell apoptosis by altering IGF actions or due to an IGF-independent as yet unidentified mechanism that involves cell membrane lipid rafts. Increasingly, the IGF pathway is being implicated in hormonal resistance, with IGFBP-3 a possible therapeutic target. We have looked at the effects of IGFBP-3 on EGF-

mediated proliferation in normal and breast cancer cells and examined if raft disruption using filipin modulates the actions of IGFBP-3.

Normal and malignant cell lines were used, with varying IGF and EGF responses and expression of HER2. The EGF dose response was characterised in each cell line with Trypan blue cell counts. Cells were dosed with IGF-I (100 ng/ml), EGF (1 ng/ml and 25 ng/ml), exogenous IGFBP-3 (100 ng/ml), and combinations of EGF, IGFBP3 and filipin (5 μg/ml).

In the normal MCF10A cells, IGF (100 ng/ml), EGF (25 ng/ml) and IGFBP-3 each significantly increased cell proliferation (1.6, 4.5 and 2.3 fold increase, respectively). The addition of IGFBP-3 to EGF caused a synergistic enhancement of cell growth (11.7 fold increase) relative to control. In the tumour HS578T cells, EGF (1 ng/ml) caused an increase in cell proliferation (1.5 fold increase) whereas IGF-I or IGFBP-3 alone each had no effect. In contrast to the MCF10A cells, the combination of EGF and IGFBP-3 markedly inhibited EGF-induced cell growth (from 1.5 to 1.1) relative to control. We further demonstrated that when MCF10A cells were dosed with IGF-I or IGFBP-3 in the presence of filipin, the proliferative effects of IGFBP-3 were blocked, but those to IGF-I were enhanced. This suggests that IGFBP-3 has differential effects on EGF-induced cell growth in normal and breast cancer cells. In addition the proliferative effect of IGFBP-3 is dependent on the structural integrity of the lipid raft, with implications for its apoptotic mechanisms.

Our results raise the possibility that targeting the IGF axis using IGFBP-3 may be useful in the treatment of breast cancer.

Acknowledgement: Funding from the Association of International Cancer Research.

O-119. Circulating levels of VEGF and soluble FLT-1 in breast carcinoma

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Aims: Levels of circulating VEGF are raised in cancer patients but little is known about sFlt-1 (sVEGFR-1), a soluble VEGF receptor, which is thought to act as a negative regulator of VEGF. The aim of this study was to investigate plasma VEGF and soluble Flt-1 levels in breast cancer.

Methods: Plasma VEGF and free (unbound) sFIt-1 levels were determined by ELISA in 51 patients with primary operable breast cancer prior to surgery together with matched controls. Results were correlated with tumour pathological factors.

Results: Whilst a significant difference was observed in VEGF-A levels between patient and control groups ($p = 0.027$), no such difference was seen with sFlt-1. There was no association between either factor and tumour pathological variables. However, there was a significant correlation between VEGF-A and sFlt-1 in both the patient and control groups ($p < 0.0001$). In the control group, free sFIt-1 exceeded VEGF-A by a factor of >40, but only by a factor of 2 in the patient group. The difference in sFlt-1:VEGF-A ratio between the groups was highly significant ($p < 0.0001$). When the sFlt-1:VEGF-A ratio was correlated with tumour pathology, there was an association with tumour size ($p = 0.01$).

Conclusion: During tumour progression there is a change in the relative amounts of free sFlt-1 and VEGF-A in the circulation. The sFlt-1:VEGF-A ratio may have more significance than VEGF-A alone and further studies need to determine whether the sFlt-1:VEGF-A ratio is of use as a prognostic marker and as a means of monitoring response to anti-angiogenic therapy.

O-120. The predictive value of VEGF-D expression in the response of young women treated by breast conserving surgery and radiotherapy

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Little is known regarding the prognostic significance of either angio- or lymphangiogenesis in the response of breast cancer patients to post-operative radiotherapy (R/T). A retrospective immunohistological study of biopsies from 82 women, <40 years of age at diagnosis, who underwent breast-conserving surgery and post-operative R/T between 1989 and 1996 was undertaken to investigate the role, and prognostic significance, of growth factors involved in regulating tumour angio- and lymphangiogenesis (VEGF and VEGF-D respectively). Tumour characteristics recorded were: size, grade, nodal status, presence of vascular invasion, and receptor status.

Tumour tissue, and accompanying stroma, was stained using monoclonal antibodies against the growth factors and against CD34, to assess microvessel density. Results, obtained via image analysis, were compared against local recurrence, overall survival (OS) and other conventional pathological criteria. The cut-off for this analysis was 12/31/01, giving a minimum follow-up period of 5 years.

During the period of observation, 14 deaths and 12 recurrences within the treated breast were documented, giving an actuarial 5-year recurrence rate of 9%. In univariate analysis, of the three markers only a high VEGF-D level was predictive of a decreased as ($p < 0.01$) and an increased risk of local recurrence i.e. such patients had a recurrence rate at 5 years of 13%, compared to 3% for those with low expression (logrank $p < 0.03$). Of all the other possible risk factors analysed, only lymph node stage correlated with local recurrence risk. Both a high level of VEGF-D staining and lymph node involvement retained independent significance in Cox multivariate analysis.

O-121. In vitro quantification of cytotoxic T lymphocyte response against human telomerase reverse transcriptase in breast cancer

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Telomerase is expressed in approximately 90% of breast cancers but not in most normal somatic cells. The enzyme plays a key role in maintaining chromosomal telomere integrity. The catalytic subunit of telomerase, human telomerase reverse transcriptase (hTERT), is a widely expressed tumour associated antigen against which specific cytotoxic T lymphocyte (CTL) responses have been identified. Human $CD8^+$ CTL have been shown to recognise hTERT synthetic peptides in both an HLA-

A2 and HLA-A3 restricted manner, and to lyse hTERT$^+$ tumour cells of multiple histologies.

This study has investigated the specific CD8$^+$ CTL response in breast cancer patients against 3 synthetic hTERT peptides. PBMC were isolated from blood samples by Ficoll-density centrifugation and screened for HLA subtype by flow cytometry. The HLA-A2 or HLA-A3 positive PBMC samples were analysed using a standard IFNγ ELISpot assay.

The results showed that 11/15 cancer patients (HLA-A2$^+$ or HLA-A3$^+$) had a specific CD8$^+$ CTL response against one of the synthetic hTERT peptides; six of these patients responded to both HLA-A2 peptides. In contrast, 5/11 normal healthy female controls responded against a single peptide only. This suggests that a specific immune response exists against hTERT peptides in breast cancer patients when compared with normal healthy controls. Such functional immune response assays indicate that hTERT deserves further investigation as a target for anticancer immunotherapeutic strategies in breast cancer patients.

O-122. Patient demographics and treatment choices for early breast cancer

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Patients with small breast cancers are eligible for various treatment options. Modified radical mastectomy (MRM) and breast conservation therapy (BCT) have equal outcomes in terms of patient survival. The purpose of this study was to examine the relationship between selected demographics to patient treatment choice for early breast cancer, and to assess patient satisfaction with their choice of cancer therapy.

