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ABSTRACTS

PARALLEL SESSION I—BREAST CANCER DETECTION DIAGNOSIS

1. Ultrasound by surgeons is accurate in the diagnosis of breast disease

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Introduction: Ultrasound forms part of triple assessment of breast lumps. The aim of this study was to evaluate the accuracy of ultrasound performed by a surgeon in the breast clinic.
Methods: Women presenting with symptomatic breast disease had diagnostic ultrasound (U.S.) by a consultant surgeon as part of clinical assessment. Patients who also had ultrasound assessment in the Department of Imaging were included. Ultrasound scans were scored as benign, indeterminate or malignant. The end point was to compare U.S. by surgeons to U.S. by radiologists.
Results: Of 229 new patients who had U.S. scans by both surgeon and radiologist, there was 88% concordance. There was complete discordance in seven patients. In five patients thought to be malignant by surgeons and benign by radiologists, four were malignant on histology. The two patients scored as benign by surgeons and malignant by radiologists were both benign on histology. Of 13 patients scored as indeterminate on U.S. by surgeons, eight were malignant on histology, and five benign. In the malignant group, the radiologists also graded three patients as indeterminate, correctly grading three patients as malignant, with two false negatives. Of five benign patients, the radiologists graded three as benign, one as indeterminate and one as malignant.
Conclusion: Ultrasound performed in outpatients by an experienced breast surgeon is accurate. This enables rapid diagnosis in 'one-stop' breast clinics, facilitating efficient use of time and resources.

2. Surgeon directed ultrasound guided core biopsies in the breast—a prospective study

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Introduction: The national shortage of radiologists and the need to achieve an increased pre-operative diagnosis initiated this study to assess the accuracy of a surgeon undertaking ultrasound guided core biopsies of small lesions identified on mammography or U.S.
Methods: Data was collected prospectively on the results of 120 consecutive core biopsies, on discrete lesions under 30 mm maximum diameter, performed by a single surgeon. Following imaging of the solid discrete lesion by an ultrasonographer, the surgeon directed the 14 gauge core biopsy needle into the lesion under ultrasound control. A minimum of two core biopsies were taken and immediately inspected for quality. All B1 or B3 lesions were subjected to open biopsy (op Bx).
Results: The results of core biopsies in relationship to size of the lesion were: 0–9 mm; N = 25; 16 = B2; 6 = B5; 3 = B1 (Two normal, one carcinoma at op Bx); 10–14 mm: N = 36; 18 = B2; 16 = B5; 2 = B1 (normal at op Bx); 15–19 mm: N = 29; 19 = B2; 7 = B5; 2 = B3; and 1 = B1 (all fibroadenomata at op Bx); 20–29 mm: N = 30; 12 = B2; 14 = B5; 4 = B1 (3 fibrocystic, 1 fat necrosis at op Bx); Total: 120; 65; 43; 12.

The B5 lesions were carcinomas. The B2 lesions included fibroadenoma, fat necrosis, lymph node, macrocyst and intraduct papilloma. The B1 lesions on open biopsies were all 'benign' except for one small cancer lying on top of a breast implant.
Conclusion: The combined effort of a surgeon and ultrasonographer achieved a 90% definitive tissue diagnosis of these solid lesions under 30 mm. Surgeon directed U.S. guided core biopsies is a practical solution to the increasing demands in achieving a high pre-operative diagnosis and both increased our pre-operative diagnosis rate of carcinomas and reduced the biopsy rate in benign lesions.

3. Fibrofatty nodule in the breast: is inadequate cytology sufficient for diagnosis?

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Introduction: The process of triple assessment comprising of clinical, radiological and cytological evaluations of all breast lesions is now well established. Some women present with a fibrofatty type nodule wherein scanty epithelial cells do not allow a definitive cytological conclusion. The purpose of this study was to prospectively document the triple assessment findings and outcome for these fibrofatty nodules.
Methods: The diagnosis of fibrofatty nodule was clinical, and was made if palpation detected a discrete, mobile, soft nodule. All such patients underwent the appropriate radiological examination and fine needle aspiration for cytology. In cases where the lump persisted FNA was repeated at 4–6 weeks. All cases were discussed at multidisciplinary meetings and followed up for 6 months, at which stage ultrasound scan of the breast was repeated if the nodule persisted.
Results: The cohort included 68 women (age 22–76 years) referred with a breast lump. Mammograms were performed in 35 cases and were normal. Ultrasound scan of the breast was performed in 68 cases and showed a hypoechoic nodule less well defined than fibroadenomata, lacking enhancement and attenuation of the sound beam behind the lesion in 16 cases, while it was normal in the others. Cytology was performed on at least two occasions in women who retained their lump. In 55 (80%) cases both FNAs were reported as insufficient for diagnosis. Detailed examination of the smear did show fibrofatty fragments in 20 women (29%). Benign cytology (C2) was obtained in only 10 women (14%). No patient had abnormal radiology or cytology. Excision was performed on patient's request in five cases. None showed atypia or malignancy. Follow-up has not revealed any malignant diagnosis.
Conclusion: We conclude that presentation with a fibrofatty nodule is not uncommon and requires multidisciplinary decision making, but an insufficient cytology may well be sufficient for safe diagnosis as a component of that assessment. This would bring about a decrease in benign biopsies.

4. An evaluation of the accuracy of imprint cytology of core biopsy

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Introduction: Core biopsy has become a valuable diagnostic tool in the management of breast lesions. Sensitivity is high but specificity may be reduced by sampling error. Histological analysis takes 24 hours in our unit, but imprint cytology of core biopsies can be reported within an hour. The aim of this study was to validate the accuracy of imprint cytology from core biopsy of breast lesions. This could then be used to provide a preliminary diagnosis or to repeat the core biopsy immediately if a false negative was suspected, reducing sampling error.
Methods: Fifty-four consecutive core biopsies from 48 patients were performed either clinically or under image guidance. The cores were placed on six microscopy slides. Half of the slides were air dried and half fixed with alcohol. They were then stained with haematoxylin and eosin and Giemsa respectively. The cellularity was considered adequate for diagnosis if more than five groups of ductal cells were seen. Imprint cytology and core histology were assessed independently by two pathologists.
Results: Two imprints were deemed to be inadequate for diagnosis. Of the subsequent histology one showed fibrocystic change on the core and a radial scar on the definitive histology, and the other showed fat and stroma only and the lesion was not subsequently excised.

	Grade	Imprints	Cores
Inadequate	1	2	1
Benign	2	16	16
Atypical	3	0	0
Suspicious	4	1	0
Malignant	5	35	37
Total number of lesions		54	

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All core biopsy results correlated 100% with the histology of lesions subsequently excised. For benign lesions, after exclusion of inadequate results, both sensitivity and specificity was 100%. For malignant lesions only one imprint was reported as benign, and subsequently showed invasive duct carcinoma, and one reported as suspicious, the remainder were reported as malignant giving a sensitivity of 97% and specificity of 100%.
Conclusion: Imprint cytology of core biopsies correlates well with subsequent histological results and could be used to provide a rapid preliminary diagnosis. This would reduce anxiety in patients with benign lesions and help treatment planning in patients with breast cancer.

5. Histological assessment of breast tissue by optical biopsy

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Introduction: Optical biopsy is a new technique under evaluation for the diagnosis of various types of breast tissue. This study assessed an optical probe, based on the principle of Elastic Scattering Spectroscopy (ESS) with spectral analysis of reflected light. The aim is to develop an optical biopsy instrument capable of giving an immediate diagnosis of breast lumps and other types of breast tissue, reliably in a clinical setting.
Methods: The system consists of a white light source, with fibre-optic delivery and collection fibres, a spectrometer for dispersion of the collected light and linear CCDs (charge coupled devices) for detection. Fifty patients were recruited to the study following informed consent. Optical spectral measurements from a range of breast tissues were correlated with the findings on conventional histology of biopsies taken from the same sites, and then analysed using artificial intelligence techniques to develop algorithms to interpret the spectra. Several methods were employed to obtain both optical and conventional biopsies including core-cut and tumour bed specimens.
Results: Preliminary results have been encouraging but depend on the type of analysis employed. Both model based analysis and artificial intelligence methods were tested. The table below illustrates the sensitivity and specificity for detection of cancer for each method.

	ANN	HCA	MBA
Sensitivity	69%	67%	94%
Specificity	85%	79%	92%

ANN: artificial neural network; HCA: hierarchical cluster analysis; MBA: model based analysis.
Conclusion: Optical biopsy offers promise as a 'real time' diagnostic tool for breast disease. Potential applications include outpatient diagnosis of breast lesions, assessment of possible Paget's disease of the breast without the need for painful incision biopsy, interrogation of the tumour bed in theatre so avoiding positive resection margins and sentinel node analysis.

6. Ultrasound core biopsy of breast lesions which are indeterminate on imaging (R3) is essential

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Introduction: To determine the value of ultrasound guided core biopsy in patients with normal (R1 and R2) and indeterminate (R3) imaging by ultrasound and mammography.
Methods: All patients who presented between March 1995 and May 2000 who underwent an ultrasound guided core biopsy were studied. The mammogram and ultrasound report of all patients were reviewed together with the histology report of the core biopsy.
Results: During the study period 413 patients had an ultrasound guided core biopsy. On histopathological examination 143 (35%) of these lesions were malignant. Forty-two patients had no recent mammogram (half of whom were under 35 years). Nineteen per cent of patients with breast cancers had mammograms reported R1 or R2, and 28% were reported R3. The size of tumour was reported on ultrasound in 389 cases. Two hundred and ninety-six (76%) lesions were 15 mm or less in diameter and 100 (34%) were malignant. One hundred and seventy-seven (46%) lesions were 10 mm or less in diameter and 61 (35%) were malignant. Two hundred and fifty-nine cases had indeterminate ultrasound (R3) and mammogram reported R3 or less (R1 and R2), of these 40 (15%) were malignant.
Conclusion: One third (1/3) of U.S. guided core biopsies were malignant regardless of size. Any lesion which is indeterminate on ultrasound (R3) should be biopsied regardless of the mammographic appearance or size.

7. Changes in vascular phenotype with the development of ductal carcinoma *in situ* (DCIS) of the breast

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Introduction: Changes in vascularity are fundamental to tumour growth, this study identifies changes in vascular phenotype as well as vessel density when comparing normal lobules with DCIS.
Methods: Twenty sections of pure DCIS were stained with factor VIII, CD31, CD141 and CD34. In each section, individual foci of DCIS were identified (up to 50/slide) and all vessels within 100 μm counted. The results were expressed as microvessel density (MVD). Normal lobules at least 2 mm away were used as controls. Dual fluorescence immunostaining for CD34+ and vWF+ vessels was also carried out.
Results: The highest MVD surrounding normal lobules was obtained using factor VIII antibody, whilst the highest count for pure DCIS was obtained using the CD34 antibody. MVD and vessel phenotype were significantly different in normal lobules compared with pure DCIS. The number of vessels staining with factor VIII decreased while the number staining with CD34 increased. MVD was higher in intermediate nuclear grade DCIS compared to low-grade DCIS, but was lowest in high-grade DCIS with necrosis. On dual staining, CD34 only positive vascular density around DCIS were significantly higher than those in adjacent normal lobules. Of those vessels that stained positive for CD34, the percentages that also stained for vWF were less in DCIS (30–38%) than in normal lobules (36–54%).
Conclusion: Microvessels in DCIS are of a different endothelial phenotype from that in adjacent normal lobules.

8. Core biopsy analysis of C3 and C4 breast lesions

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Introduction: Audit of practice at this centre reveals positive predictive values for FNA of C5 = 100%, C4 = 91% and C3 = 24%. A prospective study was undertaken to evaluate the use of core biopsy as an adjunct to triple assessment to reduce the incidence of unnecessary malignant and benign biopsies in C3 and C4 lesions.
Methods: A consecutive series of patients between 1997 and 1999 with symptomatic or screen-detected breast abnormality in whom excision was deemed necessary on existing triple assessment had core biopsies performed. Cores were performed under local anaesthetic and analysed histologically within 24 hours. Findings of FNA cytology, core biopsy histology and final histological findings were compared.
Results: Two hundred and seventy-eight patients (197 screen detected, 81 symptomatic) were studied. Overall, benign biopsy specificity was 48% for FNA and 75% for core biopsy. Sixty-eight cases were graded as C3 and 87 as C4. Core biopsy allowed accurate pre-operative benign diagnosis in 31/68 and malignant diagnosis in 12/68 C3 cases. Similarly 39/87 C4 cases were diagnosed as unequivocal malignancy on core biopsy:

		Final Diagnosis	
	B	Benign	Malignant
Core biopsy findings form C3 lesions	1	7	4
	2	31	1
	3	5	2
	4	3	3
	5	0	12
	Total	47	21
Core biopsy findings form C4 lesions	1	2	11
	2	8	9
	3	3	5
	4	1	9
	5	0	39
	Total	14	73

Conclusion: Core biopsy can significantly improve the accuracy of diagnosis of breast lesions. Use of the core biopsy technique in addition to FNA as part of the triple assessment will reduce the number of unnecessary benign and malignant breast biopsies.

PARALLEL SESSION II—COLORECTAL

9. Immunohistochemistry in the detection of microsatellite instability in colorectal cancer

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Introduction: Microsatellite instability (MSI) is a feature of tumours in Hereditary Non-Polyposis Colorectal Cancer (HNPCC). This is caused by an inherited mutation in one of the mismatch repair genes. Some patients may not fulfil the Amsterdam criteria for the diagnosis of HNPCC and nearly 15% of sporadic colorectal cancers also demonstrate MSI. A simple screening test that will identify these patients may have an impact on their management. The use of immunohistochemistry in detecting the hMLH1 and hMSH2 proteins has been proposed as a quick, easy and reliable technique for identifying MSI +ve cancers and less has been evaluated in this study.
Method: Paraffin embedded archival material was obtained from 76 colorectal cancer patients who had been followed up for at least 7 years and had not developed a second cancer. DNA was extracted from both tumour and normal mucosa. Markers for the microsatellite regions Bat 25, Bat 26, Bat 40, D2S123, D17S250 and D5S346 were amplified by the polymerase chain reaction (PCR) and run on a polyacrylamide gel. Cancers demonstrating MSI in >40% of the marker regions investigated were deemed to show high level instability (h-MSI), those with <40% of the marked regions were deemed to show low level instability (l-MSI) and those with no instability were classified as stable (MSS). Immunohistochemistry using commercially available monoclonal antibodies to hMLH1 and hMSH2 was performed on the cancer tissue using a standard technique and the results were correlated with the MSI status.
Results: There was evidence of h-MSI in 11 (14.4%) cancers while 18 (23.6%) showed l-MSI (14.4%) and 47 (61.8%) were stable. All MSS and l-MSI cancers stained +ve for both hMLH1 and hMSH2 as did two cancers with h-MSI. Cancers with h-MSI stained −ve for hMLH1 in seven cases (63.4%) and −ve for hMSH2 in two cases (18.2%). The sensitivity of the test in identifying h-MSI cancers was 81.8% and the specificity 100%. The positive predictive value was 100% and the negative predictive value 97%.
Conclusion: Immunohistochemistry using antibodies to the hMLH1 and hMSH2 nuclear proteins is a useful screening test in the identification of over 80% of cancers with h-MSI. These patient may require further genetic analysis.

10. Ten year experience of endoscopic trans-anal resection (ETAR)

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Introduction: The aim of this study was to audit the results of ETAR performed by a single surgeon in a specialized colorectal unit over a 10 year period.
Methods: The surgical outcome of all patients undergoing ETAR presenting between 1989 and 1999 was reviewed. Data were collected retrospectively; no patients were lost to follow-up.
Results: One hundred and four patients (43 female; 61 male) underwent 163 procedures. Follow-up range from 0.5–10 years.

Seventy-five patients with a pre-ETAR diagnosis of benign rectal adenoma underwent resection. Sixty were confirmed to be benign; 30 were treated with a single resection; 28 were treated with multiple resections (range 2–10, mean 3). There were two technical failures. No patients subsequently developed a carcinoma. In the remaining 15 patients the final histology demonstrated malignancy. Nine patients underwent an open-surgical rectal resection. Five of the remaining patients had complete resection of their lesion; none of these have recurred (follow-up range: 13 months–8 years). One an extensive rectal cancer, was palliated for 2 months by ETAR.

Twelve patients underwent ETAR for anastomotic stricture: successfully in 11. Seventeen patients underwent 30 ETARs for palliation of non-resectable rectal adenocarcinoma, successful palliation of symptoms was achieved in 13. The 30 day mortality was 1% (myocardial infarction). There were two further major complications: one large blood transfusion for post-operative bleeding (DIC) and one CVA.
Conclusion: ETAR proved to be safe and effective. It offers both excellent definitive treatment of some rectal lesions, and good palliation of others, with low morbidity and mortality when performed by a single experienced surgeon.

11. Colorectal anastomotic leaks regularly masquerade as 'cardiac complications'

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Introduction: The aim of this study was to identify the mode of presentation of patients with anastomotic leaks following restorative colorectal resection for carcinoma.
Methods: A prospective study with additional retrospective case note review was carried out. Extensive prospective information was collected on all colorectal cancer resections at our institution. These data were reviewed for a 5-year period (1994–1998) to identify all the patients that had suffered an anastomotic leak. Their notes were retrieved and reviewed. Patients without an anastomosis were excluded.
Results: Three hundred and ninety-seven patients underwent restorative resection for colorectal cancer during the study period (178 female, 201 male), age range 36–94 (mean 70) years. The anastomotic leak rate was 6% ($n=22$), seven (32%) patients presented with obvious abdominal peritonitis. The remaining 15 (68%) were initially misdiagnosed. Thirteen patients (59%) were treated for cardiac symptoms, one patient (5%) for obstruction and one (5%) for ascites. The delay in diagnosis ranged from 0–11 days (mean 4 days). For the whole series of 379 there were 30 patients who suffered cardiac symptoms (8%); 13 of whom (43%) had an anastomotic leak.
Conclusion: Patients who develop cardiac symptoms following restorative colorectal resection for carcinoma should have a Gastrografin enema as there is a >40% chance that they have an anastomotic leak.

12. Morbidity following colorectal resection

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Introduction: POSSUM (physiological and operative severity score for the enumeration of mortality and morbidity) and Portsmouth correction (P-Possum) have been accepted as audit tools to predict morbidity and mortality in GI surgery, and allow cross-group analysis. Observed complications ranging from UTI to anastomotic leak are all weighted equally.
Methods: A retrospective review of 148 left-sided resections between 1/1/97 and 1/2/00, of which 80 were anterior resections (AR). Of these observed: expected (O:E) morbidity and mortality were calculated for total group and anterior resection. Complications defined by POSSUM were categorized as mild (infective-urinary, chest, unknown origin, wound, line; or hypotension) or severe.
Results: Total O:E mortality ratio was 0.359 (2.70%:7.52%) and AR 0.620 (2.89%:7.86%). With Portsmouth correction O:E is 1.061 and 1.34 respectively. Total O:E morbidity is 1.74 and AR 1.963. Of these, only 31.8% of total complications were severe, similar to predicted morbidity. In AR, 61% were severe (30.3% dysrhythmias, 18.2% small bowel obstruction:ileus). Anastomotic leak rate was 3.75% (national average 5%).
Conclusion: POSSUM does not address the magnitude of the operative intervention incurred during anterior resection, possibly due to dilution of morbidity data by the original inclusion of all colonic resections. Specific complications, not isolated in POSSUM, encountered frequently in this population should be given greater emphasis in expected morbidity calculations.

13. Long-term outcome after surgery for malignant large bowel obstruction

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Introduction: Acute bowel obstruction occurs in 5–40% of patients with colorectal cancer and is associated with a higher post-operative mortality

rate than in those without obstruction. This study is to verify or refute the dismal connotation associated with obstructing colorectal cancer.
Methods: Between January 1993 and December 1999, 278 protocolized colorectal cancer patients were analysed. Forty-four patients (16%) (28 M, 16 F; mean age: 65 years, range: 23–89 years) with bowel obstruction who had undergone surgery, were studied. Eight patients (18%) underwent right hemicolectomy. Left hemicolectomy was performed in 11 patients (25%). Partial colectomy was performed in 13 patients (30%). Hartmann's procedure in one (2%), anterior resection in three (7%), and colonic decompression in eight (18%). There were four (9%) peroperative deaths. Tumour classification was based on the Astler–Coller staging system, modified by Turnbull. There was one (2%) stage B1, 11 (25%) stage B2, 10 (23%) stage C2, and 22 (50%) stage D cancers.
Results: The median survival time was 30 months, and the 5-year survival rate was 42%. Features related to long-term outcome after a median follow-up of 5 years included advanced tumour stage ($P=0.0001$), poor tumour differentiation ($P=0.0006$), and lymph node involvement ($P=0.03$).
Conclusion: Long-term outcome of patients with obstruction is related to conventional prognostic features: this finding may be useful as adjuvant therapy has been shown to improve survival in patients with high risk of tumour recurrence and death.