The target population was all patients with early breast Ca (T $\leq$ 2, N 0/1) who were offered a choice of surgery (MRM or BCT). These patients were identified at follow up clinic and were interviewed by means of a designed questionnaire based on previous research.

202 patients were interviewed with a median age at time of treatment of 57 (32-90) years. 97% were British and 3% were from overseas. 71 patients (35%) choose MRM, 10 (5%) Mastectomy and reconstruction (MRM & R) and 121 (60%) BCT. Prior to attending the breast clinic 36% thought that mastectomy was the only treatment for breast Ca, and 22% felt that this was a more effective treatment. 82% were surprised at being asked to take part in choosing their treatment and 12% would have liked more time to arrive at this decision. 94% felt that sufficient information was provided.

	MRM	MRM & R	BCT
Mean Age (years)	61 (38-90)	57 (49-85)	55 (32-79)
Married/partner	66%	70%	83%
FH 1 Relative	10%	0%	20%
Symptomatic	42%	50%	46%
Tumour size (mm)	17 (6-50)	19 (11-40)	15 (4-40)
Node + ive	34%	40%	23%

Women thought they had enough information to make an appropriate treatment choice and they were satisfied with the information provided. They did not feel rushed to decide on therapy, nor was there a substantial likelihood to regret their choice of surgical treatment. Increased patient age ($p < 0.0001$) and tumour size ($p = 0.014$) were associated with a greater likelihood of choosing mastectomy.

O-123. Local recurrence following skin-sparing oncoplastic techniques: the 10-year Winchester experience

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Background: Clear resection margins can be achieved by breast conserving surgery (BCS) or mastectomy without sacrificing the overlying skin envelope. Skin-sparing tumour resection coupled with immediate reconstruction can optimise cosmesis, but the long-term oncological safety of these procedures is unclear. This study reports on local recurrence (LR) following skin-sparing surgery.

Methods: All patients undergoing skin-sparing mastectomy and reconstruction (SSM), and BCS with reconstruction using a latissimus dorsi mini flap (BCR), were included. Data was collected from patient records and a continuously updated database. All adverse events were recorded.

Results: Between September 1991 and June 2001, 220 patients underwent 228 oncoplastic procedures. The patients were divided into 2 groups - SSM (n = 116) and BCR (n = 104). Patients undergoing BCR were younger [BCR vs. SSM; 47.2 (28-72) yr vs. 49.5 (31-67) yr], had larger tumours [24.4 (5-60) mm vs. 23.3 (3-90) mm], longer follow-up [58 (4-127) months vs. 44 (6-130) months], and underwent extensive local excisions [165 (37-381)‡ g].

Table 1. LR by treatment group

	SSM		BCR	
	RT+	RT-	RT+	RT-*
LR+	3†	3	2	6
LR-	25	85	72	24

†NPI $\geq$ 4.4 *pts in clinical trial ‡all values = mean (range).

Conclusion: Skin-sparing techniques do not compromise local control when used in an appropriate clinical setting.

O-124. Selective use of postmastectomy radiotherapy in histologically defined high risk breast cancer patients

Asgeirsson KS, Holroyd B, Morgan DAL, Pinder SE, Blamey RW, Robertson JFR, Ellis IO, Macmillan RD. *Nottingham City Hospital*

No UK national guidelines exist for the use of postmastectomy radiotherapy. Previous studies from our unit identified a subgroup of patients at a high risk of developing local recurrence after mastectomy. A protocol, whereby all high risk patients (identified histologically by grade, vascular invasion and nodal status) are treated with postmastectomy radiotherapy has been evaluated.

All patients who underwent mastectomy at the Nottingham Breast Unit from January 1993 to December 1995 were studied

(median follow-up, 76 months). 339 patients had mastectomy and by protocol 172 (50.7%) patients required chest wall radiotherapy. 19 (5.4%) local recurrences were identified, 10 of which were single spot recurrences, 4 multi-spot and 5 were field change. 30% of patients with single spot recurrence developed distant metastases compared to all 5 with field change recurrence. Field change recurrences occurred significantly earlier than single spot recurrences (12 vs. 43 months, $p < 0.001$) and the time to development of distant metastases in patients with field change recurrence was significantly shorter than in patients with single spot recurrence (34 vs. 57 months, $p = 0.022$).

Selective use of postmastectomy radiotherapy has resulted in an acceptably low rate of chest wall recurrence and a very low rate of field change recurrence.

O-125. Immediate breast reconstruction - seven years experience in a district general hospital (DGH)

Kuzhively RT, Williams MR. *Cumberland Infirmary Carlisle*

125 consecutive patients who underwent immediate breast reconstruction following mastectomy for breast cancer were studied.

Results: Total patients with operable disease presenting during the study period = 870 (360 mastectomies). Immediate reconstruction rate <60 years of age = 55%. Mean age of reconstructed patients = 51 (range 23-79 years). *Type of reconstruction:* Tissue expanders = 85, (bilateral = 4), Latissimus Dorsi myocutaneous flap (LD FLAP) = 40. *Indication for mastectomy:* Multifocality = 26%, tumour size = 20%, tumour-position = 21%, previous incomplete tumour clearance = 12%, extensive DCIS = 10%, patient-preference = 5%, tumour-recurrence after previous wide excision = 4% and Paget's disease = 2%.

Type of prosthesis: Mentor Siltex Becker = 92, Inamed McGhan Anatomical = 29, Nagor = 4. *Complications:* wound infection = 7, capsule formation = 5, intra-operative pneumothorax = I, filling port migration = 1, prosthesis leak = 1, temporary skin loss = 5, inadequate expansion= 1, hot water bottle burn during follow up = 2.

Patient Satisfaction	Expanders	L D flap	
Result Expectation			
Fully met	34 (52%)	27 (75%)	Chi Sq. = 5.34
Partially met	28 (42%)	9 (25%)	p = 0.002
Not met	4 (6%)	0	
Overall satisfaction			
Very Good	28 (41%)	25 (69%)	Chi Sq. = 5.20
Good	23 (33%)	9 (26%)	p = 0.02
Satisfactory	13 (19%)	2 (5%)	
Poor	5 (7%)	0	

Conclusion: Immediate breast reconstruction carried out by a breast surgeon in a DOH can provide acceptable results. In these circumstances the use of the LD flap appears to provide superior results to tissue expanders alone, in terms of patient satisfaction.

O-126. Skin-sparing mastectomy and immediate latissimus dorsi reconstruction is an oncologically safe procedure

Leslie T, Cook J, Rayter Z. *Bristol Royal Infirmary*

Immediate reconstruction using a skin-sparing technique is increasingly being offered to women who need a mastectomy. However, it is important that the cosmetic benefits of reconstructive surgery do not compromise the oncological safety of this cancer resection. This retrospective audit looks at the local recurrence rate in a series of patients who underwent a skin-sparing mastectomy (SSM) and immediate lattisimus dorsi (LD) reconstruction.

A 5-year retrospective audit of all SSMs with immediate LD reconstruction undertaken by one consultant team at the Bristol Royal Infirmary, was performed. Patients who had undergone this operation from 3/11/1997 to 31/12/2002 were identified. LD reconstructions were all performed using a periareolar 'keyhole' technique.

57 patients were identified with an average age of 47 (29-65). A total of 59 operations were performed, as two patients had bilateral disease. They all underwent a SSM and immediate LD reconstruction followed by a variety of adjuvant therapies. These depended on the stage, grade, lymph node status and lymphovascular invasion. Hormone therapy alone was given to 12 (20%), chemotherapy alone 7 (12%), radiotherapy alone 1 (1.7%), hormone and chemotherapy 6 (10%), hormone and radiotherapy 2 (3.3%), chemotherapy and radiotherapy 8 (13%), all three to 7 (12%) and no treatment to 16 (28%).

The average time of follow up was 709 days (1.95 years). Only 1 (1.75%) patient had a local recurrence. 6 (10%) patients died of distant disease, with the average time to 1st metastasis being 532 days (1.5 years). The patient who developed a local recurrence had poor prognostic disease and developed the recurrence at 136 days (0.37 years).

In conclusion, it appears, from this group of patients, that skin-sparing mastectomy and immediate lattisimus dorsi reconstruction is a safe oncological procedure.

O-127. Skin-sparing mastectomy and immediate latissimus dorsi reconstruction with preservation of the nipple-areola complex - is it safe?

Hassanally D, Kissin MW. *Royal Surrey County Hospital Guildford*

Introduction: Skin sparing mastectomy and latissimus dorsi (LD) flap reconstruction has become a safe option for breast carcinoma, but is it really necessary to remove the nipple, yet leave all the skin? Previous studies suggest involvement of the nipple in 16% of cases [1]. When wide local excision (WLE) is performed the nipple-areola complex (NAC) is routinely preserved but it is always removed at mastectomy. However, the principle of mastectomy is to prevent local recurrence and the basis for this is the same as WLE, namely obtaining clear margins.

Aim: The aim of this study was to determine the safety of skin and nipple-areola complex sparing mastectomy (SNACM) and immediate LD reconstruction.

Method: Data was collected retrospectively from patients' notes following SNACM and LD reconstruction between 1994 and 2002. Follow up data was obtained from time of operation to the most recent clinic visit. The outcome was determined in terms of nipple recurrence, local recurrence, distant recurrence and mortality.

Results: 296 patients (301 cases) had SNACM and LD reconstruction, 75 for non-invasive disease and 226 for invasive carcinoma. The median age was 50 years (range 24-74) and median follow up 46 months (range 1-108). 22 patients (7.3%) died.

Type of carcinoma	Number of cases	Nipple recurrences	Local recurrences	Distant recurrence
Non-invasive	75	1 (1.3%)	0 (0%)	0 (0%)
Invasive	226	1 (0.4%)	7 (3.1%)	32 (14.2%)

Conclusions: Despite preservation of the NAC, recurrence rates are very low and comparable to conventional series. SNACM and LD reconstruction makes for a superior cosmetic result without compromising outcome and saves time in theatre management

References

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O-128. Fish-tail plasty: a safe technique to improve cosmesis at the lateral end of mastectomy scars

Hussien M, Daltrey IR, Dutta S, Goodwin A, Prance SE, Watkins RM. *Derriford Hospital Plymouth*

Background and aims: Redundant skin at the lateral end of a mastectomy scar can be unsightly and uncomfortable, especially in elderly obese patients. The aim of this-study is to evaluate a technique of mastectomy wound closure designed to maximize cosmesis at the lateral end.

Patients and methods: 30 lateral skin flap advancements were performed in 28 patients. The procedure was performed primarily in 27 cases. In three cases a delayed scar revision was performed. Following anterior advancement of the skin overlying the latissimus dorsi muscle, the two areas of redundant skin were excised and the wound closed in the shape of Y-plasty.

Results: The patients mean age was 70.6 years (range 51-93) and the mean body mass index (BMI) 30.4 kg/m^2 (range 21-35). The mean weight of the excised breast tissue was 1015 g (range 356-2003). The mean lengths of the two limbs of the Y-plasty were 5.3 cm (range 3-10). The mean length of the base of the flap was 8.3 cm (range 4-14). One patient developed a small area of skin necrosis at the apex of the Y-plasty. Two further patients developed superficial wound infections.

Conclusion: Fish-tail plasty is a safe and easy technique and may be recommended following mastectomy in obese patients to improve cosmesis and avoid discomfort caused by redundant skin.

O-129. A randomised trial of the effect of quilting latissimus dorsi flap donor site on seroma formation

Daltry I, Schuijvlot M, Cook J, Flower C, Rayter Z, Winters ZE. *Bristol Royal Infirmary*

Donor site seroma following Latissimus Dorsi (LD) Flap harvesting is common, affecting up to 60% of patients. Closure of the dead space of the LD donor site is reported to significantly decrease the incidence of seroma (56% vs 0% [1]). We present the preliminary results of an RCT designed to investigate the effect of this technique following immediate breast reconstruction with an LD flap.

Consecutive patients undergoing skin-sparing mastectomy (SSM) and immediate LD flap reconstruction since February 2002 were entered into the study. Patients were randomised to routine wound closure (Control group) or closure of the dead space using absorbable 2/0 vicryl quilting sutures at 3-4 cm intervals (Quilting group). Informed consent was obtained and all patients were blinded to the closure performed. All participants had two Exudrains inserted in the donor site and a breast and axillary drain as appropriate. Volume of postoperative wound drainage and incidence and volume of symptomatic seroma were recorded.

Forty patients have been entered into the study with complete data available on 38 patients (19 patients in each group). The volume of postoperative drainage from the back drains was significantly less in the quilted group (Median: 718 ml vs 1144 ml; $P = 0.016$). Symptomatic seromas were drained in 95% (19/20) and 72% (13/18), respectively of the control and quilting patients ($P > 0.05$). However, there was a significant decrease in seroma volume (Median: 12 ml vs 255 ml; $P = 0.024$) and frequency of seroma aspiration (Median number of times: 1 vs 3) for patients in the quilting group ($P = 0.026$). The quilting sutures did not lead to an increase in postoperative complications, or morbidity.

The study is ongoing and our preliminary analysis and results confirm the findings of the previous non-randomised trial and demonstrate the value of quilting the LD donor site. The technique is simple and reliable and we believe that it has a role in reducing the impact of postoperative seroma formation.

References

[1] Titley OG, Spyrou GE, Fatah MF. Preventing Seroma in the latissimus dorsi flap donor site. Br J Plast Surg 1997 Feb; 50(2): 106-8.

O-130. Does immediate breast reconstruction delay adjuvant treatment?

Phipp LH, Macmillan RD, Robertson JFR, Perks AGB, McCulley SJ. *Nottingham City Hospital*

Immediate breast reconstruction inevitably incurs a greater risk of complications than simple mastectomy alone. This may potentially delay adjuvant therapy. This study examines the interval between surgery and adjuvant treatment in women undergoing immediate breast reconstruction.