14. Local formalin instillation: an effective treatment for uncontrolled haemorrhagic proctitis

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Introduction: The aim of the study was to evaluate the efficacy of local instillation of 4% formalin in management of uncontrolled haemorrhagic proctitis.
Methods: Eight patients were treated. They were seven men and one woman, with a mean age of 70.5 years (range 65–84). In seven patients the proctitis was radiation-induced and in one it was idiopathic, probably of ischaemic nature. Bleeding started an average of 16 months (range 12–24) after completion of irradiation. The mean duration of haemorrhage was 12 months (range 1–24). All patients had a fall of haemoglobin level requiring multiple transfusions. The median number of units of blood transfused per patient was seven (range 2–12). Patients had been treated with a variety of modalities including Argon-laser (two patients), steroid enemas (three patients), sulfasalazine enemas (five patients) and rectal resection with colostomy (one patient). All patients had an endoscopic diagnosis of haemorrhagic proctitis at the time of their referral. All patients were socially disabled by their complaints. Formalin instillation was performed under spinal or general anaesthesia. Lidocaine jelly was applied liberally around the perianal region. An endoscope was introduced. Formalin 4% solution was applied to the rectal wall for approximately 1 min. Saline was used to irrigate. This was repeated 10 times.
Results: Operation time was estimated to be 10 to 15 min. The mean hospital stay was 8 days (range 3–36). One patient required a laparotomy because of a rectal perforation due to mechanical trauma of the endoscope. Two patients experienced a short period of perianal pain.

All patients were followed for a median of 18 months (range 3–45). Two patients died from advanced disseminated malignancy. One patient died after vascular surgery. In five patients bleeding stopped after a single treatment and in three after a second one. No recurrent rectal bleeding occurred, no further medical treatment was needed and in all patients the complaints ha disappeared.
Conclusion: Local instillation of 4% formalin is an effective treatment for uncontrolled haemorrhagic proctitis.

15. Colorectal cancer—is standard intensive clinical follow-up necessary?

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Introduction: Intensive clinical follow-up for colorectal cancer surgery is controversial. We present a study of modified, non-scheduled clinical follow-up and compare the results with those of other published standard intensive clinical follow-up studies.
Methods: A prospective study of 234 consecutive patients with colorectal cancer operated on in a single unit by one surgeon at a DG Hospital was undertaken. Patients were followed-up by a modified regime. Post-operatively all patients were reviewed once as an outpatient at one month. Thereafter, for 5 years, investigations were generated by an automated computerised follow-up protocol. Outpatient appointments were made only on clinical suspicion or abnormal tests.
Results: Of the total of 234 patients, 48 were excluded from the study because of unrelated cause of death ($n=42$), or were lost from follow-up ($n=6$). One hundred and forty were curative and 46 were palliative resections. There were two operative deaths (within 30 days). Five year survival for Dukes' A, B and C were 84%, 50.7% and 19.4% respectively, compared with 70%, 50% and 28% in a standard follow-up study (BJS 1985; **72**: 698–702). Rate of recurrence detection was 29.2% compared with 26% in a standard follow-up study (BJS 1997; **84**: 669). Duration after surgery when recurrence was detected was 11 months as compared with 10.5 months, and survival for 2 or more years after resection of recurrence was 40% compared with 47% in a standard follow-up study (*Disease of Colon & Rectum* 1998, **41**: 1127–33).
Conclusion: The results were comparable in all aspects to those of any standard intensive clinical follow-up study (the difference in 5 year survival in Dukes' C stage is probably skewed by the large number of rectal cases (41.9%) in our study). Hence it is equally effective and at the same time it reduces the burden on NHS resources, though larger randomized controlled trials are necessary before it can be made a standard practice.

16. The role of positron emission tomography in the management of recurrent colorectal cancer

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Introduction: This study was designed to investigate the role of positron emission tomography (PET) in the management of recurrent and metastatic colorectal cancer (CRC).
Methods: A prospective study of 29 patients referred with suspected recurrent or metastatic CRC was undertaken. All patients underwent spiral computed tomography (CT) and fluorodeoxyglucose PET within 4 weeks of each other. PET and CT scans were read blind and independently, then findings were compared. All results were correlated with tissue biopsy or clinical and radiological course. Analysis was made of (i) the accuracy of PET for detecting and staging recurrent CRC; (ii) new information provided by PET and (iii) the impact of PET on clinical management.
Results: PET correctly diagnosed 26 (89.7%) patients compared to 21 (72.4%) by CT. PET had a sensitivity of 91.3% and a specificity of 83.3% (compared to 81.8% and 66.7% with CT). There were two false negative PET scans, one in a patient who had a necrotic liver metastasis after chemotherapy and the second in a patient in whom accumulation of tracer in the pelvis was judged to be in the bladder and not in recurrent tumour. The false positive PET scan occurred in a patient who had aberrant uptake of tracer in the uterus. Management was altered as a result of PET in 6 (20.7%) patients. In 23 patients recurrent CRC was confirmed. PET upstaged nine (39.1%) of these patients, three had multiple and not solitary liver metastases and six had previously unsuspected disseminated metastases. As a result of this four (17.4%) patients avoided inappropriate laparotomy.
Conclusion: This study confirms that PET is more accurate than CT for detecting and staging recurrent CRC. Clinical management was altered in up to 20% of patients directly as a result of PET. New information led to appropriate selection of patients for operative treatment, early treatment of those with metastatic disease and a reduction in inappropriate laparotomies resulting in decreased patient morbidity. These findings demonstrate an important area for the application of PET, which is an expanding imaging technology in the UK.

17. Extensive cytoreductive surgery and intraoperative hyperthemic intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal origin

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Introduction: Peritoneal seeding from colorectal cancer has a very poor prognosis and is relatively resistant to chemotherapy. Recently, cytoreductive surgery with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC), resulting in reduced loco–regional drug concentrations with minimal systemic side effects, has been performed for primary and secondary peritoneal malignancies. We conducted a phase I/II study to investigate feasibility and effectiveness of HIPEC in patients with peritoneal carcinomatosis from colorectal origin.
Methods: From November 1995 to December 1997 29 patients with peritoneal carcinomatosis from colorectal origin without evidence of distant metastases underwent extensive cytoreductive surgery with intraoperative hyperthermic intraperitoneal chemotherapy with mitomycin-C, followed by systemic chemotherapy with 5-fluourouracil/leucovorin.
Results: One patient died directly related to the treatment, resulting in a

mortality rate of 3%. The morbidity rate was 38%. After a median follow-up of 38 months (26–52 months) seven patients are still alive. Two of them have proven recurrence, both distant metastases. Twenty-one patients died of recurrent disease. The oco-regional recurrence rate is 57%. The actuarial 1-, 2- and 3-year survival rates (Kaplan–Meier) are 82%, 45% and 23% respectively.

Conclusion: Extensive cytoreductive surgery and HIPEC is feasible in patients with peritoneal seeding from colorectal cancer. The results suggest that a higher median survival can be achieved compared to conventional palliative surgery and systemic chemotherapy. This is now the subject of a randomized trial.

PARALLEL SESSION III—HEPATO-PANCREATO-BILIARY CANCER

18. Pseudomyxoma peritoneï treated by extensive cytoreductive surgery and intraoperative hyperthemic intraperitoneal chemotherapy

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Introduction: Pseudomyxoma peritoneï is an uncommon condition with gelatinous fluid collections and mucinous implants in the abdominal cavity. Because of its low-grade character, the disease remains confined to the abdominal cavity. However, the long-term prognosis is poor (5-year survival of 30–50%) after (repetitive) surgery alone. Recently, cytoreductive surgery with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC), resulting in increased loco-regional drug concentrations with minimal systemic side effects, has been performed for primary and secondary peritoneal malignancies. We now report on our experience with this treatment modality in these patients.
Methods: From 1996, 52 patients were treated by extensive cytoreductive surgery with intraoperative hyperthermic intraoperative intraperitoneal chemotherapy with mitomycin-C. Most patients presented with recurrent disease after multiple abdominal operations. Depending on histological grading they received systemic chemotherapy with 5-fluourouracil/leucovorin post-operatively.
Results: Optimal surgical cytoreduction, leaving tumour deposits smaller than 2.5 mm behind, was obtained in 45 patients (87%). Four patients died directly related to the treatment, resulting in a mortality rate of 9%. HIPEC-related morbidity was 37%. After a median follow-up of 17 months (1–46) 44 patients are still alive. Nine of them have proven recurrence. Acturial survival (Kaplan–Meier) at 3 years is 78%.
Conclusion: Extensive cytoreductive surgery and HIPEC is feasible in patients with pseudomyxoma peritoneï, even after multiple previous laparotomies. Our results suggest that an improved long-term survival might be achieved compared to surgery alone.

19. Intrahepatic chemotherapy via the subcutaneous Jet port® system

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Introduction: Recruitment at this centre for the CRO5 trial of intrahepatic chemotherapy has been poor because of the reluctance of patients to be randomized to laparotomy for insertion of a hepatic artery catheter. We have evaluated the use of an alternative, percutaneous technique for hepatic arterial cannulation and administration of intrahepatic chemotherapy.
Methods: Femoral artery cannulation was performed and Jet port® catheters were inserted under image intensification with the tip positioned in the appropriate arterial territory. All patients had heparin flush 2 weekly and warfarin (1 mg od). Chemotherapy was infusd by cannulation of the subcutaneous chamber using topical local anaesthetic. Patients were reviewed at 2 weekly intervals.
Results: Fourteen cannulae were inserted in 11 consecutive patients with hepatic metastases (8 males:3 females, median age 58 (1–74). In three cases themotherapy was administered as neo-adjuvant, six post-operatively and one case for recurrent disease and in one as the primary treatment. In all cases the chatheter was inserted through the femoral artery with the tip lying in the common hepatic ($n=13$) or right hepatic ($n=1$) artery. Median time for insertion was 42 mins (32–56), all inserted under local anaesthetic as daycase procedures; there were no procedural complications. The median number of cycles of chemotherapy used was four (1–20) cycles. Complications were observed in 6/14: thrombosis of common hepatic artery ($n=3$), catheter kinking/blockage/fracture ($n=3$) and superficial infection ($n=2$) requiring removal in one and replacement in three. The median duration of placement was 78 (6–530) days.
Conclusion: Percutaneous arterial cannulation for administration of intrahepatic chemotherapy by a subcutaneous Jet port® system is a safe procedure, with low morbidity and may prove a more acceptable alternative to operative cannulation for delivery of intrahepatic chemotherapy. Future studies of intrahepatic chemotherapy should include this technique.

20. Role of COX-2, APC and NSAIDs in colorectal cancer

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Introduction: Epidemiological studies have suggested aspirin ingestion reduces the risk of developing and dying from colorectral cancer. Delineation of the molecular mechanisms of anti-cancer actions of the NSAIDs will pave the way for development of new drugs.
Methods: (1) Aspirin and COX-2 selective agents Nimesulide and NS398 were added to human CRC cell lines HT-29, HCT-116 and C170HM2. Proliferation was assessed by MTT assay. (2) HT-29 APC and HT-29 βgal (negative) cell lines were used to assess the relationship between APC and COX-2 gene expression levels. (3) APC^{min} mice (Control ($n=20$) and NS398 ($n=20$)) groups were administered water and NS398 (5 mg/kg) by stomach gavage (home office approval). Number of polyps, survival and COX-2 gene expression were assessed. Quantification of the gene levels were done by the new sensitive Real Time PCR method.
Results: (1) Aspirin, Nimesulide and NS398 inhibited proliferation of the CRC cell lines in a concentration dependent manner. NS398 was the most potent with IC_{50} ranging from 150–275 μm. HT-29 cell line was resistant to the effect of NSAIDs. Metastatic cell line C170HM2 expressed highest levels of COX-2 gene (9.734; SD 20.8) and was more susceptible to COX-2 selective drugs. Good correlation between COX-2 expression and reduction in proliferation was found (aspirin $R^2=0.96$); NS398 ($R^2=1$)). Aspirin and NS398 reduced the COX-2 expression levels at growth inhibitory concentrations. (2) In our experiment we have shown that induction of wild type APC results in downregulation of COX-2 expression (28.6% reduction). (3) NS398 (5 mg/kg) significantly reduced the polyp numbers (Control (8.13); NS398 (60.5) $P=0.09$) and increased the survival (Control (13.8 weeks); NS398 (15.6) $P=0.002$). NS398 down regulated the COX-2 gene expression levels (Control (0.0052); NS398 (0.0031). Fifty-nine per cent reduction in COX-2 expression levels was found, although it did not reach significance ($P=0.40$).
Summary: COX-2 selective and non-selective drugs had anti-proliferative effects on CRC cell lines *in vitro.* APC gene regulates COX-2 at the transcriptional level. COX-2 selective drug NS398 significantly increased the survival and reduced the polyp number in APC^{min} mouse model and reduced COX-2 expression levels.
Conclusion: COX-2 dependent and independent pathways are responsible for colorectal carcinogenesis. Therefore drugs with broad spectrum of effects may be beneficial in CRC chemoprevention. Clinical trials with COX-2 selective drugs are warranted.

Key words: *CRC: colorectal cancer; APC: adenomatous polyposis coli; COX-2: cyclooxygenase-2; NSAID: non-steroidal anti-inflammatory drugs.*

21. T cells are activated in anergic patients with colorectal liver metastases

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Introduction: Although cell-mediated immunity (CMI) is depressed in patients with advanced colorectal cancer, some patients may also show evidence of immunological stimulation. This study demonstrated the paradox in such anergic patients whose immune systems, particularly T cells, were activated.
Methods: Serum levels of interleukin-2 soluble receptor α (IL-2 sRα), soluble tumour necrosis factor receptor I (sTNF RI), interleukin 6 (IL-6) and C-reactive protein (CRP) from patients with colorectal liver metastases were measured. Circulating T cells were measured for the prevalence of surface HLA-DR expression as a marker for T cell activation (DR^+ T cells). CMI was measured by delayed hypersensitivity reaction to intradermal injections of antigens. The volume of liver metastasis was measured by abdominal CT scan.
Results: Eighty-seven cancer patients (54 men; median age 57 years) and 23 'no cancer' control subjects (19 men; median age 61 years) were studied. The median survival of cancer patients was 302 days (187–531). Soluble TNF RI was elevated in 68% of patients whilst IL-2 sRα, IL-6 and CRP were increased in half of the patients. Liver metastasis volume correlated with IL-2 sRα ($r=0.33$, $P=0.01$) and with CRP ($r=0.43$, $P=0.01$). There was a negative correlation between patients' survival and IL-2 sRα level ($n=43$, $r=-0.51$, $P=0.0005$).

The level of DR^+ T cells was significantly higher in cancer patients ($n=46$; median 21.1%) than control subjects ($n=23$; median 3.4%; $P<0.0001$). CMI was measured in 17 patients of whom 15 (88%) were negative compared with positive reactions in all five control subjects ($P=0.002$). In 15 patients who had both variables measured, 12 showed no CMI reaction when DR^+ T cell levels were elevated compared with 2 patients who had positive reactions and normal levels of DR^+ T cells ($P=0.05$).
Discussion: In advanced colorectal cancer there is upregulation of immunological cytokines and T cells that correlates with greater disease burden, reduced survival, and is associated with decreased cell-mediated immunity. This suggests that incomplete T cell activation results in T cell anergy in patients with advanced colorectal cancer.

22. An *in vivo* study of two new photosensitizers following interstitial photodynamic therapy of the liver

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Introduction: Photodynamic therapy (PDT) uses visible light and a tumour localizing photosensitizer to destroy cancer tissue. We have assessed two new photosensitizers, Temoporfin and a newer compound meta-hydroxyphenyl bacteriochlorin (*m*THBC), *in vivo* to assess biological activity.
Methods: *m*THBC was injected intravenously at doses of 0.15, 0.3, 0.6, and 1.2 mg/kg into two groups of two adult large white pigs. Temoporfin was also given at the current recommended dose of 0.15 mg/kg. Interstitial PDT of the liver was performed 24 hours later. Six sites were irradiated at 740 nm or 652 nm at a light dose of 2–100 Joules/cm using a 2 cm cylindrical light diffuser at a power of 200 mW/cm. The treated areas were assessed at 48 hours after irradiation by macroscopic assessment.
Results: The volume of necrosis produced by *m*THBC was capable of producing lesions of 10.7 cm^3 (95% CIs 8.5–13.0) with a interstitial application of light. This was significantly more than the volume of necrosis of 1.8 cm^3 (95% CIs of 1.2 to 2.4) achieved with Temoporfin. The depth and volume of liver necrosis waas dependent upon both the *m*THBC dose and the light dose employed. A strong positive correlation between the extent of necrosis and the log of the light dose was observed.
Conclusion: *m*THBC is significantly more effective than Temoporfin for interstitial PDT of the liver and represents the first demonstration of clinically useful volumes of liver necrosis produced by photodynamic therapy applied using light from a single optical fibre.

23. The glutathione depleting agent BSO radiosensitizes cholangiocarcinoma cells to apoptosis

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Introduction: Cholangiocarcinoma is resistant to the apoptosis inducing effects of radiotherapy and chemotherapy. Glutathione, an important antioxidant and detoxifying molecule within the biliary tree, is produced in the liver and secreted in high concentrations into the biliary tree (8–10 mM). This tripeptide has been found to inhibit apoptosis in certain cell types through a mechanism that would appear to involve redox dependent changes in the response of the mitochondrial permeability transition pore complex (MPTC) following chemotherapy and radiotherapy.

The aim of this study was to investigate the effect of GSH levels (redox state) had on apoptosis threshold in human cholangiocarcinoma cells.
Methods: All experiments were carried out *in vitro* and monitored over 48–62 hours:

(1) Human CCA cell lines Tfk-1 and Egi-1;
(2) GSH depleting agent Buthionine sulphoximine (BSO);
(3) UV and X-ray irradiation (500–1000 cGy);
(4) Antioxidant N-Acteylcystine (NAC).

Apoptosis was analysed at single cell resolution using loss of the mitochondrial transmembrane potential ΔΨm) measured using the potentiometric dye $DiOC6_{(3)}$ in conjunction with propidium iodide (PI); this was confirmed using the caspase dependent Annexin V assay.
Results: Depleting cholangiocarcinoma cells of glutathione using BSO was found to sensitize CCA cells in both a time and dose dependent manner, to the apoptosis inducing effects of both UV and X-ray radiation therapy *in vitro*. In the presence of the GSH replenishing agent NAC the apoptosis facilitating effects of BSO on CCA was blocked. BSO alone over a 96 hour period possessed no intrinsic cytotoxic properties on CCA cells.
Conclusion: The results show that CCA cell apoptosis is partly controlled by the redox state within the cells, and suggests that the high levels of GSH found in the biliary tree may contribute to the low efficacy of radiotherapy in the treatment of this disease. Altering the levels of reduced glutathione within the bile tree may be one way of improving the response of cholangiocarcinoma to radiotherapy.

24. Electrolytic liver ablation: the effect of intermittent Pringle manoeuvre

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Introduction: We have developed a system of electrolysis using direct current (DC) to ablate liver and produce localized necrosis. The aim of this study was to investigate the effects of intermittent ischaemia on the size of electrolytically induced areas of hepatic necrosis.
Methods: Forty domestic white pigs were divided into two groups including two controls in each group. Paired experiments were performed. The liver was exposed through an upper midline incision under general anaesthesia, two electrode catheters were inserted into the right lobe. Increasing doses of DC were applied (100–1000 Coulombs). One group underwent electrolysis alone and the other concurrent intermittent Pringle manoeuvre. The pigs were sacrificed on the fourth post-operative day, the livers harvested and the electrolytic lesion measured. The volume of each lesion was calculated. Results were analysed using regression analysis and the unpaired *t*-test.
Results: There was a linear dose–response relationship between the volume of hepatic necrosis and the electrolytic dose in both groups ($P<0.005$ in both groups). There was a significant difference between the dose–response curves ($P<0.0000002$) with larger volumes of necrosis in the Pringle group (6.17 cm^3/100 Coulombs) compared with electrolysis alone (3.8 cm^3/100 Coulombs).
Conclusion: Electrolytic liver destruction is predictable and occurs in a dose dependent fashion. Concurrent intermittent Pringle manoeuvre significantly increases the volume of necrosis.

25. Expression of endothelin receptors in human colorectal liver metastases

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Introduction: Endothelin-1 (ET-1) is a vasoactive peptide that acts via two receptors ET_A and ET_B. ET-1 has known mitogenic effects on a variety of cell types including cancer cells. ET_A receptor expression is upregulated in a variety of cancer cell lines and in human colorectal cancer. The aim of this study was to assess whether ET receptors are expressed in human colorectal liver metastases.
Methods: Radiolabelled ET-1 and receptor antagonists for ET_A and ET_B were applied to sections from three normal livers and 12 liver metastases. Binding was localized using gross and high-resolution autoradiography. Concurrent immunohistochemistry was carried out on liver metastases ($n=6$), using platelet endothelial cell adhesion molecule-1 (PECAM) to identify endothelial cells.

Results: Liver metastases expressed discrete zones of increased ET-1 binding sites compared to normal livers. These zones corresponded to the areas of ET_A, and not ET_B expression. ET_A co-localized to sites of high PECAM uptake.
Conclusion: ETA receptors are upregulated in colorectal liver metastases. These receptors are localized to the endothelial cells within the tumours. The differential expression of T_A receptors provides a potential therapeutic target for colorectal liver metastases.