Over the two-year period 1/1/01-31/12/02 a total of 134 primary breast reconstruction operations were carried out at the

Nottingham City Hospital. 17% presented through the NHS-BSP, 65% symptomatically, 9% via the Family History clinic, and 7% on breast cancer follow-up. The mean age at reconstruction was 47 years (range 25-65).

67% underwent reconstruction at the time of their first cancer operation. 33% initially underwent breast-conserving surgery and required mastectomy for involved margins. 50 women required adjuvant treatment with chemotherapy, radiotherapy or both. 9 (18%) of these had a postoperative complication causing delay in adjuvant treatment of greater than 50 days from surgery. The type of reconstruction performed and the extent of delay are shown below. 9% of women undergoing flap reconstruction had a delay in adjuvant treatment compared to 3% with implant only based reconstruction.

Type of reconstruction	No.	Complications causing delay in adjuvant therapy	Range of delay (days)
TRAM	12	3 (25%)	75-82
DIEP	22	2 (9%)	77-104
LD	42	2 (7%)	63-140
Tissue Expander	50	1 (2%)	90
Immediate Implt	8	1 (12.5%)	61

Women with a high likelihood of requiring adjuvant treatment need to be counselled concerning the risk of delay and the possibility of delayed reconstruction discussed.

O-131. The effect of immediate breast reconstruction on adjuvant chemotherapy

Taylor CW, Kuman S. *Cookridge Hospital Leeds*

Immediate breast reconstruction (IBR) is being, increasingly offered to patients requiring mastectomy for breast cancer. There is a lack of data concerning it's effects on adjuvant chemotherapy delivery. An audit was carried to determine whether IBR affected time to initiation of chemotherapy, delays during chemotherapy, dose intensity and need for support with antibiotics or GCSF.

A total of 44 patients undergoing a variety of reconstructive procedures followed by chemotherapy were identified. These were compared with a control group of 49 patients undergoing mastectomy alone and chemotherapy in the same four year period and institution.

The results are summarised below:

Type of reconstruction	No.	Complications causing delay in adjuvant therapy	Range of delay (days)
Control	38	97%	22%
TRAM	43	93%	23%
LD flap	32	98%	13%
Implant	33	98%	29%

Patients undergoing TRAM reconstruction experienced an average of 5 more days delay to chemotherapy initiation than controls with the commonest reason being poor wound healing. Dose intensity, delays during chemotherapy and need for support with GCSF or antibiotics, were comparable in all groups.

O-132. Do patients prefer to be seen by a doctor of the same sex?

Muir RF, George WD, Wilson CR, Mallon EA, Doughty JC. *Western Infirmary Glasgow*

Studies in breast and gynaecological patients have suggested a preference for female doctors. The majority asking 'would you prefer to be seen by a male or female surgeon'; this may not be the best method of assessing the importance of this issue.

Questionnaire distributed to 337 patients attending new patient breast, oncology and general surgical clinics. They ranked the importance of a series of statements concerning their attendance at the clinic. A score of 0 indicated that the statement was not important and 5 that the statement was very important.

295 patients completed the questionnaire 195 females and 100 males. The results are as shown in Table 1 and are expressed as the mean for all patients followed by the mean for females and then male patients.

Table 1

Statement	Mean	Female	Male
Clear Explanation	4.675	4.723	4.560
seen within 2 weeks	4.397	4.420	4.350
I get all of my results on the same day	4.278	4.523	3.800
I do not feel rushed	4.207	4.303	4.020
My doctor is sympathetic	4.161	4.477	4.000
I would prefer to be seen by a consultant	4.051	4.010	4.130
cancer research unit	3.193	3.482	2.630
food and drink available at the clinic	2.220	2.426	1.820
I would like to take part in clinical trials	1.187	2.061	1.340
doctor of my own sex	1.620	1.513	1.830
The age of the doctor is important to me	1.166	1.328	0.850

Considered with other factors the sex of the doctor seeing the patient is not important, patients rank the presence of food and drink in the clinic as more important. Interestingly although not significant the sex of the doctor appears more important for males rather than females.

O-133. Variance in the surgical practice of Trent breast screening units

Caldon LJM, Walters SJ, Reed JA, Worley A, Reed MWR. *University of Sheffield & Trent Regional QA Centre*

There remains marked inter- and intra-regional variation in the surgical management of breast cancer. This observational audit is based on Quality Assurance data collected by the Trent Breast Screening Program between April 1997 and April 2002. During this period 653,627 women were screened in the region's 11 screening units, detecting 4036 (3153 invasive) surgically managed primary breast cancers. 1483 mastectomies (Mx) were performed (overall Mx rate 36.7%).

Significant variation in Mx rates is observed across the units (range 26% to 46%, $p = 0.001$). This significant variation persists following adjustment of unit Mx rates at an individual level for case-mix (tumour size, site, grade, patient age) and year of presentation ($p = 0.001$). Observed and expected unit mastectomy rates after case-mix adjustment are illustrated below. Expected rates are derived by logistic regression using overall case-mix adjusted practice in Trent as the reference population.

Table 1. Observed vs. expected mastectomies by screening unit, 1997-2002

Unit	Total cancers (n)	Observed (O) Mx	Expected (E) Mx	Ratio O/E
1	169	73	64	1.13
2	235	79	86	0.92
3	335	135	111	1.21
4	557	197	179	1.10
5	290	106	107	0.99
6	669	174	263	0.66
7	275	97	97	1.00
8	197	75	65	1.16
9	731	321	302	1.06
10	178	83	61	1.36
11	336	117	122	0.96
Trent	3972	1457	1457	1.00

64 patients excluded due to missing data.

Significant intra-regional variation in surgery for primary breast cancers persists that is not explained by case-mix. Research is needed to investigate the potential causative factors influencing this variation.

O-134. To what extent does non-standard management of breast cancer increase with advancing age

Moran A, Lavelle K, Bundred NJ. *University of Manchester*

Aims: Since over 50% of all deaths from breast cancer in the UK occur in women aged 70 years or older, further decreases in mortality rates will depend largely on ensuring that elderly women receive optimal management. To determine the extent to which standard management decreases with advancing age (taking into account stage at presentation) we undertook a population based study of elderly women in North West England.

Methods: Patient, tumour and management details were abstracted from the database of the North Western Cancer Registry on all women aged 65 years or older in Greater Manchester who were diagnosed with invasive breast cancer in 1999. These data were confirmed and supplemented by reviewing hospital case notes.

Age group

Aspect of Management	n	Age group			Total	Pearson Chi squared test
		65-69	70-79	80 Plus		
Triple Assessment	406	89%	76%	61%	75%	$p < 0.01$
Surgery within 90 days of diagnosis (operable tumours only)	305	97%	85%	44%	78%	$p < 0.01$
Underwent a hormone receptor test	415	75%	68%	47%	64%	$p < 0.01$
Radiotherapy following breast conserving surgery	131	98%	56%	5%	61%	$p < 0.01$

Results: Of 699 patients identified on the registry database the case notes of 562 (80%) were reviewed. 143 patients were excluded: the main reasons being the presence of distant metastases (n = 51), died within nine months of diagnosis (n = 61) and diagnosed prior to 1999 (n = 21). The remaining 419 patients constituted the study population.

The percentage of patients receiving standard management decreased with advancing age: the most striking findings were that less than half of those over 80 underwent surgery with only 5% receiving XRT following BCS (Table).

Conclusions: Elderly women with operable tumours were much less likely to undergo surgery or radiotherapy or have receptor status assessed prior to hormonal therapy underlining the importance of determining why management changes with age. Strategies to change practice need consideration.

O-135. Vascular mortality following post-operative adjuvant irradiation for early breast cancer - a long term follow up study

Kunkler IH, Kerr GR. *Western General Hospital Edinburgh*

The contribution of modern megavoltage adjuvant radiotherapy for breast cancer to cardiac mortality is unclear. It is thought that left-sided tumours would be more prone to radiation induced cardiac mortality because of the greater volume of heart irradiated. We present a large cohort study 6554 patients with Tis, 0, 1, 2 N0, 1 M0 breast cancer who were treated by wide local excision or mastectomy +/- post-operative radiotherapy (6MV photons) between 1974 and 1993 in the Edinburgh Cancer Centre. Of these 2413 patients had died of breast cancer and 1331 of other causes. The table shows no significant excess of deaths due to circulatory causes was identified among patients with left-sided cancers.

	Radical XRT		No Radical XRT	
	L	R	L	R
Total patients	2490	2252	936	876
	52.5%		51.7%	
Total deaths	1480	1280	521	463
	53.6%		52.9%	
Total vascular deaths	204	180	128	137
	53.1%		48.3%	

O-136. RT-PCR approach for the detection of disseminating breast cancer cells in peripheral blood

Salman R, Hennessy E, Uhlmann V, Curren C, McAnena O, Given F. *University College Hospital Galway Ireland*

The detection of disseminated cancer cells in peripheral blood of in breast cancer patients may help to predict disease recurrence and potential metastasis. Cytokeratin 19 (CK19) is commonly used marker for the detection of occult epithelial cells in blood. Mammaglobin I (MGI) expression is limited to mammary epithelium and is over-expressed in 95% of primary breast tumours.

Our aim was to determine whether the use of two markers (Cytokeratin19 and Mammaglobin I) for the detection of metastatic breast cancer cell using quantitative RT-PCR improves specificity as well as sensitivity of the RT-PCR assay.

In several spiking experiments, breast cancer cells (ZR-75) were added to 5 ml of human peripheral blood of a healthy donor. After epithelial immunomagnetic enrichment, total RNA was extracted using a silica-based extraction kit. RNA specific primers for MGI and CK19 were designed to amplify these genes in a single-enzyme RT-PCR cDNA amplicons were visualised in 2% agarose gel. All samples were analysed using Real-time quantitative TaqMan RT-PCR for both CK19 and MGI primers.

Our detection sensitivity for the combined method including cell enrichment, RNA extraction and subsequent RT-PCR

is less than 3 cells. We also demonstrated similar sensitivity levels for CK19 and MGI using solution phase RT-PCR We showed improved specificity using MGI as a second marker and with using quantitative RT-PCR we demonstrated increased sensitivity compared to solution phase RT-PCR.

Real-time quantitative RT-PCR is faster, less laborious and sensitive method for detecting occult metastatic breast cancer cell in peripheral blood. Combined markers are the way in the future for the detection of tissue-specific tumour cells.

O-137. The diagnostic core biopsy in breast cancer - how often is the tumour grade underscored?

Agrawal A, Bendall S, Bates T. *William Harvey Hospital Ashford Kent*

The decision to give neoadjuvant chemotherapy as the primary treatment in breast cancer is often based on the tumour grade of the diagnostic core biopsy. However the grade of the final surgical specimen has been reported as discordant in 36% cases and the aim of this study was to determine our rate of discordant reports.

The tumour grades of diagnostic core biopsies of patients with invasive breast cancer were compared with the final report on the excised specimen. Tumour type and vascular invasion were also compared.

In 189 patients the grade of tumour was changed in 24% cases. Tumour grade was worse in 20% and better in 4% on the final specimen. The grade changed from 2 to 3 in 10% of cases. Of 148 core biopsies reported as infiltrating ductal carcinoma, 5 (3.4%) were changed to a lobular carcinoma and of 31 lobular cancers, 4 (13%) were changed to ductal cancers on the final specimen. Reports of vascular invasion changed from 28% to 41%.

The preoperative grade of breast cancer may be the deciding factor for or against neoadjuvant chemotherapy but in 20% cases the grade on the diagnostic core biopsy was underscored and in 10% cases this was from grade 2 to 3. Vascular invasion is less evident on core biopsy but lobular cancer may be over-reported.

O-138. The routine use of three dimensional planning in the treatment of early breast cancer (EBC) using intensity modulated radiotherapy (IMRT)

Le Vay JH, Hames HV, Poynter AJ, MacKenzie, Boston SL. *Ipswich Hospital Suffolk*

Current NICE guidance suggests the routine introduction of 3 Dimensional Planning into radiotherapy treatment of EBC. This is not however the case in the majority of UK centres. We have piloted and now introduced this into routine practise in a District General Hospital using the facilities offered by Dynamic IMRT.

All Patients needing 'adjuvant' radiotherapy for EBC have a CT planning scan and then are planned conventionally and also with Electronic compensation using the IMRT facility, aiming to achieve a homogeneous plan in three dimensions. The best plan is chosen for the patients treatment.

Over 200 consecutive patients have now been treated. Only 5% of patients were unable to tolerate a planning CT scan. In 70% of patients the area of the breast receiving more than 105% of the prescribed dose was reduced using IMRT. Treatment delivery was more accurate, and the whole process quicker than conventionally.

Three dimensional planning and treatment of radiotherapy in EBC is possible and should be considered standard practise.

O-139. Significant differences in size of South Asian and white caucasian breast tumours (matched for age) and in tumour grade (when matched for size and age); a retrospective case control study from two West Midlands breast units

Cowley NJ, Cooper E, Aaron R, Hiller L, Gray L, Rowlands DC, Gearty J, Poole CJ. *University of Birmingham*

We tested the hypothesis that the pathological features of breast tumours diagnosed in South Asian women are worse than those of indigenous white Caucasians in respect of size, morphology presence of vascular invasion, lymph node status, oestrogen receptor status and grade. It was appreciated that any difference might reflect either uneven access to the diagnostic process, or more fundamental difference in tumour biology; both effects could influence survival and optimal treatment.

A retrospective case-control study was conducted at two hospitals in Birmingham, UK. The sample group was taken from a database of 2076 newly presenting women with primary invasive breast cancer to these hospitals between 1991 and 2000. The 89 South Asian patients were double-matched by age to 178 Caucasian patients. Size of tumour at resection was compared. 72 South Asian patients with sufficient tumour details were then rematched for both size of tumour and age to 144 Caucasian patients. Tumour characteristics were then compared.