26. Loss of taste and smell after upper gastro-intestinal surgery

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Introduction: Patients undergoing upper gastro-intestinal cancer surgery have been noted to suffer loss of taste and/or smell, a problem not previously reported. The aim of this study was to investigate the extent of this phenomenon, quantify recovery time and identify potentially associated factors.
Methods: We carried out a retrospective analysis via a postal questionnaire to all patients still alive who have undergone oesophagectomy or gastrectomy, with a minimum of 1 year's follow-up and no clinical or radiological evidence of recurrent disease; the principle exclusion was abnormal taste/smell prior to surgery. Data were analysed for prevalence of sensory deficit in relation to surgical procedure, age, sex, respiratory complications and stage of disease.
Results: One hundred and nineteen patients were sent the questionnaire: 50 gastrectomies and 69 oesophagectomies; 109 patients replied (return rate of 92%) of whom 10 were excluded. Overall 45 patients (45%) suffered loss of taste and/or smell (M:F = 1.6:1), and no association was found with type of surgery performed: rates of loss for subtotal gastrectomy, total gastrectomy and oesophagectomy were 44%, 46% and 46% respectively ($\chi^2 = 0.355$, 2df. $P > 0.5$); no other parameter was found to be associated with sensory deficit, and full recovery occurred in 30 patients (67%) in a mean of 6 months.
Conclusion: Loss of taste and smell is a significant problem following upper gastro-intestinal surgery, occurring in nearly half of all cases, but the reason for this deficit remains unexplained. A prospective study is now being undertaken in this unit in order to confirm these findings, investigate possible cause, and provide adequate pre-operative information to patients, thereby enhancing the principle of informed consent.

PLENARY SESSION I—RAVEN PRIZE

27. Surgery for breast cancer—no wound drains and early discharge—a randomized clinical trial

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Introduction: Following surgical treatment for breast cancer, standard practice involves insertion of suction drains with the purpose of reducing seroma formation. An alternative surgical approach consists of suturing skin flaps to underlying muscle, thereby potentially avoiding wound drains altogether. The aim of the study was to assess the physical and psychological impact of adopting a 'no-drainage', early discharge policy (within 48 hours post-operatively), within a randomized clinical trial.
Methods: Between March 1997 and December 1998, following written informed consent, 375 patients were randomized into the study as follows:

Group A (96): mastectomy and axillary clearance/conventional wound drainage/discharge home on drain removal (control).
Group A1: (94): mastectomy and axillary clearance/suturing of flaps/no drains/early discharge (study).
Group B (94): wide local excision and axillary clearance/conventional wound drainage/discharge home on drain removal (control).
Group B1 (91): wide local excision and axillary clearance/suturing of flaps/no drains/early discharge (study).

The following outcome measures were assessed: length of hospital stay, incidence of seroma, wound infection, shoulder mobility, health economics, psychological morbidity. Analysis was performed on an 'intention to treat' basis.
Results: There was a highly significant difference in the post-operative length of stay between the 'no-drain' *vs* the 'drain' groups (2.75 days *vs* 4.23 days, $P = 0.000$). There was no difference in the incidence of seroma formation or volume of fluid aspirated between these groups. Similarly, there was no difference in wound sepsis rates, shoulder morbidity, hospital and community resource use and psychological morbidity between the control and study arms.
Conclusion: Suturing of flaps and avoiding wound drains in surgery for primary breast cancer is a safe technique and results in a significant reduction in hospital stay facilitating early discharge, with no impact on physical or psychological morbidity and no increase in community care costs.

28. Systematic review of the methodological quality of randomized controlled trials of the surgical excision of cancer

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Introduction: Randomized controlled trials (RCT) in which patients are allocated to alternative treatment regimes are recognized as Level I evidence and frequently quoted aas the 'gold standard' in medical research. Flaws in the design and conduction of such RCTs hinders their interpretation. The aim of this study was to investigate the quality of trial design in RCT on oncological surgical techniques.
Methods: RCTs published between January 1980 and December 1999 comparing surgical oncological procedures were identified from Medline, Embase and the Cochrane Collaboration database using the parameters, 'randomized', 'controlled trial', 'surgery' and 'cancer'. The reference lists of identified papers were scanned for other suitable studies. The methodology of each published paper was evaluated by two independent observers using a modification of a previously published assessment form. Eleven questions were asked to each paper, concentrating on the aim, control group, patient selection and randomization process, the demonstration of baseline equivalence, the definition and unbiased assessment of endpoints, a clear description of the operative procedure, adequate follow-up and appropriate statistical analysis. A paper scored 0 if the criterion was not mentioned, 1 if mentioned but inadequate or 2 if the criterion was adequately reported. Individual trials scored between 0 and 22. Trials scoring <16 were regarded as methodologically unsound. Trials scoring >16 were then subjected to a more detailed review of the statistical method. This concentrated on the choice and correct use of the statistical test, the consideration of prognostic factors, clear presentation of graphs and tables, and sufficient presentation of statistical results.
Results: Fifty-seven per cent of RCT comparing surgical oncological techniques scored <16. One third of the methodologically sound trials then passed statistical review, one third failed and one third were deemed recoverable from the published results if the statistics were to be reworked.
Conclusion: These results demonstrate that the methodology of over half the RCTs in surgical oncological techniques was either inadequate or poorly reported. The statistical analysis of methodologically competent trials was frequently inappropriate or inadequate. Defects in the initial design and interpretation of surgical trials compromises any conclusions that can be drawn from their results. Evidence based surgery requires 'best evidence', RCTs in the future must be methodologically sound, clearly reported and the results analysed correctly.

29. Patient education as part of a multi-faceted strategy increases the detection of curable oesophago-gastric cancer

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Introduction: Survival from oesophago-gastric cancer is mainly determined by stage at diagnosis, and most patients present with incurable disease. We hypothesized that greater public awareness of potential cancer symptoms might improve early detection. We therefore studied the effect on stage distribution and resection rate of an intervention based on educational letters about cancer symptoms.

Methods: All patients over 40 in 12 GP practices ($n=37\,000$ app) were sent an annual letter for 3 consecutive years, asking them to report new dyspepsia or dysphagia symptoms. GPs were encouraged to refer these patients directly for gastroscopy. A control group ($n=75\,000$ app), matched for social class and age, received no education. Cancer incidence, stage and resectability were estimated from cancer registry and hospital records. Follow-up was continued for 6 years.
Results: Ninety-three cancers were detected in the study group, and 200 in the control group. Twenty-four (26%) study and 30 (15%) control patients had UICC stage I–IIIA disease ($\chi^2=2.77$, $P<0.01$).
Conclusion: Education of the public and involvement of the GP are associated with a 73% increase in potentially curable cases of oesophago-gastric cancer. This approach merits further large-scale study.

30. Monitoring of minimal residual disease (MRD) during adjuvant therapy in breast cancer

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Introduction: The majority of primary breast cancer patients receive endocrine and/or cytotoxic chemotherapy as adjuvant treatment. Only a proportion of patients benefit, and therefore many experience treatment-related side effects for little benefit. If a monitoring system could be developed, alternative therapies could be given to non-responding patients. We have developed a quantitative polymerase chain reaction (QPCR) for the detection of micrometastases using cytokeratin 19 (CK19) transcripts in bone marrow from primary breast cancer patients and compared this to immunocytochemical (ICC) techniques. The aim of this study was to determine the effects of adjuvant therapy on MRD following surgery for primary breast cancer and evaluate these assays in monitoring micrometastases.
Methods: Bone marrow aspirates were taken at the time of surgery from 96 patients with primary breast cancer and tested for the presence of cytokeratin positive cells by ICC and QPCR. Single aspirates were taken at follow-up at 3, 6 and 12 months post-surgery. Patients received standard adjuvant treatments in accordance with accepted protocols or entered ethically approved clinical trials.
Results:

Method	At surgery	3 months	6 months	12 months
QPCR	53/96 (55%)	19/64 (30%)	11/49 (22%)	22/36 (61%)
ICC	26/79 (33%)	9/61 (16%)	9/49 (18%)	18/36 (50%)
Both	23%	10%	3%	31%

A decrease in percentage positive was evident at 3 and 6 months, however, after 12 months the percentage of MRD positive patients had increased significantly using QPCR ($P=0.002\,3$ *vs* 12 month, $P=0.049\,6$ *vs* 12 month). Of the patients with 12 month samples, those negative for the first 1–3 aspirates, and subsequently positive by QPCR and ICC, were 29% and 26% respectively. Patients positive for the first 1–2 aspirates and subsequently negative represent 11% and 15% respectively. There was no apparent correlation between the QPCR and ICC results with the nodal or T status. No patients to date have relapsed with overt metastases.
Conclusion: It is possible to monitor patients post surgery using QPCR. These preliminary results indicate that between 11–15% of patients may be responding to adjuvant therapy. At 6–12 months nearly one third of patients with primary breast cancer are demonstrating the emergence of minimal residual disease (MRD) despite adjuvant therapy. These patients can be considered candidates for further adjuvant therapy, but longer follow-up is required.

31. Antioxidants enhance susceptibility to 5-FU toxicity in colon cancer cells *in vitro*

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Introduction: Most chemotherapeutic agents act partly by inducing apoptosis in cancer cells. 5-FU chemotherapy is vital in colorectal cancer management because most are advanced at diagnosis. Intracellular oxidants are carcinogenic, signal transducers in transformed cells, and induce apoptosis. Intracellular oxidant level flux in either direction also modulates response to apoptotic stimuli. Recently antioxidants have been reported to induce apoptosis, as well as augment chemotherapeutic drug induced apoptotis in colon cancer cells *in vitro.* We therefore hypothesized that antioxidants induce susceptibility to non-toxic doses of 5-FU.
Aim: To evaluate the effect of antioxidants on 5-FU induced apoptosis on colon cancer cells *in vitro.*
Methods: Colo 201 and Colo 205 cells were cultured in medium alone, with vitamin E, N acetyl cysteine or 5-FU alone and combinations of NAC or vitamin E & 5-FU. At 72 hours, the cells were harvested, washed, fixed in 70% ethanol for 45 min and incubated for 30 min in 500 µl RNAse (1 mg/ml), 250 µl propidium iodide (100 µg/ml) and 250 µl PBS. The cells were washed, resuspended in PBS and 5×10^3 cells per sample analysed by FACSCAN. The hypoploid (sub-G_0-apoptotic) events were then counted. Concentrations used: 5-FU 0.1 µM for Colo 201, 1 µM for Colo 205, NAC −25 mM, vitamin E −5 mM.
Results:

	Con.	5-FU	NAC	Vit. E	BAC + 5-FU	Vit. E + 5-FU
Colo 201	7 (4)	4 (2)	5 (1)	7 (1)	45 (4)	60 (11)
Colo 205	2 (1)	3 (0.3)	3 (1)	4 (2)	58 (10)	48 (12)

Percentage apoptotic cells detected by FACSCAN following PI staining. $n=3$. Std dev. = ( ).

Conclusion: In this study, antioxidants induced susceptibility to a nontoxic dose of 5-FU. Antioxidants alone did not have this effect. Pro-apoptotic Bax expression is also upregulated (data not shown). Although the exact mechanism of this effect is not known, modulation of one or more of the biochemical reactions of the apoptotic cascade by a reduction of intracellular oxidant metabolites may enhance response to 5-FU. Intracellular oxidants play a significant role in transformed cell metabolism including signal transduction, oncogene and oncoproteins activation. Intracellular redox alteration can inhibit or enhance response to apoptotic stimuli and the net effect on cell survival may be cell or stimulus-dependent. If reproduced *in vivo*, antioxidants may improve response to chemotherapeutic drug induced apoptotis, or reduce effective doses and perhaps side effects.

32. bFGF infusion increases 5 fluorouracil uptake in a model of established colorectal liver metastases

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Introduction: The uptake of cytotoxic drugs in solid tumours is governed by several factors including the extent of vascularity in the centre of the tumours. The response of colorectal liver metastases to chemotherapy is inadequate due to poor drug penetration to these regions. We investigate the effect of bFGF infusion on the vascularity, blood flow and uptake of 5-FU in a model of colorectal liver metastases.
Methods: Hepatic metastases were created by mesenteric inoculation of 1×10^3 HSN cells in anaesthetised CBH rats. On day 4 post-inoculation animals were re-anaesthetised and systemic bFGF infusion commenced. Control animals received saline. On day 18 the gastroduodenal artery was cannulated under anaesthetic and animals received either 1 µCi IAP or a 5 min infusion of 0.32 µCi/µl 5-FU. Animals were immediately sacrificed and livers excised and snap-frozen. Contiguous tumour sections were stained with O 48 anti-endothelial antibody for vascularity assessment (vessel count, vessel volume and vessel length density) and set up for IAP or 5-FU autoradiography over 21 days (blood flow and drug uptake assessment respectively). Blood flow and 5-FU uptake were expressed as the ratio of IAP or 5-FU between tumour and tumour edge.
Results: There were significant increases in vessel count (75.8 [57.9–97.4] *vs* 9.35 [5.83–21.6]/mm^2; $P<0.0001$†), vessel volume (7 [5.1–8.6] *vs* 1 [0.7–2.6]%; $P<0.0001$†) and vessel length density ($P<0.0001$‡) in bFGF-infused tumours as compared to saline. The vascularity changes were associated with a significant increase in blood flow at 0.5, 1.5, 2 and 2.5 mm from the tumour edge ($P<0.0001$‡) in bFGF animals. The enhanced blood flow also corresponded to a significant increase in 5-FU uptake at 0.5, 1.5 and 2 mm from the tumour edge ($P<0.0001$‡) in bFGF-infused animals. (†: Median [IQR]; Mann–Whitney *U*-test. ‡: Repeated Measures ANOVA).
Conclusion: bFGF infusion enhances vascularity, blood flow and chemotherapeutic drug uptake in established experimental liver metastases. This increase in concentration of drug in the centre of the tumour may lead to a greater cytotoxic effect.

(bFGF: basic fibroblast growth factor; 5-FU: 5 fluorouracil; HSN: hooded sarcoma-N; CBH: Chester Beatty hooded; IAP: iodoantipyrine).

33. Axillary node staging in the Trent Breast Screening Programme 1996–99: audit of surgeons' protocols and practice

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Introduction: The National Breast Screening Programme (NBSP) requires surgeons to perform staging of the axilla by removing at least four axillary nodes. We undertook a survey of surgeons' management of the axilla and audited their practice, between 1996 and 1999, in relation to their own protocols and the guidelines of the NBSP.
Method: Surgeons involved in the National Breast Screening Programme in Trent were sent a questionnaire regarding their management of the axilla in screen detected invasive cancers. The surgical options included four-node sampling, level 1, level 2 and level 3 axillary node clearance, and other. Surgical case notes were reviewed for the audit of axillary node surgery between 1996 and 1999.
Results: Of the 20 surgeons involved in breast screening in Trent, 19 responded to the questionnaire. Eleven surgeons routinely perform a four-node sample, five a level 1 clearance and three a level 3 clearance. A total of 1330 invasive cancers were diagnosed in the region between 1996 and 1999. The number of patients found to have had <four nodes harvested, in each surgical group, are given in the table.

Procedure	No. of surgeons	Total no. of patients	No. of cases with <4 nodes taken
4 node sample	11	700	196 (28%)
Level 1 clearance	5	476	26 (5.5%)*
Level 3 clearance	3	154	5 (3.2%)*

* Chi-squared analysis: $P<0.001$.

Surgeons performing four-node sampling did show a year-on-year improvement in the proportion of cases with >4 nodes retrieved.
Conclusion: The most commonly performed procedure in Trent is four-node sampling which is associated with the highest rate of failure to adequately stage the axilla. By contrast, axillary node clearance achieves accurate staging, but is recognized to carry an increased morbidity.

34. Outcome of local recurrence following sarcoma surgery

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Introduction: Local recurrence following treatment of a sarcoma is generally accepted to be a poor prognostic sign and an indicator both of inadequate local control and of the failure of adjuvant treatment. Little information is available about the outcome of patients with local recurrence following sarcoma surgery.
Method: Of 2589 patients with non-metastatic Ewings, osteosarcoma, chondrosarcoma or a soft tissue sarcoma, 316 have developed local recurrence at some stage following initial treatment of their tumour. One hundred and twenty were already known to have metastases elsewhere when they developed LR or were found to have them at time of restaging but 196 developed LR as the first sign of relapse.
Results: The mean time to development of LR was 24 months but was somewhat less in osteosarcoma and Ewings (both 18 months), but greater in chondrosarcoma (31 months). Thirty-nine per cent of all LRs arose in the first year after treatment whilst 72% had arisen within the first 2 years. LR arising for the first time more than 5 years after original treatment only occurred in low grade tumours (chondrosarcoma, parosteal osteosarcoma and low grade STS). Overall survival following LR was 25% at 5 years and 20% at 10 years. In patients with metastases at the time of LR or who were found to have them at the time of restaging the median survival was 6 months with only 12% being alive at 2 years. In those with LR as first sign of relapse median survival was 3 years with 30% long-term survivors. Patients with low grade tumours had a better outcome than those with high grade—50% being cured by further surgery. Of the high-grade tumours without metastases at time of diagnosis, relapsed Ewing's had the worst prognosis with median survival of 8 months compared with 22 months for osteosarcoma, 36 months for STS and 36 months for chondrosarcoma, despite which overall survival was 16% for both Ewing's and osteosarcoma patients but was 30% for chondrosarcoma and STS.
Conclusion: Local recurrence following sarcoma surgery and a combination of aggressive disease with inadequate surgery and by metastatic disease. The prognosis is dismal for patients with synchronous metastases but for patients with LR alone the outlook is similar to that for patients with solitary metastases and warrants aggressive further treatment.

PLENARY SESSION III—ALAN EDWARDS PRIZE

35. Magnetic resonance imaging as an adjunct to triple assessment in equivocal breast disease

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Introduction: The aims of this study were (1) to evaluate the role of MRI in a selected subset of patient with breast disease who present diagnostic challenges in clinical practice because of non-concordance between the components of triple assessment; (2) to evaluate whether MRI confers advantages in determining the extent of malignancy within the breast.
Methods: T2 weighted turbo spin echo plus 2D gradient echo dynamic breast scanning with Gadolinium was performed on 137 patients for the following indications:

(1) diagnostic uncertainty following triple assessment;
(2) determination of extent of probable multicentric disease;
(3) assessment of primary distortion of breast or of post-operative scarring;
(4) elucidation of primary carcinoma in axillary lymphadenopathy;
(5) assessment of lumps in patients with breast implants;
(6) monitoring response to neoadjuvant chemotherapy.

Results:

Parameter	Mammography	Ultrasound	MRI
Sensitivity (%)	75.4	82	100
Specificity (%)	90.7	89.7	96.1

The sensitivity of mammography and ultrasound was understandably low reflecting the cohort selected. MRI accurately identified tumour in five patients where both mammograms as well as ultrasound were normal/benign. These included three patients with invasive lobular cancers where the clinical presentation was distortion without a focal palpable abnormality. In 14 cases MRI provided additional information about the extent of tumour including seven patients with unsuspected multicentric or contralateral cancers that potentially had an impact on surgical decision making.
Conclusions: MRI has a higher sensitivity and specificity as compared to conventional imaging and is a very useful adjunct to triple assessment in the diagnosis of difficult breast lesions. By accurately assessing the size of primary tumours and extent of multicentric disease it also provides valuable information for preoperative planning and single stage resection in breast cancer, especially invasive lobular cancers.

36. PK11195, a mitochondrial benzodiazepine receptor antagonist radiosensitizes Bcl-X_L and Mcl-1 expressing human cholangiocarcinoma to apoptosis

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Introduction: Inoperable cholangiocarcinoma (CCA) responds poorly to chemotherapy and radiotherapy. DNA damage with the induction of

apoptosis following chemotherapy and radiotherapy plays a major part in the mode of action of these forms of cancer treatment. The mitochondria have emerged as key players in apoptosis. Members of the bcl-2 family of apoptosis regulating proteins that localize to the mitochondria play an important role in apoptosis through regulating the release of cytochrome c from the intermembrane space. High levels of bcl-x_L and mcl-1 proteins are localized to mitochondria in cholangiocarcinoma, but their role in the control of apoptosis in this disease remains unknown. The aim of the study was to investigate if these mitochondrial proteins block apoptosis in CCA cells.
Methods: We used Pk11195, a mitochondrial benzodiazepine receptor antagonist that is known to block the cytoprotective effects of bcl-2 like proteins. We investigated the role the highly expressed mitochondrial bcl-x_L and mcl-1 proteins in Egi-1 and Tfk-1 (two human cholangiocarcinoma cell lines) played in radioresistance of cholangiocarcinoma, by studying the effects blocking mitochondrial bcl-x_L and mcl-1 with Pk11195 had on the response of Tfk-1 and Egi-1 to UV irradiation and 50–1000 cGy of radiotherapy over 72 hours. Apoptosis was monitored through measuring the collapse in the inner-mitochondrial membrane potential ($\Delta\Psi_m$) detected at single cell resolution by flow cytometry using the $\Delta\Psi_m$ sensitive lipophilic flourochrome $DiOC6_{(3)}$ and by the caspase dependent annexin V assay.
Results: We found that inhibiting mitochondrial bcl-x_L and mcl-1 in cholangiocarcinoma cells sensitizes (three-fold, $P<0.05$) cholangiocarcinoma cells to UV light and radiotherapy induced apoptosis an effect that was both dose and time dependent. Pk11195 alone had no intrinsic apoptosis inducing effects over 96 hours on either cell line.
Conclusion: Antagonizing the function of the anti-apoptotic bcl-2 proteins at the mitochondria sensitizes cholangiocarcinoma cells to radiotherapy. Expression of these proteins in this disease may explain the low efficacy of radiotherapy in this disease.

37. Changed pattern and incidence of first site recurrences following sentinel node procedure in melanoma patients

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Introduction: According to literature before the SN era, the average incidence of developing recurrences during follow-up in melanoma patients is about 40%. The regional lymph node basin is the most common first site, followed by cutaneous loco-regional and distant metastases. Approximately 75% of regional lymphatic basin recurrences manifest within the first 2 years following the initial diagnosis. The aim of this study is to determine the influence of the SN procedure in melanoma patients on the first site of recurrence after follow-up of at least 2 years.
Methods: From 1993–1998 we performed a triple technique SN procedure ((dynamic) lymphoscintigraphy, Patent Blue V® and a gamma probe) in 289 melanoma patients. Breslow thickness varied from 0.5–9.0 mm. The harvested lymph nodes were step-sectioned and examined by routine haematoxylin/eosin and immunohistochemical staining. If the SN contained tumour cells, a lymphadenectomy was performed at a later date.
Results: In 54 patients (19%), the SN(s) appeared to be histologically positive. The median follow-up was 44 months (range 24–77). So far, in total 50 patients (17%) developed a recurrence of the disease. The distribution of localization of the first site metastases was as followed: cutaneous loco-regional recurrence in 26 patients (52%), systemic metastases in 18 patients (36%), recurrence in the regional lymph node basin in four patients (8%) and two patients developed (4%) a metastasis in an extraregional lymph node station. Of the patients with a positive SN 44% developed a recurrence and with a negative SN 11% (chi-squared test; $P=4.2$ E-9).
Conclusions: The SN procedure changes the pattern of recurrence due to the infrequency of appearance of regional lymph node recurrences during follow-up after an SN biopsy.

The lymph node status is still one of the most important prognostic parameters: patients with a positive SN do have an increased risk to develop loco-regional and distant metastases.

38. Angiogenesis in ductal carcinoma *in situ* (DCIS) of the breast and its relationship to the risk of recurrence

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Introduction: This study identifies vascular changes associated with the risk of recurrence in DCIS.
Methods: Three groups of DCIS were identified—(1) DCIS which did not recur; (2) DCIS with *in-situ* recurrences; (3) DCIS which recurred as invasive carcinoma. Periductal vascular density was determined using morphometry and anti-CD34 antibodies. For each section, the entire number of stained vessels within 100 μm of foci of DCIS were counted. Up to 50 foci of DCIS on a single slide were scored and the microvessel density (MVD) was calculated for each focus. Normal lobules at least 2 mm away were used as controls. Vascular density was related to the risk of either invasive or *in-situ* recurrence.
Results: Periductal vascular density increased significantly from DCIS which did not recur through DCIS with *in-situ* recurrences, to DCIS which recurred as invasive carcinoma. There was no significant difference in MVD among the normal lobules in these groups.

		Mean MVD (mm^{-2})
Normal lobules	non-recurrence	80
Normal lobules	*in-situ* recurrence	79
Normal lobules	invasive recurrence	79
DCIS	non-recurrence	95
DCIS	*in-situ* recurrence	119
DCIS	invasive recurrence	126

Conclusion: This study shows that increases in periductal vascular density, as detected with the CD34 antibody, correlates with recurrence, either as *in-situ* or invasive carcinoma.

39. Anorectal irradiation in pelvic radiotherapy: an assessment using *in-vivo* dosimetry

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Introduction: Radiation damage to the anorectal region following pelvic radiotherapy causes severe morbidity. Functional and structural changes in the anorectum, in relation to the site and dose of pelvic radiation received, have not been fully investigated. We planned to measure radiation doses received by the anorectum during pelvic radiotherapy using *in-vivo* techniques and compare these with doses predicted by a GE *TARGET*™ treatment planning system.
Methods: Nine patients with cancers of the prostate, bladder, cervix and uterus were CT planned using the *TARGET*™ system. A Scanditronix rectal probe containing five n-type photon-detecting diodes was placed in the anorectum during the planning CT. The probe position was standardised with the five diodes at 2 cm intervals from the anal verge. The probe diodes were calibrated for 10 MV photons. Doses were measured for each diode on two consecutive fractions in the first four patients and on five consecutive fractions in the remaining five. Thermo-luminescent dosemeters (TLDs) were used initially to verify diode doses. *TARGET*™ and diode measured doses were compared.
Results: In all patients, diodes situated in the target volume were within 7% of predicted doses. This improved to 2.5% after measurement on five fractions. At the edges of the target volume wide variability existed between measured and predicted doses. (Measured dose range −68% to +54% of predicted dose). Outside the target volume considerable doses (up to 30 cGy per fraction) were measured in the anal canal, which were not predicted by *TARGET*™.
Conclusion: *TARGET*™ planned doses are accurate within the confines of the target volume. Greatest variability was seen at the edges of the target volume where dose can vary by 50% across a 1 cm distance in the anterior/posterior plane. *TARGET*™ does not account for scattered dose beyond the field edges and therefore underestimates the anal dose.

40. Pathological response of breast cancers to primary docetaxel is predicted by HER-2 and ER status

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Introduction: Expression of the growth factor receptor Her-2 has been shown to predict susceptibility of breast cancers to doxorubicin and resistance to cyclophosphamide therapy. Docetaxel is increasingly being used to improve response rates. This study correlated Her-2, ER and PR expression with pathological response to primary docetaxel therapy.
Methods: Core biopsy specimens were taken from 35 patients prior to receiving primary docetaxel. Tumours were typed and graded and immunohistochemistry for Her-2, ER and PR protein expression was

performed. Operative specimens following completion of chemotherapy were assessed to determine pathological response.
Results: Univariate analysis revealed that ER negativity ($P=0.023$) and Her-2 positivity ($P=0.023$) differentiated patients with a complete pathological response. Multivariate analysis revealed that Her-2 positivity ($P=0.045$) and ER negativity ($P=0.010$) independently predict which tumours will undergo a complete pathological response to docetaxel.
Discussion: Breast cancers that express Her-2 oncoprotein and/or are oestrogen receptor negative can be identified as most likely to achieve a complete pathological response to primary docetaxel.

41. Thrombin regulation of vascular endothelial growth factor (VEGF) and tissue factor (TF) in human breast cancer cells

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Introduction: Thrombin, the key enzyme in normal haemostasis, has multiple actions of its protease activity. Thrombin receptors are expressed on human colonic and pancreatic adenocarcinoma cells and melanoma cells. Thrombin is mitogenic for human breast carcinoma cells in culture, and it enhances tumour cell adhesion to the endothelium and extracellular matrix and is able to promote tumour cell metastasis. These findings suggest that thrombin plays an important role in tumour cell biology, although its mechanism of action is still unclear. The aim of the current study was to examine the effect of thrombin on vascular endothelial growth factor (VEGF) and tissue factor (F) expression in human breast cancer cell T47D.
Methods: The human breast carcinoma cell T47D, which expresses progesterone receptor strongly, was stimulated with human α-thrombin in doses from 0.01 to 10 unit/ml. Conditioned media was collected at various time points. VEGF and TF levels were determined by standard ELISAs. RT-PCR was used to examine the effect of thrombin stimulation on transcriptional gene expression for VEGF and TF.
Results: Thrombin stimulation enhanced VEGF release in a dose dependent fashion from 311 pg/ml to 809 pg/ml at 1 unit/ml at 24 hours ($P=0.013$); the effect was lost at higher doses. It resulted in an increase of TF release from 273 pg/ml to 515 pg/ml at 0.01 unit/ml but in a shorter time frame of 30 min ($P=0.005$). RT-PCR showed that thrombin stimulation up-regulates the gene transcription of TF but not that of VEGF gene.
Conclusion: These data indicate that thrombin stimulation has a stimulatory effect on VEGF and TF release from T47D breast cancer cells and may explain a potential proangiogenic mechanism.

42. Endoscopic assisted intrathoracic oesophagogastrectomy without thoracotomy for tumours of the lower oesophagus and cardia

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Introduction: Some patients with oesophageal tumours would not tolerate a thoracotomy. The aim of this study was to evaluate the efficacy of novel technique that enables a transhiatal oesophagectomy with intrathoracic anastomosis under direct vision, without the need to perform a thoracotomy.
Methods: The transhiatal dissection of the oesophagus was performed using a combination of direct and laparoscopic visualization. The oesophagus was transected above the tumour with a linear endo-GIA-60mm stapler (Autosuture UK). The stomach was transected and a gastric tube fahioned. The anvil of an appropriately sized CEEA circular stapler (Autosuture UK) was modified enabling it to flatten. It was attached to a novel delivery system introduced under direct vision along a guidewire into the stapled oesophagus. The anvil was realigned to its original position in the distal oesophagus, docked with the body of the stapler and an intrathoracic anastomosis performed.
Results: Ten patients (female $n=3$, male $n=7$) age range 39–77 (mean 65 years) were treated. All patients had distal third tumours (gastro-oesophageal junction $n=6$, true oesophageal $n=4$). Five patients had an ASA grade of 3, the other five had an ASA grade of 2. The duration of procedure ranged between 2 and 5 hours (mean of 4 hours). Blood loss ranged between 80 and 500 mls (mean 200 mls). One patient suffered two post-operative complications: chest infection and an anastomotic leak treated successfully with a covered self-expanding metal stent. Length of stay ranged between 6 and 28 days (mean 17 days). There was no mortality.
Conclusion: This technique allows a safe intrathoracic anastomosis to be performed trans-hiatally, under direct vision, and avoids the need for one lung anaesthesia and thoracotomy. This technique may permit resection in a cohort of patients previously unresectable because of significant cardiorespiratory disease.

PARALLEL SESSION IV—BREAST ORAL POSTERS

43. The effect of the 2 week rule on providers, users and cancers

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Introduction: Hospitals and general practitioners (GPs) have had to adapt their practices following the introduction of the 2-week directive in April 1999 for urgent breast referrals. The aim of this study was to assess the influence of these changes on providers, users and cancer referral patterns.
Methods: Clinic data is routinely collected prospectively and was complemented by a questionnaire study involving GPs and patients.
Results:

GP Questionnaire $n=47$

Effect of the directive on	Good	Reasonable	Mediocre	Poor
urgent referrals	60%	38%		2%
routine referrals	36%	49%	7%	8%

	Yes	No	Don't know
Are patients aware of the 2-week directive?	15%	55%	30%
Pressured into giving urgent appointment?	26%	72%	2%

Patient Questionnaire $n=38$

	Yes	No
Are you aware of the 2-week rule	39%	61%
Did you ask for a quick appointment?	18%	82%
Did you think your appointment was?	Too long	Just right
urgent referrals	17%	83%
routine referrals	50%	50%

One thousand and one (41%) of all referrals occurred in women <40. Three hundred and twenty-one of these were referred urgently, yet this age group accounted for only 10 (5%) cancers. Nine hundred and eighty-four (40%) were aged 40–60, 403 were referred urgently producing 58 (30%) cancers. Four hundred and seventy-three (19%) were >60, 232 were referred urgently, accounting for 128 (65%) cancers.
Conclusion: Since the introduction of the directive we have noticed a steady increase in the rate of urgent referrals from 26–36% prior to the directive, to 41–59% over the last 6 months. This may be accounted for by increased pressure on GPs by knowledgeable, anxious, young patients. This has resulted in a high urgent referral rate and low yield of cancers in this group.

44. The relevance of reported symptoms in a breast screening programme

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Introduction: The aim of the breast screening programme is a reduction in breast cancer mortality of asymptomatic women aged 50–64 years. Inevitably, some patients attending for screening examination report breast symptoms but few studies have examined the relevance of these symptoms. At Breast Test Wales (BTW) a system is in place for the identification of women with important symptoms or signs. Radiologists are provided with this information when reading films and can choose to recall patients on the basis of symptoms alone.
Methods: Women with symptoms were identified retrospectively over a 5-year period from 1991 to 1996, so that cases could be compared to BTWs interval cancer database. Cases were classified according to radiological opinion as either suspicious (any mammographic abnormality) or benign.
Results: Of 285 793 women screened in Wales between 1991 and 1996, 1394 had reported significant symptoms at their initial appointment. Of these 756 (54%) were assessed and 125 (9%) were found to have breast cancer at subsequent assessment.

Symptoms	Not assessed	Assessed: Benign	Assessed: Suspicious	Totals
Lump	246	337 **(7)**	169 **(74)**	752 **(81)**
Distortion	150	84	65 **(37)**	299 **(37)**
Pain	191	44	18 **(4)**	253 **(4)**
Discharge	51	29	10 **(3)**	90 **(3)**
Totals	638	494	262	1394
Cancers	**0**	**7**	**118**	**125**

(Figures in bold type are number of cancers).

Conclusion: This gives a cancer detection rate of 90 per 1000 for patients with symptoms compared to the screened group (7.6 per 1000). However, 94% of those with cancer had abnormal mammograms and would have been recalled on that basis. For those with normal mammograms and symptoms 494 were assessed and only seven cancers detected (6.2 per 1000). All of the seven patients with cancer had described a breast lump. No patient with bilateral symptoms had cancer. Finally, the interval cancer rate was investigated. Twelve patients developed cancer within 3 years of screening of which six had been assessed.

It appears that recording symptoms in the screening programme is useful. However, the study shows that only those with significant symptoms should be recalled and protocols should be revised to avoid unnecessary assessment.

45. Factors affecting breast cancer risk perception in women attending a family history clinic

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Introduction: Previous studies on women at increased risk of breast cancer have shown that risk perception and risk-related anxiety need to be targeted in any counselling session. The factors affecting risk perception are varied and include media exposure and a woman's own experience of the disease.

We set out to determine whether a woman's perception of her own risk category was in any way influenced by her age, employment or her actual risk.
Methods: Ninety-five women attending our Breast Cancer Family History Clinic were asked to fill out a risk perception questionnaire prior to their risk counselling session. They were asked in which category they thought their risk was compared to the general population 'less', 'the same', 'slightly higher', 'moderately higher', 'much higher' and 'very much higher'. This answer was then compared with the woman's actual risk category and assessed as 'accurate', 'over-perceived' or 'under-perceived'. The accuracy of the risk perception was then correlated with the woman's actual risk category, age and education/employment level.
Results: Nineteen women belonged to the low risk category, 57 to the moderate risk category and 19 to the high-risk category for developing breast cancer. Fifty per cent of the women across all categories identified their own risk category accurately. Accurate risk perception had no relationship with age or level of education/employment. However, when correlated with their actual risk category, it was seen that a significntly higher proportion of women in the low and moderate risk categories tended to over-perceive their risk (9/19 and 22/57) compared to no women in the high-risk category (0/19). Surprisingly, more women in the high-risk category tended to under-perceive their risk (11/19) compared to women in the moderate risk group (4/57).
Conclusion: Understanding the factors influencing risk perception is important for effective counselling and risk explanation. Personalized risk counselling is currently targeted at the moderate and high-risk categories of women. It may be important to offer counselling to low-risk women as well, as they are most likely to over-estimate their risk and suffer needless anxiety because of it.

46. Survival of patients with screen detected cancer—is the effect limited to ER negative patients?

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Introduction: The presence of oestrogen receptor in symptomatic breast cancer is associated with improved prognosis as compared to patients where this marker is absent. There is little such data relating to screen detected cancers.
Methods: Four hundred and fourteen women aged between 50 and 64 presented either symptomatically or via the screening clinic with invasive cancer. All were treated according to standard protocols at the time and were followed up prospectively for up to 9 years. One hundred and eighty-five patients were screen detected and 229 were symptomatic.
Results: Survival analysis was performed with respect to ER status, and correction made for 2 years lead time bias in the screeen detected group. Overall survival, after correction for 2 years lead time bias, was not significantly different for ER positive tumours between symptomatic and screen detected tumour at follow-up. However, after correction for lead time bias there remained a significant survival advantage for screen detected patients who are ER negative as compared to their symptomatic counterparts.
Conclusion: Much of the benefit for the screening programme is mediated by detection of ER negative tumours. This population of patients should be aggressively sought and treated if the benefits of the screening programme are to be maximized.

LOCALIZATION, CYTOLOGY

47. Fine needle aspiration cytology of breast—audit of number of slides required for diagnosis

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Introduction: Fine needle aspiration (FNA) of breast is forming an increasing proportion of workload in cytology departments. We have seen a 500% increase in aspirated cases and an 1100% increase in the number of slides over the past 4 years. In 40% of the cases more than four slides were prepared with a range of up to eleven. We therefore decided to look at the minimum number needed for assessing adequacy and reaching a diagnosis.
Methods: A total of 135 cases were randomly selected from the breast unit dealing with palpable or symptomatic breast cases. The vast majority were aspirated by a single breast surgeon. For each case slides were numbered serially in order of preparation, fixed and stained. All cases were examined by a single pathologist with an interest in breast pathology. For each case the number of slides prepared, the slide number needed for adequacy and diagnosis and the final diagnosis were recorded.
Results: In 96.3% of cases, the specimen was regarded as adequate on the first slide, and in only four cases was it necessary to look at the second slide to confirm adequacy. These four cases were benign (C2). In 94.4% of cases the diagnosis was reached on the first slide. In six cases the second slide was reached on the first slide. In six cases the second slide was needed to make a diagnosis and of these, four were benign (C2). The remaining two were suspicious of malignancy (C4) and malignant (C5).
Conclusion: This study shows that in a unit where the inadequate rate is 3%, the adequacy and diagnosis could be established on the first two slides prepared from the FNA in all cases. This raises the question of whether all slides submitted from a breast aspirate need to be examined. We recommend that at most the first four slides are examined in order to provide ample material and the remaining slides be only looked at if there is a discrepancy in the clinical, radiological and pathological diagnosis. This could substantially reduce the workload in cytology without affecting quality.

48. Does accuracy of localization influence the benign breast biopsy weight?

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Introduction: Targets for benign breast biopsy weight aim to minimize cosmetic disadvantage from benign biopsy. We have sought to investigate the relationship between specimen weight and accuracy of localization wire placement.
Methods: In 55 cases, the following parameters were measured:

(1) lesion centre to wire tip distance;
(2) lesion centre to wire nearest point distance;
(3) whether the wire passed the periphery of the lesion;
(4) whether the wire was short or deep to the lesion centre.

The relationship of these factors to specimen weight was assessed.
Results: Weight: Needle tip distance—correlation coefficient 0.14. Weight: Needle nearest point distance—correlation coefficient 0.33. Wire passes through periphery of lesion in 73%. Average weight 20.1 g. Wire misses periphery of lesion in 17%. Average weight 29.4 g. Wire tip short of lesion centre in 31%. Average weight 29.2 g. Wire tip level or deep to lesion centre in 69%. Average weight 20.4 g.
Conclusion: The relationship between wire placement accuracy and specimen size is weak. There is no significant correlation between the distance of the needle tip and the specimen size. As expected, wires which pass through the lesion are better than wires that miss the periphery of the lesion altogether. The position of the needle tip is less relevant than might be expected.

Measurement protocols for the targets have not been established and we suggest that a standardized methodology should be adopted. While radiologists should place wires as accurately as posible, they need to be aware that wire course may be more important than wire tip accuracy. Surgeons should understand that factors other than wire placement influence specimen size.

49. Routine hospital follow-up of breast cancer—time for a new approach?

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Introduction: The purpose of this study was to determine how recurrent breast cancer presents to our hospital, with the aim of revising our follow-up strategy. The study was prompted in part by the increased pressure on breast clinics from new patient referrals and the need, since 1999, to see all cases classified as urgent within 2 weeks of referral.
Methods: All patients who underwent surgery as primary treatment for breast cancer between 1992 and 1998 were reviewed. Details about recurrent disease were obtained from our breast cancer database and the clinical notes.
Results: Of 643 patients, 108 developed recurrence. We were able to retrieve the required information on 108 of these, of whom 67 had metastatic, 19 local and 14 regional recurrence. Second primary tumours in the contralateral breast were seen in four cases.

When symptoms or signs of recurrence developed, 77 (74%) of these 108 were seen at an early (interval) clinic appointment. Fifty-five were referred by their GP, 16 from another hospital department and six self-referred. Eighteen (17.3%) brought attention to their symptoms at a routine appointment. Unsuspected disease, loco–regional in all cases, was elicited on routine examination by the clinic doctor in seven (6.7%) patients, who thus represented 1.1% of the 643 from this period, attending for follow-up. Surveillance imaging detected two cases. The median time to histological confirmation of recurrence was 9 days (range 1 to 208 days) and to confirmation by means of imaging 4 days (range 1 to 68 days).

Patients seen as an interval referral had had symptoms of recurrence for a median time of 3 weeks (range 2 days–1 year) before consulting a doctor. This compared with a median of 4 weeks (range 2 days–4 months) for those attending routinely.
Conclusion: Our experience establishes that recurrent breast cancer is rarely detected as the result of routine clinic examination. Surveillance imaging also has a low yield. In our practice most recurrent disease is confirmed as the result of an interval appointment at the next available clinic followed by prompt investigation. Routine hospital-based follow-up of breast cancer patients appears to be inefficient and unnecessary. We believe that given adequate preparation and education an improved system should be implemented whereby patients are discharged to their GPs upon completion of their treatment, with immediate access to specialist clinic review should the need arise.