Tumours were found to be highly significantly larger in Asian women than in Caucasians when matched for age alone ($p = 0.001$). Furthermore, Asian women had significantly higher grade tumours when controlling for both age and size ($p = 0.005$). No significant difference was found in any other pathological parameter investigated.

Given that tumour size and grade at diagnosis are know independent prognostic factors, these findings may have important implications for social policy and to the allocation of resources for the diagnosis of early breast cancer in regions with significant South Asian populations.

O-140. Variation in patient choice of operation for primary breast cancer in the Trent region 2002/03

Reed JA, Murphy A. *East Midlands QA Reference Centre Nottingham*

The EMQARC has conducted an audit of screen detected breast cancers to determine the proportion of women in the Trent region who are offered choice of operation. The information was collected via a nurse administered questionnaire. Pre-operative radiological opinions and final pathology data were examined

to assess the degree of adherence by screening units to their treatment protocols. 287 cancers were audited from the screening year 2002/03. The overall mastectomy rate for first operation was 30%. When advice on clinical factors was taken into account size, site, breast/tumour ratio and disease extent, the revised rate for women actively choosing mastectomy over breast conservation surgery was only 13%. The range according to units within the Trent region was from 3% to 21%. 56 mastectomies were advised on clinical grounds, and following audit, the units had followed their treatment protocols extremely well. Of the 231 cases given the choice, 192 chose breast conservation surgery. Regionally, the vast majority made the decision on the type of surgery at the initial results clinic suggesting the importance of the consultant's contribution to the decision making process. The variability of mastectomy rates remain after adjusting for case mix but the audit shows a much smaller number of women actually opting for mastectomies overall.

O-141. The effect of cyclooxygenase 2 (COX-2) inhibition on tumour growth in a xenograft model

Barnes N, Warnberg F, White D, Anderson E, Bundred NJ. *South Manchester University Hospital*

COX-2 is an inducible cyclooxygenase that is active in the pathway of conversion of arachidonic acid to prostaglandins, which in turn induces aromatase expression in tumours. Expression of COX-2 in invasive breast cancer is associated with increased tumour growth and decreased survival. We aimed to determine the effect of COX-2 inhibition on tumour growth and cell proliferation.

Oestrogen receptor (ER) positive (including a HER-2 transfected MCF-7 cell line), and ER negative cancer cell lines, were injected into the flanks of nude mice and allowed to form tumours. The mice were divided into two groups receiving either 0.15% Celecoxib (a COX-2 inhibitor), or control chow. Tumour growth was measured. At the end of the experiment the tumours were harvested and the percentage of proliferating cells were determined by Ki67 immunohistochemistry.

Cell line		MCF7/HER2-18	SKOV3	MDAMB231
COX-2 Expression		+	±	++
ER Expression		++	+	–
Tumour Growth				
Inhibition (%) Median		48.7	76.8	46.3*
Interquartile Range		16.2-89.5	-43.1-105.5	3.7-97.4
Ki67 (%)	Treated	77.4	33.4	57.4
(Median)	Control	74.2	32.0	56.5

*p = 0.0003 (Mann Whitney U Test)

Celecoxib inhibits tumour growth *in vivo* in ER positive and ER negative cell lines, by mechanisms other than inhibition of cell proliferation. Effects of celecoxib on apoptosis and angiogenesis need to be investigated. COX-2 inhibition is a potential therapy for breast cancer.

O-142. Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme

Evans DG, Amir E, Shenton A, Lalloo F, Boggis C, Wilson A, Howell A. *St Mary's Hospital & Withington Hospital Manchester*

Background: Accurate individualized breast cancer risk assessment is essential to provide risk-benefit analysis prior to initiating interventions designed to lower breast cancer risk. Several mathematical models for the estimation of individual breast cancer risk have been proposed, however, no single model integrates family history, hormonal factors and benign breast disease in a comprehensive fashion. A new model by Tyrer and colleagues has addressed these deficiencies. Therefore, this study has assessed the predictive and discriminatory value of the Tyrer-Cuzick model against established models namely: Gail, Claus and Ford.

Methods: The goodness of fit and discriminatory accuracy of the models was assessed using data from 3151 women attending the Family History Evaluation and Screening Programme. All models were applied to these women over a mean follow up of 5.26 years to estimate risk of breast cancer.

Results: The ratios of expected to observed numbers of breast cancers (95% confidence intervals [CI]) were 0.68 (0.53-0.88) for Gail, 0.75 (0.59-0.97) for Claus, 0.65 (0.51-0.84) for Ford and 1.07 (0.84-1.39) for Tyrer-Cuzick. Of the 65 cases of breast cancer, 59.7% of women were assigned risks using the Gail compatible with chemoprevention under the IBIS protocol. The proportion for Claus, Ford and Tyrer-Cuzick were 48.4%, 38.7% and 74.2% respectively.

Conclusion: The Tyrer-Cuzick model is the most consistently accurate model for prediction of breast cancer. Gail, Claus and Ford all significantly underestimate risk although the accuracy of Claus may be improved by adjustments for other risk factors. Tyrer-Cuzick model also shows good sensitivity.

O-143. HRT and the risk of screen detected breast cancer

Boran SA, Merrigan BA, Sweeney KJ, Smith C, Fitzpatrick P, Flanagan F, Kerin MJ. *Mater Misericordiae Hospital Dublin Ireland*

Introduction: 20 million world-wide are using HRT. HRT users have a significantly increased risk of breast cancer. Screening mammography improves mortality by earlier detection. However HRT may reduce the efficiacy of mammography by increasing the density of the breast.

Aims: (1) To determine the use of HRT among the screening population. (2) To examine the effect of HRT on the interpretation of screening mammography. (3) To assess the relationship between HRT and final histopathological diagnosis in the screened population attending the Eccles breast screening unit between 2000-2002.

Methods: In this study we have prospectively assessed HRT use in: (a) In a population of 2000 women undergoing mammographic screening. (b) In patients recalled to assessment because of abnormal mammograms. (c) In screen-detected cancers.

Results: 35,589 women, between 50-64 years were screened. 33,612 women had entirely normal mammograms. 2000 of these normal women were randomly selected and 32% of them were found to be taking HRT. 1,977 were recalled to assessment. There was a significantly higher number of women on HRT vs the normal population, suggesting that HRT led to an increased recall rate. Similar results were seen in those that required a biopsy and those who ultimately were found to have breast cancer. Screen-detected tumours in women on HRT were found to be of a smaller size, lower grade, more differenciated, node negative, ER positive.

Conclusions: HRT impacts not only on the incidence of breast cancer but also in its diagnosis and treatment. However increased incidence of good prognosis tumours detected by screening calls into question the impact of HRT on mortality.

O-144. Preoperative imprint cytology, frozen section and immunohistochemistry in sentinel nodes from breast cancer patients - a prospective study

Frisell J, Celebioglu F, Sylvan M, Bergkvist L. *Huddinge University Hospital & Central Hospital Vasteras Sweden*

Introduction: The aim of this study was to compare the sensitivity between peroperative use of imprint cytology (IC), frozen section stained with eosin-hematoxylin (HE) and immunohistochemistry (IHC) in sentinel nodes (SN) from breast cancer patients.