50. Breast conservation surgery versus mastectomy afer primary chemotherapy—changing clinical practice

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Introduction: Primary chemotherapy is used to downstage primary breast cancer and reduce occult metastatic disease. Therefore, this approach may increase the rate of breast conservation surgery in patients with large primary breast cancers. With more experience in using primary chemotherapy is the rate of breast conservation surgery increasing?
Methods: Patients with locally advanced breast cancer (T_3, T_4) received six pulses of CVAP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy. All patients underwent surgical resection of the residual tumour after completion of chemotherapy. The rates of mastectomy and

wide local excision were compared in two groups of patients; the first recruited between 1990 and 1995; the second between 1996 and 1998.
Results: Eighty-five patients were recruited into each group. In the first group (1990–95) 70 patients (82%) underwent mastectomy and 15 (18%) wide local excision. In the second group (1996–98) 50 patients (59%) underwent mastectomy and 35 (41%) wide local excision. Clinical response rates to chemotherapy and residual tumour sizes after completion of chemotherapy in the two groups of patients are not statistically different.
Conclusion: The rate of breast conservation surgery is increasing with longer experience of using primary chemotherapy for locally advanced breast cancer.

51. Does immediate reconstruction after mastectomy for breast cancer delay adjuvant therapy?

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Introduction: Mastectomy may be indicated in the treatment of some cases of primary breast cancer and local recurrence after conservative surgery. Loss of the breast is often psychologically traumatic to the patient and immediate reconstruction involves a longer operation time and a larger area of dissection. This may lead to complications resulting in delayed wound healing. Would this then lead to a delay in adjuvant therapy?
Methods: A total of 419 women underwent mastectomy for breast cancer between April 1995 and May 2000. Of these, 55 patients received irradiation to the mastectomy flap as their first adjuvant therapy while 88 received chemotherapy as their first adjuvant therapy. In the former group, 19 had immediate reconstruction and 36 did not. The mean time to the start of radiotherapy was 46.3 days. Those who had reconstruction had an average delay of 15 days compared to those without reconstruction ($P<0.0013$). Patient age, neo-adjuvant chemotherapy, use of implants and whether the reconstruction was unilateral or bilateral did not affect radiotherapy delay.
Results: In the group of patients who received chemotherapy as their first adjuvant therapy ($n=88$), 59 had immediate reconstruction and 29 did not. The mean time to the start of adjuvant chemotherapy was 31.8 days. There was no difference between the reconstructed group (32.9 days) and those without reconstruction (29.4 days). Age, previous radiotherapy, implant use and whether the reconstruction was unilateral or bilateral did not influence the time to the start of chemotherapy.
Conclusion: Immediate reconstruction does not delay the commencement of adjuvant chemotherapy but may result in an average delay of 2 weeks to the start of radiotherapy if given as the first post-operative therapy. This delay is unlikely to impact on the efficacy of adjuvant radiotherapy and supports the safe practice of immediate breast reconstruction.

BASIC SCIENCE, IMMUNOLOGY

52. Mononuclear phagocytes but not tumour cells are the main source of elevated interleukin (IL)-10 levels in human breast cancer

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Introduction: IL-10 is a cytokine with strong immunosuppressive properties. High expression of IL=10 mRNA has been detected in breast carcinoma. However, there are few reports regarding circulating levels of IL-10 in patients with breast carcinoma. None of these studies have investigated the possible source of the IL-10. The aim of this study, therefore, is to determine the IL-10 profile in blood and to delineate its possible cellular source.
Methods: Serum levels of IL-10 were measured in 10 patients with operable breast cancer just prior to undergoing surgery using the enzyme-linked immuno-adsorbent assay. Also, its expression in breat carcinoma tissue was investigated using specific monoclonal antibodies and standard immunohistochemical techniques.
Results: Significantly elevated levels of serum IL-10 were found in patients with breast carcinoma, compared with healthy controls (172.8 ± 46.0 pg/ml *vs* 27.8 ± 13.1 pg/ml; $P<0.001$). A few tumour cells only were found to express IL-10. On the other hand, specific cells within the tumour milieu and/or surrounding stroma and draining lymph nodes expressed IL-10. Morphology and staining of serial tissue sections by CD68 (specific macrophage marker) identified these cells as macrophages. In all cases, the appropriate control sections were negative. Tonsils removed from patients with chronic tonsilitis were used as positive controls.
Conclusion: The source of IL-10 in patients with malignancies is unclear. In breast carcinoma, however, we have demonstrated in our study that the main source of IL-10 is tumour-associated macrophages and not tumour cells. We found few tumour cells expressing IL-10. On the other hand, significant numbers of the tumour infiltrating macrophages (identified by morphology and staining with CD68) were shown to express IL-10. Our findings suggest that certain subsets of tumour-associated macrophages (i.e. circulating levels of IL-10 in tumour bearing hosts, resulting in induction of immune suppression and, subsequently, progressive tumour growth.

[1] *Studentship funded by the Jordanian Royal Private Purse.*

53. Defective function of dendritic cells in patients with breast cancer

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Introduction: Dendritic cells (DCs) play a crucial role in presenting antigens to T lymphocytes and inducing cytotoxic T cells. The functions of DCs in cancer, however, are poorly defined. The aim of this study is to characterize DCs in patients with breast cancer in order to understand the factors leading to failure of an effective loco–regional anti-cancer host response and resultant progressive tumour cell growth.
Methods: DCs were obtained from the peripheral blood of women with operable breast cancer by a cocktail of specific monoclonal antibodies and using immuno-magnetic bead selection, depleting all monocytes and lymphocytes subsets except DCs. The stimulatory capacity of DCs in the allogeneic mixed leukocyte reaction (MLR) and autologous T cell proliferation test (PPD as stimulator) from patients with breast cancer and normal controls were determined and compared.
Results: Using this method, approximately 70–75% purified DCs were isolated. DCs from patients with breast cancer demonstrated a significantly lower capacity to stimulate an MLR, compared with DCs from a normal control ($P<0.05$). Also, antigen-driven autologous T cell proliferation in patients with breast cancer had a significantly decreased response to PPD, when compared with a normal control group ($P<0.05$). To characterize the mechanisms of the observed effects, purified T cells from breast cancer patients and DCs from normal controls were incubated in a MLR. T cells from breast cancer patients responded as well as control T lymphocytes in the presence of control DCs.
Conclusion: These data suggest a defective DC function in women with operable breast cancer. This may be an important reason for the inhibition in cellular immune function documented in patients with breast cancer.

54. Are the anti-tumour effects of conjugated linoleic acid mediated by increased p53 expression?

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Introduction: Studies have shown that dietary fatty acids play an important role in carcinogenesis. Recent interest has focused on the fatty acid, conjugated linoleic acid (CLA). Its anti-tumour effects may be mediated through enhanced apoptosis. However, effects of CLA on genes involved in apoptosis are unknown and this study has examined the effects of CLA on p53 and bcl-2 expression.
Method: Breast cancer cell lines (MCF7) were grown to sub-confluence and treated with CLA in concentrations of 0 to 200 μM for 24 hours. After this, RNA was subsequently extracted and Northern blotting was performed to determine the expression of p53 and bcl-2 and quantified by 18S.
Results: After incubating MCF7 cells with CLA, there was a dose dependent effect on p53 expression, with an increase of 275% at 12.5 μM, 325% increase at 100 μM and 495% increase at 200 μM of CLA ($P<0.01$). In contrast, there was a reduction in bcl-2 expression after incubation with CLA but this was not significant.
Conclusion: This study is the first demonstration of the effect of CLA on gene expression in breast cancer cells. These results now indicate a possible mechanism for the anti-tumour activity of CLA, by increasing the expression of the p53 gene.

PARALLEL SESSION V—GI ORAL POSTERS

DIAGNOSIS

55. Improving access to barium enema examinations in suspected colorectal cancer

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Introduction: Whilst it is admirable that all patients with suspected colorectal cancer are assessed by a specialist within 2 weeks, it is also important that a framework exists to investigate patients rapidly when seen. Initial audit of our outpatient service suggested that a bottle-neck existed within our hospital for processing barium enema examinations.
Methods: To solve this problem our Information Technology department, in conjunction with the Cancer Services Collaborative Initiative, developed a rapid access barium enema request screen for use on our hospital computer intranet. All hospital clinicians had unlimited access to this facility. The request form highlighted high-risk symptoms as defined by NHS Executive National guidelines such that if one is chosen, fast-tracking of the barium enema request was automatically initiated.
Results: From February to the end of May, 52 fast-track barium enemas were undertaken and reported. Seven studies (13%) were highly suggestive of cancer, equivalent to one cancer per seven patients investigated, whilst 14 (27%) were normal, 24 (46%) showed diverticular disease and five (10%) were non-diagnostic due to faecal residue of inability to retain barium. Importantly, use of this system has reduced our waiting time for barium enemas from 91 days for all-comers to less than 14 days for high-risk patients. Rationalization of the service also allows less urgent barium enemas to be completed in just 40 days.
Conclusion: A logical approach to the problem of improving patient access to barium enema examinations in cases of suspected colorectal cancer has not only improved our service for this group of patients but also to those with other conditions.

56. Pelvic CT scanning for rectal cancer—a useful predictor of extraluminal disease?

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Introduction: Pre-operative radiotherapy aims to reduce local recurrence after surgery for rectal cancer and should be considered where the circumferential resection margin (CM) or lymph nodes may be involved or where tumour is tethered. These factors are difficult to detect by clinical assessment alone and pelvic CT staging is the most readily available investigation for assessing extraluminal rectal cancer. This study assessed the accuracy of pre-operative pelvic CT in the staging of rectal carcinoma, to aid in the planning of preoperative radiotherapy.
Methods: A comparison was made between pre-operative CT scan reports and histopathological staging of 46 patients who underwent surgical resection for rectal carcinoma between January 1997 and April 2000. Data was obtained on patient demography, staging and accuracy of CT in detecting lymph node involvement and depth of tumour invasion.
Results: In the study 70% of patients underwent anterior resection of the rectum and the median age was 70 years. Most of the tumours were advanced 21/46 (46%) Dukes' C, and CM involvement was present in 20%. Overall, CT scanning understaged rectal cancer (46%) and was only accurate in 32% of cases. CT had low sensivity and specificity for lymph node status (N) and tumour (T) invasion (59%, 58% N and 54%, 57% T staging respectively).
Conclusion: Most patients in this group would benefit from pre-operative radiotherapy, however CT scanning understaged rectal cancer in 46%. It was more accurate (67%) when analysing those with involved CM, most of who had palliative resections and pre-operative radiotherapy. CT scanning alone is of limited value in predicting the stage of rectal cancer unless patients have extensive disease, and therefore should not be used solely in planning radiotherapy regimes.

GUIDELINES, 2 WEEK RULE

57. Knowledge of cancer symptoms among patients attending one-stop breast and rectal bleeding clinics

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Introduction: The aim of this study was to identify knowledge of the symptoms of breast and colorectal cancer among patients attending one-stop breast clinics and rectal bleeding clinics and to determine the source of the information.
Method: A questionnaire was given to 100 patients attending one-stop breast clinics and 100 patients attending either direct access flexible sigmoidoscopy or rectal bleeding clinics. The questionnaire examined knowledge of breast and colorectal cancer symptoms, sources of information and family history of either disease.
Results: Seventy-five breast (mean age 46, all female) and 78 colorectal (mean age 59, 51% male) clinic patients responded. Knowledge of breast cancer was significantly greater than bowel cancer in both groups ($P<0.0001$ McNemar's Chi-squared). The difference in the percentage of respondents with knowledge of the two diseases (breast—bowel) was 31% (95% confidence interval 18.8% to 43.2%) for the breast clinic patients and 29.5% (95% confidence interval 15.6% to 43.2%) for the colorectal clinic patients. There was no difference in knowledge of symptoms of breast cancer or bowel cancer between patients attending either breast or colorectal clinics. Family history of both diseases was similar in both groups but did not guarantee knowledge of symptoms. More sources of information were identified for breast cancer than for bowel cancer in both groups. The internet was not a significant source of information.
Conclusion: Knowledge of colorectal cancer is much less than breast cancer. Knowledge was similar for both clinic groups suggesting that attendance at a clinic does not increase knowledge of a condition. Seventy-five per cent of patients attending breast clinic could name a breast cancer symptom whereas 37% of patients attending colorectal clinic could name a bowel cancer symptom. This has implications when considering patients' anxiety, expectations of a cancer diagnosis and breaking bad news.

58. Coping with the 'two week rule' in suspected colorectal cancer—a pilot study

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Introduction: By July 2000, according to Health Service circular 1999/999, all patients with suspected colorectal cancer must be seen by a specialist within 2 weeks. We conducted a pilot study to ascertain feasibility and to identify potential problems.
Methods: Five local GP practices serving a population of 34 350 patients were invited to take part. A rapid referral proforma based on national guidelines for high-risk colorectal symptoms was distributed to participating GPs at the start of the study. Initially rapid access places in a normal consultant colorectal clinic were booked but as from the 12 June 2000 we have instituted a dedicated weekly consultant clinic. Routine examination included rigid sigmoidoscopy.
Results: From January to May inclusive, 24 patients were referred to our rapid access clinic from the practices involved and all were seen within 2 weeks of referral. Only nine (38%) of the 24 referral proformas were completed correctly. Of these 19 (79%) were considered appropriate referrals by the consultant who assessed them, four were inappropriate and one was referred as low risk. Presenting symptoms included three unexplained iron deficiency anaemias, one with weight loss; four PR bleeds, one associated with change in bowel habit and two had change in bowel habit alone. Fifteen (63%) patients were discharged back to the care of their GP with no further treatment planned. Of the remaining nine patients, one had a rectal polyp and one a rectal cancer both diagnosed in clinic, whilst seven (29%) proceeded to further investigations, six to barium enema and one to flexible sigmoidoscopy. Overall implementing a rapid access referral system has reduced our barium enema requests by 67%, which at £140 per examination represents a considerable cost saving.
Conclusion: Fears have been raised over the implementation of the 'two week rule' and its presumed effects on outpatient clinic waiting time and cost. This small pilot study demonstrates that within a collaborative framework,

GPs and colorectal specialist units can provide rapid access assessment of patients with potential cancer symptoms and deliver quality of service whilst perhaps paradoxically reducing cost.

SURGERY, CHEMOTHERAPY

59. A new technique for combined synchronous on table antegrade–retrograde colonic lavage

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Introduction: On table colonic lavage is a well recognized technique to allow single stage primary colonic resection and anastomosis. Previous descriptions involve antegrade lavage using equipment not specifically designed for this purpose. This new technique allows combined synchronous on table antegrade and retrograde lavage using a closed system comprising of specific components which have been designed for this use.
Methods: The patient should be positioned supine on the operating table with the legs positioned in a Lloyd Davis type of support. This system comprises: an Entero-vent which is a combined inflow and suction aspiration unit for insertion into an enterotomy wound via the appendix, appendix stump, caecum or terminal ileum. Tie-Lok cable ties are provided for securing the entero-vent component to the caecum. The Colo-clens distal colonic infusion inflow and outflow drainage device is combined with a flexible tube and closed (15 l) bag system. Large cable ties are provided for securing the Colo-clens device to the distal descending colon. The Procto-clens component is an ano-rectal infusion inflow and outflow drainage device also with a combined flexible tube and closed (15 l) bag system. This component may also be used to test the anastomosis using a saline pressure test. It is recommended that the inflow infusion channels for these components should be linked to a normal saline (37°C) infusion irrigation system of the kind used in Urology e.g. Flowfusor.

The precise stage at which the intraoperative colonic lavage procedure should be performed will be determined by the clinical findings. Following the formal dissection and mobilization of the sigmoid and distal descending colon, the abdominal intestinal contents should be carefully arranged within the abdomen and isolated with surgical packs to avoid any contamination of the laparotomy wound. In addition it may be necessary to mobilize the hepatic and splenic flexures. Prior to commencement of the lavage procedure, non-crushing intestinal clamps should be placed across the distal terminal ileum to prevent reflux of the irrigation fluid into the small bowel. Similarly, non-crushing intestinal clamps should be applied at the selected sites distal and proximal to the colonic lesion.
Results: This technique has been used in 60 patients in acute left sided colonic surgery without any of the previously recorded technical problems.
Conclusion: This new technique provides a safe and effective method of both antegrade and retrograde colonic lavage using components specifically designed for this purpose.

60. A phase I study of photodynamic therapy of patients with advanced colorectal cancer using temoporfin

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Introduction: Photodynamic therapy (PDT) uses visible light and a tumour localizing photosensitizer to destroy cancer tissue. Temoporfin is a new and possibly more effective photosensitizer and we have assessed its safety and efficacy for PDT in patients with advanced colorectal cancer.
Methods: Seven treatments were given to six male patients mean age 56.4 range (46–72) with recurrent advanced colorectal carcinoma. Temoporfin 0.15 mg/kg was administered intravenously followed by subsequent light delivery at 652 nm from a diode laser. Strict light sensitivity precautions were adhered to from day 0. Six patients received direct interstitial PDT (IPDT) to $n=10$ liver metastases from a cylindrical 2 cm light diffuser at a dose of 50 to 100 Jcm^2. One patient received adjuvant intraoperative PDT to a tumour bed following surgical excision of a recurrent tumour using a spot lens in three overlapping applications at a dose of 20 Jcm^2.
Results: Following PDT the 30 day mortality was zero. Two patients suffered hepatic pain after IPDT from perihepatic bleeding from the optical fibre puncture sites. No patient suffered skin photosensitivity complications. Seven hepatic metastases after three PDT treatments were evaluated pre- and post-IPDT using CT scanning. Following IPDT negative and static growth was observed in three metastases. The mean diameter growth of liver metastases ($n=7$) after IPDT was 4.79 (arb units (range -3–6.6)) and reduced when compared to pre-treatment 7.05 (3.5–11.0) but did not reach statistical significance (paired t-test).
Conclusion: This study demonstrates that PDT using Temoporfin can be administered safely with no skin photosensitivity reactions. Treatment complications do occur but are related to the surgical aspect of the treatment. Biological efficacy is confirmed by reduced growth of hepatic colorectal metastases but is variable and may be related to the accuracy of the optical fibre localisation.

61. 5 ASA induces susceptibility to 5 FU in colon cancer cells *in vitro*

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Introduction: 5 fluorouracil (5 FU) chemotherapy is important in the management of colorectal cancer, as most tumours have breached the basement membrane at diagnosis. 5 FU and most chemotherapeutic agents act partly by inducing apoptosis in cancer cells. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce incidence and mortality from colorectal cancer. 5 aminosalicylic acid (5 ASA); an NSAID, reduces incidence and mortality from colorectal cancer in ulcerative colitis patients below that of the general population. In addition to chemoprophylactic action, several NSAIDs also induce apoptosis in colon cancer cell lines, and may cause colon polyp regression. The mechanism of NSAID action is unknown, but colorectal adenocarcinomas overexpress COX-2 and prostaglandin E (both inhibited by NSAIDs). We therefore hypothesized that NSAIDs may induce apoptosis, and augment 5 FU toxicity in colon cancer cells. The aim is to evaluate the apoptotic effect of 5 ASA alone and in conjunction with 5 FU on colon cancer cells *in vitro.*
Methods: Colo 201 and Colo 205 cells were cultured in medium (control), with 5 ASA or 5 FU alone, and a combination of 5 ASA and 5 FU. At 72 hours, the cells were harvested, washed, fixed in 70% ethanol for 45 min and incubated for 30 min in 500 µl RNAse (1 mg/ml), 250 µl propidium iodide (100 µg/ml) and 250 µl PBS. The cells were washed, resuspended in PS and 5×10^3 cells per sample analysed by FACSCAN, and the hypoploid (sub-G_0-apoptotic) events counted. Concentrations used: 5 FU 0.1 µM for Colo 201, 1 µM for Colo 205, 5 ASA -7 mM.
Results:

	Control	5 FU only	5 ASA only	5 FU + 5 ASA
Colo 201	3% (0)	6.7% (0.6)	4.8% (1.2)	17.3% (0.6)
Colo 205	2.7% (0.6)	7% (1)	1.3% (0.6)	20% (3.5)

Percentage apoptotic cells detected by FACSCAN following PI staining. $n=3$. Std dev. $=0$.

Conclusion: 5 ASA alone did not induce apoptosis, however it enhanced susceptibility to a non-toxic dose of 5 FU. This implies that 5 ASA reduces the threshold for 5 FU toxicity. We had previously shown that 5 ASA augmented 5 FU induced upregulation of pro-apoptotic Bax expression (data not shown). Modulation of one or more of the biochemical reaactions of the apoptotic cascade by altered eicosanoid metabolism may enhance 5 FU induced apoptosis. Tamoxifen, the metabolite anti-breast cancer drug is being investigated for similar dual chemoprophylactic and oncotherapeutic action as suggested here. 5 ASA is poorly absorbed and any effects would be limited to the intestinal epithelium, however sulindac and better-absorbed NSAIDs may enhance 5 FU chemotherapy or even reduce effective doses.

BASIC SCIENCE

62. Investigating the role of IGFBP-4 in colorectal cancer

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Introduction: The IGF system has been recently implicated in the progression of colon cancer. IGF-I itself has been shown to be strongly mitogenic in human colon cancer cell lines, its actions are regulated by the activity of insulin like growth factor binding proteins (IGFBP) which serve to inhibit, potentiate or maintain IGF-I. Insulin like growth factor binding protein 4, has been shown to be secreted by many human colon cancer cell lines and to inhibit the actions of IGF-I. We set out to determine if IGFBP-4 is expressed and secreted in human colonic tissue *in vivo* and to what degree this profile is altered in adenocarcinoma of the colon.
Methods: Samples were removed from the proximal, cancerous and (where possible) distal resected colonic tissue from over 30 patients undergoing

surgery for cancer. Protein was extracted from samples and separated using SDS PAGE and probed using a Polyclonal antibody to IGFBP-4. RNA was extracted from colon tissue and a fragment of IGFBP-4 was cloned using RT-PCR. The Roche light-cycler was then used to quantify mRNA for IGFBP-4. Immunohistochemistry was used to determine the distribution of IGFBP-4 in the colonic tissue.
Results: Western immunoblots revealed that the amount of IGF-BP4 secreted in the cancerous tissue was less than that secreted by the adjacent normal colonic tissue. Using densitometric analysis this difference was quantified and shown to be significant. IGFBP-4 was cloned and sequenced from all samples examined. We managed to illustrate the distribution pattern of the IGFBP-4 using immunohistochemistry.
Conclusion: Previous work *in vitro* has shown IGFBP-4 to be inhibitory to IGF-I. This study confirms the presence of binding protein 4 in all samples, but also demonstrates that the secretion is less in neoplastic tissue. The finding that this inhibitory peptide appears to be downregulated in the neoplastic samples, offers an exciting prospect for future work to further clarify its role and potentially to develop therapies centred on manipulating the regulation of this protein.

63. The value of P15 and P16 in the prognosis of colorectal cancer

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Introduction: P15 and p16 are two members of the family of mitotic inhibitors that inhibit the binding of G1-cyclin dependent kinases (cdk) to their designated cyclins e.g. cdk 4 to cyclin D, and thus inhibit the phosphorylation of Rb. This stops the progression of cells through the G1/S checkpoint. Their loss can thus lead to tumour growth. P16 has been found to be deleted in many melanoma cell lines. It has been suggested that p16 may be lost in many colorectal cancer cell-lines; p16 is also lost in some hepatocellular cancers and head and neck squamous cell carcinomas. P15 is implicated in gliomas and haematological malignancies such as acute lymphoblastic leukaemias. The possible role of p15 and p16 in the pathogenesis and prognosis of colorectal cancer was investigated.
Methods: Frozen tissue specimens from 112 primary colorectal cancers were studied prospectively. Sections were stained with monoclonal antibodies to p15 and p16. The ABC avidin–biotin system and the chromogen diaminobenzidine (DAB) were used to visualize antibody binding. The slides were scored according to the percentage of cells that stained positive and the intensity.
Results: P15 was lost in 10/112 (9%) specimens, while p16 was lost in only 2/112 (1.8%). This did not relate to the Dukes' stage nor the grade of the tumour. Furthermore, the intensity of staining and the proportion of tumour cells stained were also unrelated to the Dukes' stage and grade.
Conclusions: There is no correlation between (1) the loss of expression and (2) the pattern of expression of the mitotic inhibitors p15 and p16, and the stage and grade of the cancers in this series. They are thus of no prognostic value in colorectal cancer.

64. Comparison of orthotopic cell implantation (OCI) *vs* orthotopic tumour implantation (OTI) in the HaP-T1 Syrian hamster pancreatic cancer model

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Introduction: The Syrian hamster pancreatic cancer model is chosen for its morphological, clinical, biological and immunological resemblance to human pancreatic cancer. However, the best method of tumour induction is not well established.

The aim of this study was to compare the OCI and OTI techniques of induction of pancreatic cancer in the Syrian hamster model.
Methods: Pancreatic cancer was induced in 16 Syrian hamsters using the OCI technique by injection of 2×10^6 HaP-T1 cells into the pancreatic gastric lobe via midline laparotomy under general anaesthesia. Similarly, 16 animals were implanted with tumour by the OTI technique using 1 mm grafts harvested from tumour, induced separately by prior subcutaneous inoculation. OCI and OTI groups ($n=4$) were sacrified at 1, 2, 5 and 8 weeks. Tumour weight and extent of spread were assessed at autopsy.
Results: There were two failures to implant, both in the OTI group. Mean tumour weight was 1.7 g in the OCI group and 0.26 g in the OTI group. ($P=0.0004$, z test for sample means)

	OCI	OTI	P*
Invasion of adjacent organs	12/16	2/14	0.001
Lymph node metastasis	7/16	1/14	0.039
Liver metastasis	5/16	0/14	0.045
Peritoneal metastitis	9/16	2/14	0.026
Widespread peritoneal dissemination	4/16	0/14	0.102
Other metastasis	0/16	0/14	1.000
Malignant ascites	2/16	0/14	0.485
Early sacrifice/death	1/16	0/14	1.000

* Fisher's exact test.

Conclusion: The OCI technique shows more rapid, local tumour growth as well as regional and distant metastatic spread, resulting in earlier development of the spectrum of advanced pancreatic malignancy in Syrian hamsters.

UPPER GI

65. The diagnostic yield of extended *en bloc* resection for (adeno)carcinoma of the oesophagus or gastric cardia

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Introduction: The extent of lymph node dissection might influence the staging of (adeno)-carcinoma of the oesophagus or gastric cardia. To investigate the impact of two-field lymph node dissection in staging (adeno)carcinoma of the oesophagus or gastric cardia a prospective analysis was performed.
Methods: Patients undergoing transthoracic oesophagectomy with two-field lymph node dissection for adenocarcinoma of the mid/distal oesophagus or gastric cardia were enrolled. Operations were performed with curative intent in the absence of distant metastases and/or local irresectability. Extended fields were marked separately.
Results: Between 1994 and 2000, 74 patients underwent extended oesophagectomy: 67 men and seven women, median age was 63 (40–78) years. The median number of resected nodes (and identified by the pathologist) per patient was 31 (15–78), with a median number of five (0–31) positive nodes. Overall, 27 patients (36.5%) showed tumour-positive lymph nodes in the extended fields: 15 patients (20.3%) in the abdomen and 15 patients (20.3%) in the mediastinum. The subcarinal nodes (18.9%) were most often affected. An extended resection in abdomen and chest led to upstaging of the tumour in 17 patients (23.0%): two patients had isolated positive subcarinal nodes, 15 other tumours all became M1a due to positive (resectable) lymph nodes near the celiac axis, hepatic artery and/or splenic artery. Tumour positivity in the paratracheal nodes or in the aorta-pulmonary window occurred in 8.1% of the patients, without influencing staging.
Conclusion: Two-field lymphadenectomy alters staging in 23% of patients with adenocarcinoma of the oesophagus or gastric cardia. This is mostly due to positive lymph nodes near the celiac axis; although the subcarinal nodes are affected in one-fifth of patients, they rarely change N-status.

66. Electrolytic liver ablation: the effect of multiple electrodes

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Introduction: We have developed a system of electrolysis using DC current to ablate liver and produce localized necrosis. The aim of this study was to investigate the the effects of multiple electrodes on the size of electrolytically induced areas of hepatic necrosis.
Methods: The liver was exposed through an upper midline incision in 50 pigs under general anaesthesia. Two electrode catheters were inserted into the right lobe. The electrolytic dose (100–1000 Coulombs) or separation of the electrodes was varied. Two control pigs were used. All pigs were sacrificed 96 hours post-operatively and the diameter of the electrolytic lesion measured, the volume calculated, and all specimens examined microscopically.
Results: All animals survived to 96 hours. No necrosis was seen in the control pig livers. Areas of necrosis around each anode and cathode could be identified and the histological appearance was primarily ischaemic necrosis. Only when the areas of necrosis were confluent was treatment considered satisfactory. No post-operative bleeding or bile leaks occurred. The dose–response curve was linear ($P<0.005$) with lesions up to 7 cm diameter created. Comparison of this data with our data from single catheter experiments demonstrated significant advantages in terms of size of lesion produced and rapidity of treatment.
Conclusion: Electrolysis is simple, safe and reproducible. This treatment has huge clinical potential for patients with unresectable liver tumours.

PARALLEL SESSION VI—BREAST SHORT PAPERS

67. Review of Trilucent breast implants in South Manchester

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Introduction: Trilucent implants containing soya oil were withdrawn by the Medical Devices Agency in March 1999 and further advised explantation of all Trilucent implants following adverse publicity and possible risk of carcinogenesis.
Method: In all, 100 women were recalled and underwent triple assessment of clinical examination, ultrasound (U.S.) and magnetic resonance imaging (MRI). The implantation was done by a total of six surgeons, three breast and three plastic surgeons. All implantations were done between 1995 and 1998.
Results: Of 100 women, 55 had bilateral implants making a total of 155 implants. Sixty-one women had following mastectomy, 33 for cosmetic augmentation and six following prophylactic mastectomy. Forty-one women were symptomatic (pain and discomfort, swelling, contracture and rippling), of which three had ruptured implants. Fifty-nine women were asymptomatic of which five had ruptured implants.

	No	Fluid	Rupture
USG	95	30 (32%)	8 (8.5%)
MRI	75	21 (28%)	6 (8%)

Conclusion: Trilucent implants were symptomatic in >40% of the patients and they had a rupture rate of 5% over a 4 year period. Both U.S. and MRI equally predicted rupture of Trilucent implants.

68. Breast reconstruction in the UK and Ireland—is there uniformity of care?

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Introduction: Within the last 10–15 years, the trend has been towards breast reconstruction post-mastectomy for cancer. Recent guidelines recommend that all women should be provided with the opportunity to receive advice on reconstruction where appropriate. Results of a questionnaire survey on breast reconstruction conducted by the breast specialty group of BASO 1997 showed that only a minority of breast units in the UK provided a comprehensive breast reconstructive service and relatively small numbers of immediate reconstructive procedures were being performed. Those enjoying formal links with plastic surgeons offered the most comprehensive reconstructive service. The aim of the present survey was to assess current breast reconstructive practice in the UK and Republic of Ireland.
Methods: A detailed database of breast surgeons in the UK and Ireland was compiled. A total of 498 surgeons was identified—337 (England), 37 (Scotland), 18 (Wales), 11 (Northern Ireland) and 95 (Republic of Ireland). The survey gained information about personal characteristics, surgical practice, availability of reconstructive service, preference between immediate and delayed reconstruction and perceived disadvantages of immediate reconstruction. Of 498 surveys sent, 376 were returned (response rate—76%).
Results: Response rates were England 76%, Scotland 84%, Wales 83%, Northern Ireland 91% and Republic of Ireland 55%. In all 368 responses were suitable for analysis. A wide variation in attitudes in methods of reconstruction amongst breast surgeons has been identified. The reasons for this variation in practice are multifactorial and include misconceptions related to oncological and psychological aspects of immediate reconstruction and perceived financial constraints within the health services.
Conclusion: This variation in practice of post-mastectomy reconstruction needs to be addressed in order to ensure uniformity of delivery of care in the UK and Ireland. Adequate funding must be identified to facilitate this service which is an integral part of breast cancer care.

69. Assessment of breast form using biodimensional implants in immediate reconstruction after mastectomy with geometric measurements

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Introduction: Immediate reconstruction after mastectomy for breast cancer is safe and acceptable. Advancement in implant technology has led to the development of shaped implants. As patients' expectations increase, biodimensional anatomical implants may give a superior cosmetic result. The aim of this study was to use geometric measurements to evaluate the restoration of breast contour using biodimensional shaped implants for immediate reconstruction.
Methods: Between 1997 and 1999, 96 patients with primary breast cancer underwent immediate reconstruction with implant with/without autologous tissue. Of these, six patients had incomplete data and four lost their implants due to infection. Analysis was based on 86 patients. Symmetry between the reconstructed and the contralateral breast was assessed. Eight parameters were obtained: transverse breast width (TBW), vertical breast height (VBH), sternal notch-nipple (SNi), midclavicular-nipple (MCNi), inframmary fold-nipple (InNi), midline-nipple (MNi), vertical nipple difference (VND) and projection (P).
Results: Subpectoral implant reconstruction was performed in 35 patients while 51 had latissimus dorsi myocutaneous flaps and implant. Synchronous adjustments of the contralateral breast was performed in 21 patients. Median difference (m) between the reconstructed breast and the contralateral breast for each of the parameters was minimal: TWB = 0 (−3 to 5), VBH = 0 (−2 to 4), SNi = 0 (−1.5 to 6), MCNi = 0 (−5 to 6), InNi = 0 (−1.5 to 5.5), MNi = 0 (−1.5 to 4), VNH = 0 (−7.5 to 1.5), $P = 0$ (−1.5 to 1.9).
Conclusion: Objective assessment of breast reconstruction can be made using geometric measurements. Good symmetry can be achieved using biodimensional shaped implants in immediate reconstruction after mastectomy with careful patient selection.

70. The role of harmonic scalpel in breast surgery

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Introduction: The Harmonic Scalpel (HS) uses ultrasonic energy converted into high frequency mechanical motion to simultaneously achieve precise cutting and controlled coagulation. Compared with the conventional monopolar electrosurgery, the HS has many benefits including electric safety, reduced blood loss, less tissue damage, better visualization of tissue planes, greater efficiency and faster wound healing. The HS has been demonstrated to be superior in many fields of surgery. The present study aims to examine the potential benefits of the HS in breast surgery.
Method: Thirty-four women who underwent mastectomy (segmental or total) were prospectively randomized to the HS (Group 1) or the scissors and electrosurgery (Group 2) group. In each group there were 17 women—10 women underwent segmental mastectomy and axillary clearance and seven women underwent mastectomy and axillary clearance. The following parameters were assessed: operating time, post-operative pain (linear scale 1–10) for 2 days, total drainage volume, drop in haemoglobin (Hb) concentration on day 1, hospital stay and wound complications.
Results: In Group 1, the mean for the following was: age—59.5 years, operative time—89.7 mins, change in Hb—1.4 g/dl, total drainage—656.8 mls, pain score—1.6 and hospital stay—7.2 days. There were two mild wound infections. In Group 2, the mean for the following was: age—59.4 years, operative time—95.6 mins, change in Hb—1.8 g/dl, total drainage—582.9 mls, pain score—2.4 and hospital stay 7.1 days. There were four mild wound infections. There was no statistical difference in all of the parameters measured between the two groups. This is probably because of small sample size.
Conclusion: In this small prospective study, no significant benefit for using the HS in breast surgery has been demonstrated. Larger studies are required to validate or dispute these findings.

71. The clinical outcome of two new breast reconstructive procedures

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Introduction: Skin-sparing mastectomy with immediate latissimus dorsi (LD) myocutaneous flap reconstruction (SSM + LD) and partial mastectomy with LD miniflap reconstruction (LDMF) are new procedures which have been developed to minimize the disfigurement of breast cancer surgery. The aim of this study was to compare and contrast the physical, oncological, cosmetic and psychological outcomes of each procedure.
Methods: One hundred and forty-one of 179 disease-free patients reconstructed between 1990 and 1999 (66 SSM + LD, 49 LDMF and 36 other reconstructions), follow-up 47.8 (6–116) months, consented to the study. Measured outcomes included complications, local recurrence (LR), sensory loss, restriction of activities, cosmetic outcome using breast retraction assessment (BRA) and panel assessment (PA) and quality of life (QOL) using known psychometric scales and study-specific questions with visual analogue scales.
Results: SSM + LD outcomes compare less favourably with LDMF with regard to complications (46% *vs* 24%, 95% CI 0.03 to 0.37), further surgical interventions (79% *vs* 12%, 95% CI 0.50 to 0.77), nipple sensory loss (98% *vs* 2%, 95% CI 0.85 to 0.98%), restricted activities (73% *vs* 54% CI 0.01 to 0.35). LDMF had slightly better cosmetic outcome: BRA 2.27 *vs* 2.04 (95% CI −0.338 to 0.797), PA 3.60 *vs* 2.79 (95% CI 0.479 to 1.157) and patient satisfaction 74.11 *vs* 69.34 (95% CI −3.825 to 13.367). Anxiety about residual cancer, LR rates and ease of breast self-examination were similar in both groups. SSM − LD patients reported higher self-esteem ($P<0.05$), but were more self-conscious about the treated breast ($P<0.05$), experienced greater disturbance of body image ($P<0.01$), and their partners were more likely to avoid touching the treated breast ($P<0.01$). Disturbance of body image correlated with anxiety and depression ($P<0.01$), which was uncommon in both groups.
Conclusion: Good cosmetic results can be achieved with SSM + LD and LDMF without compromising local control. The physical and psychological advantages of LDMF should be considered when informing patients with tumours which are suitable for treatment by either technique.

72. Optical biopsy for the assessment of sentinel lymph nodes of the breast

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Introduction: Optical biopsy is a new technique under evaluation for the assessment of lymph nodes in breast cancer patients. This study tested an optical probe, based on the principle of Elastic Scattering Spectroscopy with spectral analysis of reflected light. The aim is to develop an optical instrument capable of determining the metastatic status of a sentinel lymph node, whilst still in the operating theatre.
Methods: The system consists of a white source, with fibre optic delivery and collection fibres, a spectrometer for dispersion of the collected light and linear CCDs (charge coupled devices) for detection. Each reading takes less than 1 sec, allowing virtually 'real time' analysis. Spectra were obtained from 42 negative and 14 positive nodes removed either by sentinel node biopsy or following routine lymph node excision. Optical measurements were taken from the cut surface of the node after each was bi-valved along its longitudinal axis. The optical data were then correlated with the findings on conventional histology of the lymph nodes.
Results: Both model based analysis and artificial intelligence methods were tested to develop algorithms to interpret the spectra. Depending on the type of analysis employed, preliminary results for detection of cancer produced sensitivities between 57% and 91% and specificities between 76% and 93% (table).

	ANN	HCA	MBA
Sensitivity	58%	91%	57%
Specificity	93%	76%	85%

ANN: artificial neural network; HCA: hierarchical cluster analysis; MBA: model based analysis.

Conclusion: Optical biopsy offers promise in determining the status of a sentinel lymph node. This would allow the surgeon to make an immediate decision in theatre, whether to proceed to full axillary lymph node clearance rather than having to wait for conventional histology. Work is ongoing to refine the analysis methods with the aim of improving overall accuracy of the system.

73. Mammaglobin expression in sentinel and non-sentinel nodes.

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Introduction: Sentinel node biopsy allows the opportunity for more focused examination of those nodes most likely to harbour metastases. The mammaglobin gene is expressed solely by the adult mammary gland and detection in axillary lymph nodes would seem to indicate the presence of metastases in breast cancer patients. This study compared routine histology with mammaglobin RT-PCR in both sentinel and non-sentinel nodes.
Methods: Fifty-two patients with proven carcinoma of the breast underwent sentinel node biopsy, complete axillary lymphadenectomy and tumour excision. All nodes were bisected: half was sent for routine histology and half for mammaglobin RT-PCR
Results: One hundred and forty-four sentinel and 233 non-sentinel nodes were excised from 50 patients and examined by both techniques. The sentinel node identification rate was 96.2%. The false negative rate was 0% (0/19) using histology results and 9.5% (2/21) using mammaglobin RT-PCR results. Mammaglobin expression was detected in 7.6% (Clopper–Pearson 95% C.I. 3.5–13.9%) of histologically negative sentinel nodes and 5.3% (95% C.I. 2.8–8.8%) of histologically negative non-sentinel nodes ($P<0.001$, McNemar's test). Mammaglobin expression was detected in 12.9% (95% 3.6–29.8%) patients with histologically negative sentinel nodes and 13.6% (95% C.I. 5.2–27.4%) of patients with histologically negative non-sentinel nodes ($P = 0.03$).
Conclusion: Mammaglobin RT-PCR significantly increases the number of nodes and patients with breast cancer metastases compared with routine histology. Using mammaglobin RT-PCR may result in more false negative sentinel biopsy results than routine histology.

74. Small breast tumours. Is axillary dissection necessary?

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Introduction: Though axillary dissection provides a definitive answer to the prognosis and need for adjuvant treatment, it carries a considerable morbidity. We carried out a retrospective audit to determine whether axillary dissection could be avoided in small breast cancers and also whether the size of invasive component and vascular invasion were indicative of axillary status.
Method: Two hundred and thirty-four cases of small breast cancers (10 mm or less) were treated surgically at three centres between 1991 and 2000. One hundred and fifty of these had axillary dissection. Data for tumour type, invasive component, vascular invasion and margins were recorded. Where axillary dissection was done number of axillary nodes removed and number of positive nodes was also recorded.
Results: Forty-two cancers (18%) were ≤4 mm, 79 (34%) were ≤8 mm and 113 (48%) were >8 mm size invasive component. One hundred and fifty of these cases had axillary dissection of which 24 (16%) had positive nodes. Only one patient (2.38%) with tumour ≤4 mm had positive nodes in axilla irrespective of type or grade of the tumour, and this was the only tumour with vascular invasion in this group. Axillary node positivity rate for tumours <8 mm and 8–10 mm was 7.6 and 15% respectively. We found that the size of tumour was the best indicator of axillary status. Tumours of special type had no axillary positive nodes (0/34) even when the tumour was up to 10 mm in size.
Conclusion: We conclude that when the tumour has invasive component of less than 4 mm or the tumour is of special type no axillary dissection is necessary. For tumours 5–10 mm, axillary sampling seems to be more appropriate than axillary clearance.

75. Incidence of nodes in completion mastectomy specimens following breast conservation and axillary clearance

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Introduction: The inferior border of an axillary clearance is not defined. Sentinel node biopsy often locates nodes in lower positions than might be expected. Therefore, when axillary clearance is performed with breast conservation, nodes at high risk of involvement may be left *in situ*.
Methods: Pathology records were obtained of 45 patients who underwent axillary clearance and breast conservation, and then required a completion mastectomy. The reports were examined for the status of the nodes from the axillary clearance, an the presence and status of nodes in the completion mastectomy specimen.
Results: Seven patients (15.6%) had documented nodes in the completion mastectomy specimen. These were positive in two patients (4.4% of total patients and 28.6% of patients with nodes in the completion mastectomy specimen), although no patients were upstaged.