Material and Methods: 118 women with invasive, unifocal breastcancer with clinically no metastases in the axilla, were operated with sentinel node technique at Huddinge University Hospital during a 22 month period. SN was examined peroperatively with frozen section, stained with hematoxylin-eosin (118 patients and 199 SN), immunohistochemistry with cytokeratin antibodies (109 cases and 186 SN) and imprint cytology (102 patients and 177 SN). Imprint cytology was analysed postoperatively without knowledge of the axillary status in order to confirm the sensitivity of the method. Axillary clearence was performed in all cases.

Results: In 118 breast cancer patients a mean of 1.7 SN were retrieved. In 58 cases 1 SN was found, in 39 women 2 SN and in 21 patients 3 SN. Metastases in the axillary lymph nodes were found in 55/118 cases (46.6%), and were found only with IHC in 6 cases. Micrometastases (size <2 mm) as the only metastases were found in 16/55 (29%). Frozen section was positive in 42/55 patients with axillary metastases, sensitivity 76.3% and peroperative IHC was positive in 39/52 cases with axillary metastases, sensitivity 75%. IC was only positive in 23/47 patients with axillary involvement, sensitivity 48.9%. The combination of both HE and IHC peroperatively increased the sensitivity to 82.7% (43/52), whereas addition of IC did not increase the sensitivity.

Conclusion: Peroperative use of frozen section with HE and IHC were used with acceptable sensitivity (76.3% and 75% respectively) and the combination of the two methods increased the sensitivity to 82.7%. IC had in our hands an unacceptable low sensitivity, and gave no further clinical information when used alone or in combination with the other two. The use of peroperative frozen section and/or peroperative IHC will reduce the number of patients with more than 80% who need a second operation for axillary clearance after a positive sentinel node biopsy in breast cancer.

O-145. Local control and survival following breast conservative treatment of invasive lobular carcinoma

Jain P, Magee B, Stewart AL, Swindell R. *Christie Hospital Manchester*

Infiltrating lobular, carcinoma (ILC) of the breast is the second most frequently occurring type of invasive breast cancer. These lesions have a tendency to be multi-centric and multi-focal. Consequently mastectomy was considered to be the safest option for the management of this type of carcinoma. There is however conflicting data on local recurrence rates and survival in patients with lobular breast cancer treated with conservative surgery when compared with mastectomy in the various published literature to date.

Data is presented from one of the largest series, reporting survival and local recurrence rates in patients with lobular breast cancer treated with a combination of breast conserving surgery and radiotherapy. A total of 4653 patients with breast cancer were given adjuvant radiotherapy following wide local excision from 1989-1996. Of these 338 (7%) were lobular carcinomas and 3587 were ductal carcinomas. The median follow up on this group is 5.8 years. At 5 years 95.5% of patients with lobular cancer were free of local failure compared with 93.1 % of patients in the ductal cancer group, $p = 0.32$. Similarly 5 year survival for patients with lobular cancer was 90.9% vs. 85.4% in the ductal cancer group, $p = 0.14$. The two groups were similar for clinical and pathological stage; patients with lobular cancer had a median age of 61.6 years compared to an age of 59.3 years in patients with invasive ductal cancer $p < 0.05$.

In summary, our data shows that patients with lobular cancer do not have an inferior outcome compared to ductal cancer if they are treated with conservative surgery and radiotherapy. Hence a histological diagnosis of lobular cancer should not in itself lead to mastectomy as the treatment of choice.

O-146. Update of the BASO II trial of primary treatment of tumours of excellent prognosis

Blamey RW, Chetty U, George D, Mitchell M *on behalf of the BASO Breast Group Trialists*

This trial examined additional treatments to Wide Local Excision with clear margins, in Grade I, node negative tumours of 2 cm or less. The trial began in 1992 and closed in 2000, when the numbers required for power calculations were exceeded. 1172 patients were randomised to a 2×2 design. The primary outcome measure is local recurrence (LR) (defined as tumour in the treated breast.

This report is at a median of 5 years follow-up. Survival is excellent, with only 7 deaths from breast cancer (0.2% PA).

The local recurrences by randomisation are will be presented in the following groups:

Adjuvant treatment	n	LRn	LR %
Radiotherapy (RT) to intact breast	554		
No RT	549		
Tamoxifen	208		
No Tamoxifen	207		
RT plus Tamoxifen	96		
No RT, No Tamoxifen	95		

Since for those entering only to the RT or the Tamoxifen comparisons, the other therapy could be given electively, the results by treatment received will be analysed according to:

	n	LRn	LR %
Neither therapy	174		
RT only	191		
Tamoxifen only	411		
RT plus Tamoxifen	396		

These results will be available at the meeting.

O-147. Ductal carcinoma in situ (DCIS) - the role of prognostic indicators in informing treatment and reducing local recurrence

Lawrence GM, Clements KE, Macartney JM, Lee MR, Wheaton MJ, Kearins O, Wallis MG, Bishop HM. *West Midlands Cancer Intelligence Unit Birmingham*

The incidence of Ductal Carcinoma *In Situ* (DCIS) has risen dramatically in the West Midlands since the introduction of the National Health Service Breast Screening Programme (NHS-BSP). There is a wide variation in the treatment provided to these patients and uncertainty as to the best management policy to follow. 840 cases of DCIS diagnosed during the period 1st April 1988-31st March 1999 were identified in 10 breast screening services in the West Midlands. Treatment and follow-up data were collected from hospital case notes and from the West Midlands Cancer Intelligence Unit's cancer registration database. A pathological slide review was undertaken by a consultant pathologist to provide consistent information on diagnostic characteristics, 624 cases were, identified with a full pathology dataset and 711 cases were identified with a full treatment dataset. The 579 cases with both a full pathology and treatment dataset were analysed. Follow up data were attained for a maximum of 14 years and a minimum of 3 years. Data will be presented which demonstrate the differing treatment methodologies utilised in the treatment centres in the West Midlands and how these policies have varied over time. The relationships between surgical technique, margin status, and the use of radiotherapy and the rate of local recurrence will be presented, and the extent to which prognostic indicators were used to inform appropriate management will be evaluated.

O-148. The UKCCCR trial of the frequency of breast cancer screening

Duffy S, Blamey RW. *for the Breast Screening Frequency Trial Group. Nottingham City Hospital & Cancer Research UK*

This randomised trial between 1989 and 1996 compared screening at the standard NHS BSP interval of 3 years (Controls - C) with screening annually (Trials - T), in women aged 50 -64.

A previous publication (EJC 2002: *38:* 1458-1464) used to the Nottingham Prognostic Index (NPI) to predict outcome. The predicted survivals within each NPI prognostic group were based on the survival figures for breast cancers prior to 1988.

However survival within each NPI group has since then improved, due to improved therapies. Recalculation of the predictions is here based on these new survival figures:

	n diagnosed (%)		n surviving at 10 years	
	Control	Trial	C	T
GPG	92 (46)	113 (49)	84	103
MPG	8 (43)	96 (42)	65	72
PPG	22 (11)	20 (9)	9	8
Total	108	235	158 (76%)	183 (78%)

Conclusion: Although there were more cases in the GPG and less in the PPG from annual screening, this did not significantly alter the predicted deaths. The absolute figure of 2% less deaths represents a relative risk reduction of 8%.