Conclusion: Nodes at high risk of involvement are often left *in situ* after axillary clearance and breast conservation. The actual rate may be even higher than that in this study, as detection of these nodes is dependent on the thoroughness of pathological examination. A prospective study with a larger sample size and more detailed pathological assessment may detect a subgroup of patients who are currently being understaged.

76. Pathological assessment of the sentinel node in breast cancer: comparison of H&E and immunohistochemical staining of frozen sections with paraffin sections

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Introduction: Haemotoxylin and eosin (H&E) paraffin sections are well established for pathological assessment of metastasis to axillary nodes. However, when used in sentinel node biopsy, patients with positive sentinel nodes would require further treatment to the axilla. Frozen sections would enable immediate axillary clearance to be performed. Metastases may be difficult to detect on H&E frozen sections. However, cytokeratin 19 (CK19) is reliably expressed by breast cancer cells and is a suitable target for immunohistochemistry (IHC).
Method: Thirty-six sentinel nodes were bisected. Half of each node was processed routinely for paraffin H&E. Frozen sections were cut from the remainder and both H&E and IHC were applied to detect metastasis. The IHC can be performed in 20 minutes, during the mastectomy/wide local excision.
Results: There were 13 positive sentinel nodes on H&E paraffin section. Both H&E and IHC frozen section detected metastasis in 10 of these nodes (sensitivity 77%, false negative rate 23%), and found no metastasis in the remaining 23 nodes (specificity 100%, false positive rate 0%). There was much greater contrast between cancer cells and the background using the IHC.
Conclusion: Frozen sections allow rapid assessment of the sentinel node. Although false negative results do occur, this would affect only a small proportion of node-positive patients. The great majority of patients would have all necessary surgery in one procedure. The false negative results could be due to sampling error, as metastasis may be present in one half of the node only. The excellent contrast provided by IHC indicates the potential for improved accuracy over H&E frozen sections. This may be detected by further study.

77. A comparison of the modes of detection of minimal residual disease (MRD) in breast cancer

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Introduction: Detection of bone marrow (BM) micrometases in primary breast cancer patients is important as identification of even single cancer cells has been shown to increase relapse and reduce survival. A sensitive, rapid and reproducible system is therefore required for analysis of clinical samples. The aim of this study was to compare (i) immunocytochemistry (ICC), with manual versus automated screening of slides, against (ii) immunomagnetic bead separation (IMS), using the Dynal immunolabelled bead system to extract tumour cells followed by cytokeratin (CK) staining, and finally (iii) quantitative PCR (QPCR) for CK19 transcripts.
Methods: We have to date analysed the BM from 19 patients with primary breast cancer and no evidence of distant metastases on clinical staging, using ICC, IMS and QPCR, to look for minimal residual disease (MRD). Samples from a further 20 patients were analysed using ICC, directly comparing manual microscopy with automated imaging and QPCR. In all cases, ICC was carried out using a pan-cytokeratin monoclonal antibody.
Results: We found that with IMS, 63% of patients were positive for MRD as compared with 37% with ICC and 58% with QPCR. Spearman rank correlation ceofficients were 0.93353 for IMS *vs* PCR, 0.90187 for IMS *vs* ICC but the best correlation was with ICC *vs* PCR (0.99674). The dynal beads interfered with immunostaining making screening difficult and this may explain the higher correlation between ICC and QPCR. In the second group of 20 patients, automated screening of the immunostained slides led to more patients being identified as positive (8/20 as compared with 5/20 for manual screening). The specificity of automated screening was substantiated by the improved concordance of the results with QPCR (65%) as compared with manual microscopy and QPCR (46%). No patients were positive by manual screening, which were negative by automated screening. In addition a higher total number of rare events were detected per positive patient. Therefore, tumour cells are being missed by manual microscopy.
Conclusion: These data indicate that IMS and QPCR are more sensitive than ICC. However, IMS needs optimization in view of the technical problems. ICC is the current gold standard for the detection of MRD and automation of screening significantly improved detection and saved time. We recommend using both ICC with automated analysis and QPCR in assessing patients for MRD. Furthermore, automation of screening means that detection and monitoring of MRD can now be carried out in large-scale clinical trials.

78. Predictive factors of local recurrence and distant metastasis in malignant phyllodes tumours of the breast

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Introduction: Phyllodes tumours of the breast are uncommon fibroepithelial tumours classified as benign, low-grade (borderline) and high-grade malignant. Local recurrence and systemic metastases are occasional and occur most commonly in the high-grade malignant group of patients. The aim of the study was to determine parameters that influence outcome in high-grade malignant phyllodes tumours.
Methods: Three hundred and twenty-two phyllodes tumours were reviewed between 1947 and 1999, of which 48 were classified as high-grade. All women were treated with primary surgical excision by local excision (LE, margins <1 cm), wide local excision (WLE, margins ≥ 1 cm) and mastectomy. Cox's regression test was used for multivariate analysis of the data.
Results: The mean patient's age was 47 years, with an average tumour size of 7.5 (range 1.5–20) cm. Ten patients were treated with LE, 14 with WLE and 24 with mastectomy. The average follow-up was 7.3 years (range 5 months–28 years). Local recurrence occurred in 21 patients (44%). The mean time to local recurrence was 28 (range 5–84) months after primary treatment. Distant metastasis occurred in 13 patients at an average time of 25.6 (range 6–120) months. Eleven women had local recurrence prior to developing distant metastasis. In total, 12 out of 48 patients died of metastatic disease. Disease free survival was related to tumour size, excision margins and type of operation, but not to other clinical or histopathological characteristics. Local recurrence and subsequent metastatic spread were, in addition, related to mitotic activity.
Conclusions: Tumour size, surgical margins and mitotic activity were significant factors that predicted local recurrence and metastasis, or metastasis after complete therapy for local disease. Complete surgical excision, by mastectomy if necessary, is important in the primary surgical treatment of malignant phyllodes tumours of the breast.

PARALLEL SESSION VII—BASIC SCIENCE

79. Effect of oestradiol on integrin β1 expression and function

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Introduction: Integrins are αβ-heterodimeric transmembrane proteins that play a leading role in tumour metastasis. There is substantial evidence that breast cancer risk is associated with prolonged exposure to oestrogens. The aim of this study was to assess the effects of oestradil (E2) on integrin β1 expression and cellular function.
Methods: The breast cancer cell line MCF-7, was used to measure integrin β1 expression by Western blot. Cell adhesion assays to matrix proteins were performed to assess integrin function.
Results: MCF-7 cells incubated overnight in different concentrations of E2

demonstrated varying effects on integrin β1 expression. At higher concentrations (10^{-7} M), expression was significantly upregulated by 1.7-fold. At lower concentrations (10^{-11} M), expression was down-regulated by 29%. At E2 concentrations of 10–9 M, an effect on integrin expression could be seen within 15 min and a peak effect at 2 hours. Oestradiol enhanced cell adhesion to both collagen IV and fibronectin, with a significant maximal effect at 10^{-10} M.
Conclusion: Integrins play a leading role in breast cancer metastasis by regulating cell adhesion and invasion. Our data has shown that E2 has an effect on both integrin β1 expression and cellular function. Modulation of integrin function may provide a functional approach to the development of novel anti-metastatic therapies.

80. Purification and characterization of primary breast cancer cells

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Introduction: Human breast cancer cell lines have been the major experimental models in breast cancer research over the years. It has long been appreciated that functional studies using pure populations of primary human breast cancer cells would be more relevant to the *in vivo* situation. The aim of this study was to develop a technique to purify malignant cells from breast cancers and to culture them for a time length sufficient to be able to perform functional studies.
Methods: Tumour tissues were partially digested with collagenase and after appropriate filtration malignant epithelial cells were isolated using Ber Ep4 immunolabelled beads (Dynal). Cells were characterised by cytology, fluorescent *in situ* hybridization (FISH) (using centromere specific DNA probes to chromosomes 6, 7, 11, 12, 17 and 18) and immunostaining for oestrogen receptor and cytokeratin 8 and 18. Epithelial cells from reduction mammoplasties were used as controls. Conditions were optimized for short-term culture.
Results: Cytological examination confirmed >95% purity of malignant cells in 15 tumour samples. FISH performed on cells from six tumour tissues showed a high rate of aneusomy (see table). Broad-spectrum cytokeratin (Dako) immunostaining showed 100% staining demonstrating purity of epithelial cells. Oestrogen receptor staining showed that ER is retained for at least 8 days in malignant cultures but is lost within 3–6 days in benign epithelial cultures (see graph).
Conclusion: We are now in a position to investigate further this novel finding or ER retention in the malignant cells (whether this is at the protein or gene level) and the effect on expression of ER regulated genes. We are now investigating ER function in primary breast cancer cells, studies which until now have been limited to cell lines.

No.	No. purified cells ($\times 10^5$)	% malignant Cytology		% aneusomy FISH	
		Day 0	Day 7	Day 0	Day 7
1	2.0	97	97	80	92
2	2.8	97	98	94	89
3	3.6	97	100	92	90
4	2.2	95	96	88	91
5	4.5	96	95	88	88
6	1.2	99	97	89	88

81. Stimulation of peritoneal macrophage activity by non-cytotic components of intraperitoneal chemotherapy

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Introduction: Chemotherapy drugs adsorbed to activated carbon particles have been employed to prevent the rapid loss of drug molecules from the peritoneum during intraperitoneal chemotherapy. Peritoneal macrophages respond to particulate material by increased activity, including the release of the cytotoxic substances nitric oxide (NO) and tumour necrosis factor (TNF-α). We report the effects of activated carbon (AC) and the wetting agent polyvinyl pyrrolidine (PVP) on peritoneal macrophage function.
Methods: Rat peritoneal macrophages were harvested and cultured for 24–72 hours in the presence of (a) AC (150 μg/ml), (b) PVP (60 μg/ml), (c) AC (150 μg/ml) and PVP (60 μg/ml), (d) bacterial lipopolysaccharid (LPS), (e) γ-interferon 10 iu/ml. Macrophage release of NO and TNF-α were measured colorimetrically using the Griess reagent, and by ELISA respectively. Cytotoxic effects were tested by measuring LDH release from rat Mtln3 carcinoma cells.
Results: γ-interferon, PVP, AC and PVP plus AC all induced large increases in NO production, whilst LPS did not. LPS, AC, PVP and AC plus PVP, but not γ-interferon, all increased TNF-α expression. Unstimulated macrophages did not induce LDH release from Mtln3 cells, but TNF-α did.
Conclusion: The supposedly inert components of this intraperitoneal chemotherapy regimen induce potentially important responses in peritoneal macrophages. The implications for therapeutic and adverse treatment effects deserve further study.

82. Transforming growth factor-beta induced IGFBP-3 prevents ceramide-induced apoptosis in human breast cancer cells (Hs578T)

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Introduction: Cytotoxic drugs induce apoptosis via ceramide production in tumours and this correlates with their efficacy. This action can be mimicked *in vitro* using a synthetic ceramide analogue (C2). In Hs578T cells exogenously added IGFBP-3, independently of IGF-I, can (a) accentuate C2-induced cell death and (b) alone has the ability to dephosphorylate focal adhesion kinase (FAK), a key integrin signalling molecule. TGF-β has been reported to inhibit cell growth in Hs578T cells through the induction of endogenous IGFBP-3. The aim of the study was to investigate the interaction of C2 with TGF-β-induced endogenous IGFBP-3 in Hs578T human breast cancer cells.
Method: (1) Hs578T cells were treated with 5 ng/ml TGF-beta for 5 days ±20 μM C2 on the last day for either 30 min or 24 hours. Growth inhibition was assessed by trypan blue counts, and endogenous IGFBP-3 measured by radioimmunoassay of the conditioned media (CM). Apoptotosis was measured by trypan blue counts and flow cytometry. FAK phosphorylation was investigated using immunoprecipitation with anti-phosphotyrosine and Western immunoblotting with anti-FAK. (2) Dosing was repeated as above with 20 μg/ml antisense mRNA to IGFBP-3 added on days 1, 3 and 5 with the same assessments.
Results: (1) TGF-β caused no cell death but a 53% inhibition of cell growth ($P<0.01$) with a significant increase in endogenous IGFBP-3 ($P<0.001$). C2 caused a 63% induction of apoptosis which was decreased when cells were incubated with TGF-beta and C2 ($P<0.001$). (2) TGF-β alone had no effect on FAK phosphorylation, whereas C2 dephosphorylated FAK at both 30 min (50%) and 24 hours (60%) of treatment. On coincubation with TGF-beta, the dephosphorylation of FAK was reduced at both time points (to 28 and 6% respectively). (3) The antisense mRNA to IGFBP-3 caused a significant decrease (approximately 60%) in endogenous IGFBP-3 to 370 ng/ml ($P<0.001$) and abrogated anti-apoptotic effect of TGF-beta on C2 action, with a significant increase in apoptotic vells ($P<0.001$).
Conclusion: Although exogenously added IGFBP-3 accentuates C2-induced apoptosis the endogenously produced IGFBP-3 in response to TGF-beta inhibited C2-induced apoptosis. The ability of TGF-β induced IGFBP-3 to prevent FAK dephosphorylation may in part influence the subsequent response of the cells to apoptotic stimuli. These findings may have important implications for optimising the efficacy of cancer therapy.

83. Chronic glucose deprivation inhibits aminolaevulinic acid induced photodynamic therapy

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Introduction: Photodynamic therapy (PDT) is a cancer treatment based on the interaction of light, oxygen and a photosensitizer. Protoporphyrin IX (PpIX) is a photosensitizer derived from aminolaevulinic acid (ALA) by the enzymes of the haem biosynthetic pathway. Solid tumours contain areas of poor oxygenation and hypoglycaemia. Tumour cells adapt to these conditions by induction of stress proteins which may render cells resistant to certain cancer therapies.
Methods: The influence of chronic hypoglycaemia on MCF-7 breast cancer cell sensitivity to ALA-induced PDT *in vitro* was studied. Cells were either exposed to 1 or 25 nmol glucose for 48 hours. One mmolar glucose was found to inhibit cellular proliferation (increase $G_{1/0}$ cell cycle phase on DNA staining and flow cytometry) but not impair viability. Cells were cutured in 1 and 25 mMol glucose, then treated with 1 mMol ALA for 4 hours. The amount of intracellular PpIX was measured by spectrofluorimetry. PDT sensitivity was compared between cells cultured for 48 hours in 1 or 25 mmol glucose. Cells were treated with 1 mmol ALA, followed by violet light at an LD 50 dose. Cell survival (%) was determined by clonogenic assay.

Results:

mmol. glucose	25	1
PpIX ng/cell	5×10^{-5} (0.7×10^{-5})	3×10^{-5} (0.3×10^{-5})*
% cells $G_{1/0}$ phase	67.1 (1.6)	79.8 (2.5)*
% PDT survival	39.6 (4.2)	80.5 (16.5)*

($n=9$; * denotes statistical significance compared to 25 mmol value, $P<0.05$, ANOVA plus Mann–Whitney. Data represents means plus standard error).

Conclusion: Chronic exposure to low glucose concentrations may render tumour cells resistant to PDT. This may be the result of reduced intracellular concentrations of PpIX or due to induction of stress proteins.

84. Modulation of protein kinase C (PKC) isoforms in prostate cancer cells by dietary fat

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Introduction: The lipid derived cellular second messenger diacyl glycerol (DAG) is found in high concentrations in malignant prostatic tissue. DAG is considered to be a tumour promoter acting via the PKC signalling pathway. PKC is a family of 10 isoenzymes playing crucial roles in key cellular functions such as proliferation, apoptosis, metastases and expression of oncogenes. We have previously demonstrated that the total PKC activity is significantly increased by fatty acids (FAs) in prostate cancer cells (LNCaP). We have now analysed the modulation of specific isoforms of PKC by FAs.
Methods: One $\times 10^7$ LNCaP cells grown under standard conditions were treated with 100 μM of n-3 eicosapentaenoic acid (EPA). n-6 linoleic acid (LA) and n-9 oleic acid (OA) for 48 hours and the modulation of different isoforms of PKC in the cytosolic and membrane protein extracts were observed using Western blot analysis.
Results: The PKC isoforms β, η, θ and ε were not detected in the LNCaP cells. The PKC isoforms α, ζ and μ were detected but were not modulated by any of the FAs. PKC-δ was down regulated by 60% in the membrane by all the FAs ($P<0.05$). PKC-τ was upregulated in the cytosol by 72–90% by all FAs ($P<0.05$). In addition LA and EPA up regulated PKC-τ in the membranes ($P<0.05$). EPA also down regulated PKC-γ in the membranes ($P<0.05$).
Conclusion: Specific regulation of particular isoforms of PKC by FAs indicates that dietary fat can modulate specific signalling pathways in prostate cancer cells. This observation indicates the potential for modulating these pathways to therapeutic benefit in prostate cancer.

85. Thrombin regulation of vascular endothelial growth factor (VEGF) and tissue factor (TF) in human breast cancer cells

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Introduction: Thrombin, the key enzyme in normal haemostasis, has multiple actions of its protease activity. Thrombin receptors are expressed on human colonic and pancreatic adenocarcinoma cells and melanoma cells. Thrombin is mitogenic for human breast carcinoma cells in culture and it enhances tumour cell adhesion to the endothelium and extracellular matrix and is able to promote tumour cell metastasis. These findings suggest that thrombin plays an important role in tumour cell biology, although its mechanism of action is still unclear. The aim of the current study was to examine the effect of thrombin on vascular endothelial growth factor (VEGF) and tissue factor (TF) expression in human breast cancer cell T47D.
Methods: The human breast carcinoma cell T47D, which expresses progesterone receptor strongly, was stimulated with human α-thrombin in doses from 0.01 to 10 unit/ml. Conditioned media was collected at various time points. VEGF and TF levels were determined by standard ELISAs. RT-PCR was used to examine the effect of thrombin stimulation on transcriptional gene expression for VEGF and TF.
Results: Thrombin stimulation enhanced VEGF release in a dose-dependent fashion from 311 pg/ml to 809 pg/ml at 1 unit/ml at 24 hours ($P=0.013$); the effect was lost at higher doses. It resulted in an increase of TF release from 273 pg/ml to 515 pg/ml at 0.01 unit/ml but in a shorter time frame of 30 min ($P=0.005$). RT-PCR showed that thrombin stimulation upregulates the gene transcription of TF but not that of VEGF gene.
Conclusions: These data indicate that thrombin stimulation has a stimulatory effect on VEGF and TF release from T47D breast cancer cells and may explain a potential pro-angiogenic mechanism.

86. Transcription of components of the renin angiotensin system in human breast and relationship with severity of disease

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Introduction: The angiotensin II type I (ATI) receptor is present in a wide variety of human tissues and is particularly abundant in epithelial cells. In view of this, and the knowledge that tissue renin angiotensin systems (RASs) exist which have specific local functions such as regulation of growth and development of tissues, they may be an important factor in tumour progression. Using the monoclonal antibody 6313/G2 we have previously confirmed that the ATI receptor was characteristically distributed in the epithelial cells of both diseased and non-diseased breast tissue. The aim of the study was to confirm the transcription of components of the renin angiotensin system (RAS) in the breast and relate this to disease severity.
Methods: Samples were obtained from 62 patients. These were examined by reverse transcriptase polymerase chain reaction (RT-PCR) using specific primers designed to amplify a fragment of the ATI receptor (210 bp) and renin cDNAs (142 bp) respectively. Transcription of the respective components was confirmed using northern blot and *in-situ* hybridisation, quantification of ATI receptor mRNA with competitive PCR. Renin and ATI receptor protein were demonstrated by immuno-histochemistry.
Results: ATI receptor and renin were localized to epithelium and myo-epithelium respectively. mRNAs for various components of the RAS were amplified with RT-PCR in all samples analysed ($n=62$) though ATI receptor more so compared to others. The sample groups consisted benign ($n=7$), non-diseased breast ($n=8$) and breast cancer ($n=47$). Densitometric analysis revealed higher transcription of the ATI receptor in benign compared to malignant ($P<0.01$), this difference was less well marked between normal and malignant breast samples ($P<0.05$). This observation was confirmed by obtaining the expected 2.4 kb transcript for ATI with Northern blot analysis. Competitive PCR showed a higher transcription of the ATI receptor in benign samples compared with the others. Confirmation of renin mRNA transcription was obtained by demonstrating a continuous band of (pro) renin transcribing cells in the stroma and myoepithelial layer of the normal and benign samples, whilst in the malignant sample there appeared to be a disruption of the staining (mRNA) using ISH.
Conclusion: These results confirm the existence of a local RAS in breast, furthermore angiotensin II may prevent disease progression.

87. Intraperitoneal gene therapy for desmoid disease in familial adenomatous polyposis

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Introduction: Desmoid disease is unusual in the general population but is a well-recognized extra-intestinal manifestation of the pre-malignant condition Familial Adenomatous Polyposis (FAP). It is now the commonest cause of mortality in FAP patients who have undergone prophylactic colectomy. Currently there is limited available treatment and no prophylaxis. Surgery appears to aggravate the situation, and chemotherapy is minimally effective. Therefore there is a need for minimally invasive, safe prophylaxis and/or treatment.