There is no significant advantage to annual screening over the standard 3 yearly NHS screening and shortening of the screening interval would certainly not be cost effective.

At the meeting the agreement between the predicted and the observed deaths will be presented.

O-149. Primary medical therapy directed by ER: the Edinburgh randomised trial in operable breast cancer

Cameron DA, Jack W, Forouhi P, Keen J, Dixon JM, Leonard RCF, Chetty U . *Western General Hospital Edinburgh on behalf of the Edinburgh Breast Unit*

Between Jan 1990 and Oct 1995; 171 women with large operable (>3 cm, T2, T3, N0, N1, M0) breast cancer were randomised between either:

- Primary systemic therapy for 3 months directed by tumour ER (n = 84):
  - ER $\geq$ 20 fmol/mg cytosol protein: hormonal therapy (goserelin 3.6 mg/month, or tamoxifen 20 mg/day as per menopausal status).
  - ER < 20: prednisolone 40 mg po $\times$ 5 days, cyclophosphamide 1 g/m^2 iv, adriamycin 50 mg/m^2 iv every three weeks $\times$ 4 cycles.
  - Patients progressing on hormonal therapy switched to chemotherapy.

  Patients on endocrine, therapy continued the same for 5 years post-op.
- Conventional (1980's) post-operative systemic therapy (n = 86):
  - 6 cycles of CMF for premenopausal node +ve patients
  - tamoxifen 20 mg a day for 5 years for all other patients.

To date, 40 Primary systemic therapy and 47 Conventional therapy patients have relapsed at a median follow-up of 8 years (see table).

After 4 years the curves diverge in favour of the PST arm ($p < 0.1$). Patients with ER +ve tumours had significantly better survival ($p < 0.05$).

Relapses	Chemo	Endo	End→chem	6 yr DFS	6 yr OS
Clinical CR	5/10	0/0	0/1	57%	57%
Path CR	2/5	0/0	0/0	80%	80%
Clinical PR	5/16	4/19	1/5	79%	77%
SD/PD	5/8	13/25	4/4	41%	48%
PST Node -ve	6/23	3/14	0/2	83%	85%
PST Node +ve/uk	9/11	10/21	5/8	50%	50%
CT Node -ve		15/37		64%	70%
CT Node +ve/uk		32/49		42%	45%

These data suggest no disadvantage to using PST directed on the basis of ER status, compared to conventional therapy, and that pathological response in the nodes matters more than the primary tumour response.

O-150. Meta analysis of Trilostane (Modrenal) in advanced, post menopausal breast cancer evaluated by prior exposure to anti oestrogen treatments

Leonard RCF, Bundred N, Canney P, Rea D, Rowland C, Spittle M, Stewart A, Verrill M, Vinson G, Wood C. *SW Wales Cancer Institute Swansea, Manchester University Hospital, Beatson Oncology Centre, Glasgow, Queen Elizabeth Hospital Birmingham, Middlesex Hospital London, Christie Hospital Manchester & Newcastle General Hospital*

Background: Trilostane (Modrenal) was investigated in a series of 11 multicentre, international trials involving 893 post-menopausal women with assessable, progressing, advanced breast cancer. Trilostane has been shown recently to modulate binding of oestrogen to both ERα and ERβ and to inhibit cell proliferation in breast cancer cells mediated through both the ERE and AP1 dependent pathways.

This meta-analysis aims to identify the role for trilostane in patients previously treated with anti oestrogenic therapies.

Results: Of the 893 post menopausal women in the database, 783 received trilostane. Of these, 714 received full dose trilostane (≥720 mg/day) and low dose glucocorticoid; 660 (92%) had received prior anti-oestrogen therapy; 307 (43%), including all patients in the anti-oestrogen naive group, had previously received chemotherapy regimens. The clinical benefit rate (CBR = CR + PR ≥ 3 mos DS ≥ 6 mos) was 35%.

The cohort was stratified by the number of previous anti-oestrogen therapies the patients had received (see table).

	Number of previous anti-oestrogen therapies			
	0	1	2	3+
Number of patients	54	360	198	182
Clinical benefit rate (%)	22 (41%)	137 (38%)	56 (28%)	32 (31%)

Discussion: This meta-analysis confirms that trilostane has good clinical activity in a poor-prognosis population, having relapsed following conventional hormonal therapy.

Trilostane's unique mode of action offers an additional hormone treatment even in patients who have become refractory to standard hormonal therapy.

O-151. NEAT (National Epirubicin Adjuvant Trial) and SCTBG BR9601 (Scottish Cancer Trials Breast Group) phase III adjuvant breast trials show a relapse-free and overall survival advantage for sequential ECMF

Poole CJ, Earl HM, Dunn JA, Hiller L, Bathers S, Spooner D, Grieve R, Agrawal RJ, Foster L, Twelves C *on behalf of the NEAT Investigators and the SCTBG. Cancer Research UK Birmingham & Beatson Oncology Centre Glasgow*

The ***NEAT*** and **SCTBG BR9601** trials address the role of Epirubicin in adjuvant chemotherapy for women with early breast cancer. ***NEAT*** compared Epirubicin (100 mg/m^2 × 4 cycles) followed by classical (c)CMF (×4 cycles) with cCMF (×6 cycles); **SCTBG BR9601** compared Epirubicin (100 mg/m^2 × 4 cycles) followed by iv dose modified 3-weekly CMF (750:50:600 × 4 cycles) with iv 3-weekly CMF (×8 cycles). 2021 eligible patients were entered into ***NEAT*** and 370 into **SCTBG BR9601**. Prophylactic growth factors and antibiotics were not required. Prognostic characteristics were balanced across treatments: 72% were node +ve; 59% ≤50 years old; 58% of tumours grade 3; 57% >2 cms; 32% ER -ve, 50% ER +ve (18% NK). For the more intensive cCMF-containing ***NEAT*** regimens, median delivered dose intensity was 93% course, with similar myelosuppression, amenorrhoea, supportive treatment requirements, treatment-related mortality rates and global Quality of Life scores. The first pre-planned interim analysis is based on 309 deaths/428 relapses or deaths; median follow-up for surviving patients is 32 months (IQR 21-45 months). Despite lower than anticipated rates in the control arm, there is a highly significant benefit in favour of ECMF for both relapse free survival (HR 0.70, 95% CI 0.58-0.85; p = 0.0003) and overall survival (HR 0.64, 95% CI 0.51-0.81; p = 0.0001) when data from both trials are combined, which hold when adjusting for prognostic factors; ECMF advantage is irrespective of lymph node status, age and ER status stratification groups. The ***NEAT*** and **SCTBG BR9601** regimens are tolerable, with achievable optimal dose intensities. These data add to those of the Overview in respect of an anthracycline advantage and augur for ECMF as an established standard adjuvant therapy.