In FAP, loss of heterozygosity of the Adenomatous Polyposis Coli (APC) gene occurs in the majority of these tumours, so it is reasonable to consider that replacement of a functioning APC gene may prevent or decrease the rate of progression of the disease. This study has looked at the feasibility of injecting additional copies of the normal human APC gene in the plasmid vector pCMV-APC-NeoBam directly into the peritoneal cavity in combination with liposomes to enhance tissue uptake of the gene.
Methods: Eight wild-type mice were treated in this manner and four controls were treated with lipofectamine only. Two treated mice and one control animal were killed at daily intervals from 1 to 4 days. Samples of peritoneum, mesentery, liver, gonads, small and large bowel were collected, snap frozen and examined for the presence of the transgene as mRNA, using techiques of RNA extraction and rtPCR.
Results: The APC transgene was expressed as mRNA within the peritoneum of all the animals treated with the plasmid, in the liver and mesentery of seven, and in the gonads of three out of eight mice treated with plasmid respectively. None of the control animals were positive for the transgene mRNA in any samples, and no signal was generated from tissues in the absence of reverse transcriptase, thus ensuring that the PCR products were not derived directly from the exogenous plasmid, but from mRNA. There was no mortality and no side effects were noted.
Conclusion: Lipofection (unlike viral gene therapy) appears to be safe and we have shown that it allows prolonged expression of the APC gene in the target tissues of mesentery, peritoneum and liver with minimal systemic effect

on the host. The next step is to look at the clinical effect of this treatment in a murine model of desmoid disease in FAP.

88. Bispecific antibody derived from high affinity monoclonal (323A3) to 17.1A antigen (EpCAM) reduces pulmonary metastases, inhibits local tumour growth and prolongs survival in mice given challenge with syngeneic tumour expressing human 17.1A

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Introduction: Low affinity monoclonal antibody to 17.1A has demonstrated a significant survival advantage as adjuvant therapy in Dukes' C colorectal carcinoma. We have demonstrated that high affinity bispecific antibody molecules can retarget lymphocytes to kill human and murine tumours bearing 17.1A *in vitro.* In this study, in order to evaluate the same bispecific antibody *in vivo*, we used a murine model.
Methods: Groups of C57/BL mice were given B16C215 syngeneic cells which have human 17.1A on their surface in two experiments: (i) tumour intravenously then a single i.v. dose and 10 i.p. doses of antibody; animals culled on day 21 and pulmonary surface metastases counted, this was repeated with survival being recorded. (ii) tumour subcutaneously then 10 i.p. doses of antibody; tumour appearance, growth and survival recorded.
Results: In the intravenous tumour model treatment with bispecific antibody (323A3 × CD3) reduced mean pulmonary metastases: (4.6 cf. 208.5 (control); $P<0.001$) and prolonged survival (median 56 days cf. 32 (control); $P<0.01$); low affinity 17.1A IgG and high affinity 323A3 IgG had no significant effect. In the local tumour model 323A3 × CD3 therapy retarded tumour appearance (median 25.5 days cf. 16 (control); $P<0.0001$) and growth (mean volume 5.16 mm^3 cf. 1036 mm^3 (control) on day 18; $P<0.01$); 17.1A IgG and 323AA3 IgG did not have a significant effect. 323A3 × CD3 prolonged survival (median 37 days cf. 23 (control); $P<0.0001$).
Conclusion: In our animal models bispecific antibody (323A3 × CD3) has been shown to be highly effective as therapy for syngeneic tumour with human antigen 17.1A on its surface both as microscopically disseminated and local disease. In view of these findings and the low toxicity of immunotherapy this approach shows promise for human therapy.

89. Studies of APC and β-catenin in the Min/+ mouse

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Introduction: Germline truncating mutations in the Adenomatous Polyposis Coli (APC) gene give rise to the pre-malignant condition Familial Adenomatous Polyposis (FAP). An homologous murine mutation occurs in the Min/+ mouse, an animal model for the human disease, that demonstrates adenomatous polyps predominantly within the small bowel. Somatic mutations in this same gene occur in over 60% of sporadic human colorectal tumours.

It is becoming increasingly clear that a major function of 'normal' APC is to downregulate intracellular levels of another protein, β-catenin, which has been shown to play a vital role in both cell–cell adhesion and signal transduction. We wished to investigate β-catenin levels in the macroscopically normal intestinal tissue of the Min/+ and wild-type (WT) mice to see if this correlated with polyp load and distribution.
Methods: Immunoblotting for β-catenin, co-immunoprecipitation of Apc and β-catenin, and immunohistochemistry for both proteins was performed on small and large bowel tissue from Min/+ mice and WT mice ($n=8$).
Results: There was no difference in total or sub-cellular levels of β-catenin in colonic samples. However, Min/+ mice demonstrated elevated levels of total and membrane bound β-catenin in samples of small intestinal epithelium when compared to their wildtype counterparts. This was supported on immunostaining of tissue slices. Co-immunoprecipitation of Apc and β-catenin also revealed decreased binding of β-catenin by the Min/+ Apc when compared to WT Apc.
Conclusion: The Min/+ mouse develops many small bowel polyps and fewer colonic tumours. This study has shown that intestinal epithelium in the Min/+ mouse has abnormally elevated levels of β-catenin when compared to WT controls, but colonic levels of the protein are not significantly different from that seen in WT controls. This supports a change in β-catenin a a factor underpinning tumourigenesis, in this animal model of FAP.

90. Polymorphism in the Interleukin-1 receptor antagonist gene is associated with an increased risk of breast cancer

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Introduction: Cytokines may play an important role in the pathogenesis of breast cancer by their involvement in angiogenesis, oestrogen synthesis and immunoregulation. Polymorphisms within cytokine genes are therefore suitable candidates for investigation as susceptibility loci for breast cancer. Interleukin-1 (IL-1) α and β are major pro-inflammatory cytokines, with IL-1 receptor antagonist acting as a natural inhibitor. This study aims to determine whether polymorphisms within the IL-1 gene cluster are associated with susceptibility to breast cancer.
Methods: Using a case-control study design, 359 patients with breast cancer, attending two hospitals in North Trent, were recruited. Three hundred and eighty-eight controls were obtained from Blood Transfusion Services. DNA extracted from peripheral blood leucocytes was genotyped for IL-1 polymorphisms, utilising Taqman™ fluorogenic probes for allelic discrimination. The following polymorphisms were assessed: IL-1A +4845, IL-1B −511, IL-1B +3954 and the polymorphism at +2018 in the interleukin-1 receptor antagonist gene (IL-1RN). Carriage rates were compared using chi-squared statistics.
Results: There was a significantly increased carriage of allele 2 of the IL-1RN polymorpism in intron 2 in breast cancer patients compared with controls (Odds ratio 1.46, 95% CI = 1.09–1.96). There was no association between polymorphisms in the IL-1A or IL-1B and breast cancer risk.
Conclusion: Allele 2 of IL-1RN is associated with susceptibility to breast cancer. Although the association confers only a small risk to an individual, it may contribute to a high attributable risk in the population, due to the high allelic frequency.

PARALLEL SESSION VIII—SARCOMA AND OTHERS

91. The role of a plastic surgeon in providing a sarcoma service

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Introduction: Sarcomas, in view of their rarity, are best treated in a specialist centre as part of a multidisciplinary team. The plastic surgeon forms an important part of that team in both advising on wound healing problems and possibilities for limb salvage and as a reconstructive surgeon following resection of primary or recurrent tumours.
Methods: We have retrospectively reviewed the notes of patients where we have been involved in the management decisions or surgical reconstruction.
Results: Over the previous 4 years, there had been 52 patients with a mean age of 42 years (range: 4–83 years) who have required plastic surgical attention. Three had been referred to the sarcoma service but didn't have a tumour, a few had benign tumours. The majority had sarcomas—nine were recurrent tumours whilst 13 had had previous treatment elsewhere that was suboptimal. Fifteen patients had primary bone tumours.

We present the reasons for plastic surgical involvement, the reconstructions required and the complications. Twenty-three patients received adjuvant therapy. Patients were followed up for a median interval of 12 months (range 2 weeks–231 months).

Conclusion: We discuss some of the logistical problems involved with operating a joint service and the impact this has on other service commitments over time.

92. Retroperitoneal sarcoma: a one-centre 10-year experience

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Introduction: Ten per cent of soft tissue sarcomas (STS) are retroperitoneal. The prognosis of patients with retroperitoneal sarcoma is poor with a 5-year survival rate between 12 and 70%. Stage at presentation, high histological grade, unresectable primary tumour and incomplete resection are associated with a more unfavourable outcome. We report our experience of 22 patients with retroperitoneal STS.
Methods: Thirty patients with retroperitoneal soft tissue sarcomas were treated between 1990 and 2000. Follow-up data were available on 22 patients. Patient, tumour and treatment variables were analysed including use of adjuvant therapy and survival status.
Results: Eighteen patients underwent surgery for primary disease, four patients were treated for recurrent disease or metastases. Ten patients presented with pain, seven with an abdominal mass, other presentations included weight loss and haematuria. Tumours included seven liposarcomas, six leiomyosarcomas, three malignant fibrous histiocytomas, two rhabdomyosarcomas, two malignant schwannomas and two non-specified sarcomas. Six primary tumours were completely excised. Median follow-up is 16 months (range <1 month–20 years). Median survival for patients with primary disease was 36 months. Local recurrence rate was 45% and recurrence free interval for 10 patients with recurrence was 11 months. Thirteen patients presented with tumours larger than 10 cm. Five patients received radiotherapy and five received chemotherapy. Five-year survival in this series was 29%. Adjuvant therapy was not associated with higher survival rates.
Conclusion: This study re-emphasizes the poor outcome of patients with retroperitoneal STS. Radiotherapy and chemotherapy do not appear to be of proven benefit and the single most important prognostic factor is aggressive *en bloc* resection of primary disease. Our resection rate and 5-year survival rates are comparable with previous reported UK series although lower than large reports from North American centres. This can partly be explained by difficulty in data collection in a retrospective analysis, but may reflect inadequate subspecialization in UK centres.

93. Neuropilin-1 expression is associated with increased vascular endothelial growth factor (VEGF) production in colorectal carcinoma

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Introduction: A $VEGF_{165}$ isoform specific receptor, identical to neuropilin-1 (NP1), is thought to regulate VEGF induced angiogenesis. We investigated whether the expression of NP1 in human colorectal carcinoma affected local VEGF production and influenced overall survival.
Methods: Sixty-six paraffin embedded colorectal tumour biopsies were stained with anti-VEGF and anti-NP1 monoclonal antibodies by standard immunohistochemistry. VEGF staining was analysed with a microscope based image analysis system (CAS 200, Becton Dickinson) and 2 investigators graded NP1 staining as positive or negative.
Results: Thirty-five per cent of tumours stained positive for NP1. The median percentage positive staining for VEGF was significantly higher in the NP1+ tumours as compared to the NP1− tumours: 59 *vs* 50 ($P=0.002$: Mann–Whitney *U*-test). Following multivariate analysis with a Cox proportional hazards model, intra-tumoural VEGF was found to be a significant prognostic factor for disease recurrence ($P=0.0292$), and overall survival ($P=0.0239$). Sex, age, tumour site, histology and tumour depth were not significant prognostic indicators in multivariate analysis.
Conclusion: This study demonstrates that NP1 expression in colorectal carcinoma is associated with an overproduction of intra-tumoural VEGF and a reduced disease free and overall survival time. We suggest that NP1 might therefore be a candidate for targeting by anti-angiogenic immunotherapy.

94. Pantogens: all the information for quality control and training in oncological operations

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Introduction: Rapid changes in oncological operations, the need for genuine high quality, plus limited training time make the provision of very large amounts of expert surgical information in the operating theatre an imperative. Traditional methods of training require some computer based assistance.
Methods: A simple structure has been devised to provide an unlimited amount of operative surgical information. Each operation is broken down into very small fundamental steps. Eah step consists of up to 16 useful categories. All the information is stored on a word processor, allowing unlimited additions, modifications and updates. Some pantogens have been adapted into interactive multimedia versions on CD-ROM.
Results: Pantogens cover 30 oncological procedures in general surgery, ranging from fine needle aspiration to three-stage oesophagectomy. They contain more than 20 times the information of traditional operative texts. They are used in loose leaf folders in the operating suite, on floppy disks and on the Internet. Colleagues have edited versions to match their own personal preferences. They are suitable for research into the influence of surgical technique on outcomes.
Conclusion: Pantogens are suitable for any operations no matter how simple or complex. Pantogens may well become the benchmark for the performance of the best oncological surgical procedures in the future. Examples will be demonstrated.

95. Tc-99m MIBI-only parathyroid localization—early experience

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Introduction: The purpose of this study was prospectively to evaluate the accuracy of the dual-phase sestamibi scanning technique for parathyroid localisation in patients due to undergo surgery for primary hyperparathyroidism (HPT).
Methods: Consecutive patients referred with primary HPT underwent pre-operative localization using technetium (Tc-99m) labelled sestamibi only, in a dual phase gamma camera technique. Following localization patients underwent a bilateral neck exploration and the actual location of the parathyroid tumour(s) was compared with the scintigraphic localization.
Results: Forty-two patients were recruited over a 24-month period. Six patients were referred for re-operative surgery and 36 underwent a primary exploration. Median age 61 years (range 12–89), raised calcium 2.85 mmol/l (2.60–3.50) and raised PTH 115 ng/l (60–2200). Forty-one (98%) patients are normocalcaemic following surgery (100% re-do, 97% primary). Median tumour weight was 600 mg (130–3200). Seven tumours (17%) were in ectopic sites (one retro-oesophageal, six thymic). The median operative time was 55 min (35–195); seven patients underwent additional surgical procedures (subtotal thyroidectomy—1, CABG—1, varicose vein—1, thyroid nodule—4). For those patients in whom the location of the tumour is known ($n=41$), Tc-99m MIBI scanning correctly localized tumours in 38 (93%) patients. All ectopic tumours were correctly localized. There were two false negatives (sensivity 95%), both in patients with small tumours (320 mg, 335 mg). There was one false positive from a retro-oesophageal thyroid nodule. Four patients (10%) had multi-gland disease (one double carcinoma, three hyperplasia), but this was only predicted by one preoperative scan (25%).
Conclusion: Tc-99m sestamibi dual phase scanning localizes tumour with a very high degree of success and should be used routinely. It has the advantage that it can be used for patients on thyroxine replacement, but is unreliable in detecting multi-gland disease. Bilateral neck exploration remains necessary to diagnose multi-gland disease and does not result in prolonged operative times.

96. Modulation of vascular endothelial cell behaviour by extract from normal human dermis *in vitro*

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Introduction: The extracellular matrix is known to have a major role in organogenesis, angiogenesis, tissue repair and in limiting neoplastic invasion. It is well established that inhibition of neovascularization is important in suppressing neoplastic growth. We have shown previously that there is a factor present in the extracellular matrix of normal human dermis (extracted by citrate buffer) which inhibits fibroblast proliferation in a collagen lattice (blocking cell cycle in S phase) and migration *in vitro*. The aim of the present study, therefore, was to investigate the effect of the buffer dermal extract on the behaviour of endothelial cells *in vitro.*
Methods: Dermal extracts were prepared from human dermis, by using successive solvents (water, normal saline, 1 M saline, citrate buffer and urea). Endothelial cells were obtained from human umbilical cord (primary culture) and grown *in vitro* and the effect of citrate buffer dermal extract was examined over 4 days in culture. Trypan blue was used to assess the toxic effect of the

extract on endothelial cells. The MTT proliferation assay was carried out. The effect of extracts on endothelial cell migration was assessed, using a fibronectin-coated polycarbonated filter.
Results: Citrate buffer dermal extract demonstrated significant inhibition of endothelial cell proliferation without any overt toxic effects ($P<0.05$; Student's *t*-test), particularly in the first 2 days. MTT absorbances (mean $\pm$SD) for the treated cells were 0.66 ($\pm$0.03), 0.52 ($\pm$0.05), 0.65 ($\pm$0.03), 0.68 ($\pm$0.05) and 0.70 ($\pm$0.06) after 12, 36, 60, 84, 108 hours, respectively, compared with control cultures at the same timepoints 0.67 ($\pm$0.03), 0.72 ($\pm$0.1), 0.89 ($\pm$0.05), 0.97 ($\pm$0.08) and 0.99 ($\pm$0.04), respectively. Also, endothelial cell migration was significantly reduced when the dermal extract was used in doses above 0.075 mg/ml ($P<0.05$; Student's *t*-test).
Conclusion: Human dermis contains factor(s) which inhibit(s) proliferation and migration of vascular endothelial cells. These findings may have important implications in different pathophysiological processes where control of vascularization is biologically important.
(MTT: (3[4,5-Dimethylthiazol -2-yl] -2, 5- diphenyltetrazolium bromide Thiazolyl blue).

97. Reliability of the sentinel node procedure in melanoma patients ($n=289$): incidence of failures after long-term follow-up

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Introduction: The sentinel node (SN) procedure seems valuable only if the identification and retrieval of the SN can be performed with the utmost accuracy. The reliability of the procedure especially ensues from the rate of successful identifications and from the number of failed procedures occurring during follow-up. The aim of the present study is to determine the reliability after a follow-up period of minimal 2 years.
Methods: From August 1993 to May 1998, 289 consecutive patients with stage I or II cutaneous melanoma, underwent SN biopsy by a triple technique.
Pre-operatively, all patients underwent (dynamic) lymphoscintigraphy. A gamma probe and blue dye helped in localizing the SN(s) during surgery and these nodes were subsequently excised. These lymph nodes were step-sectioned and examined by routine and immunohistochemical staining. If the SN contained tumor cells, a total lymphadenectomy was performed at a later date.
Results: The median follow-up time was 44 months. A positive SN was found in 54 patients (19%), and a negative SN in 230 patients (79%). In five patients (2%), the SN was not retrieved as a consequence of its localization, which yielded an identification rate of 98%. Four patients developed a recurrence in the negative S basin during follow-up, without simultaneous appearance of (loco-regional) metastases, which is a failure rate of 1% (4/289) and a false-negative rate of 7% (4/58).
Conclusions: With a 98% identification rate and 1% failed SN procedures (7% false-negative rate) after a median follow-up of 3.5 years, it is obvious that the combined triple technique approach of detecting the SN is a reliable method to accurately identify and retrieve the SN.

98. Prognostic factors and survival in malignant pleural mesothelioma

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Introduction: Although the incidence of malignant pleural mesothelioma (MPM) is increasing in the UK and Western Europe, it is unclear as to which patient and tumour-related factors are of prognostic value.
Methods: We have conducted a retrospective study of 553 patients presenting with histologically confirmed MPM. In particular we have analysed the influence of age, sex, presenting symptoms, histology, diagnostic delay and asbestos exposure on survival.
Results: Survival analysis confirmed a predictive value for two factors: age at diagnosis and histology ($P<0.00005$). Patients less than 55 years old survived longest. Histological subtype of tumour was also highly predictive. Epithelioid mesothelioma was associated with the best survival. The desmoplastic variant had the worst prognosis, with a 1-year survival of only 4%. Age and histology were confirmed as independent prognostic factors on regression analysis. Women enjoyed a slight survival advantage over men ($P=0.04$) but this effect was lost when histological subtype was corrected for. No particular symptoms were associated with a poorer prognosis. Asbestos exposure and the length of diagnostic delay did not affect survival.
Conclusion: This study confirms the prognostic value of age and histology in MPM and emphasizes the need to control for these factors in any future studies of treatment.

99. Periosteal osteosarcoma—evaluation of surgical and adjuvant measures in improving survival

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Introduction: Periosteal osteosarcomas are rare cartilage-rich bone tumours characterized by a juxtacortical eccentric position. While there is general agreement that wide surgical excision is required, there is a paucity of evidence regarding adjuvant therapy. Previous reports have not indicated any consistent approach to this to allow appraisal. We compare our experience with previous studies to evaluate both surgical and oncological methods of treating this tumour.
Methods: We retrospectively reviewed 17 cases treated at our centre over 16 years. All patients underwent surgery to remove the tumour. Limb reconstruction was usually necessary either at the time of primary excision or subsequently. Our policy was to use chemotherapy when the tumour showed any features of high grade.
Results: Ten of 17 patients received an endoprosthesis primarily, 4/17 had excision only and 3/17 excision and bone graft. Fourteen of 17 received chemotherapy. There was one local recurrence in the excision group treated by re-excision and endoprosthesis. To date, no deaths have resulted from recurrence or metastasis of the tumour although there have been two deaths from other causes.
Conclusion: Our survival figures compare favourably with those reported previously. We suggest that this is probably the result of the evolution of surgical techniques and the contribution of adjuvant therapy. Further research is required to establish who benefits most from chemotherapy, but at present we would recommend it be considered in all cases of periosteal osteosarcoma showing any features of high grade.

100. Factors predictive of survival of patients with retroperitoneal soft-tissue sarcoma: does surgical experience influence survival?

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Introduction: Surgery is the principle modality of therapy in the management of retroperitoneal soft-tissue sarcomas (RSTS). Individual experience is usually limited and may be of prognostic importance. Among other possible prognostic factors the influence of surgical experience on outcome was studied in a population based study in the Netherlands.
Methods: With help of the Dutch Network and National Database for Pathology (PALGA), data were collected on 143 patients in the Netherlands in whom a RSTS was diagnosed between 1/1/1989 and 1/1/1994. Median age was 60 (range 18–88) years, there were 79 females (55%). Follow-up was done until February 1999. The prognostic importance of tumour- and treatment-related factors was evaluated.
Results: After a median follow-up of 84 months, 1-, 3- and 5-year survival for all patients were 66%, 49% and 39% respectively. Univariately, complete resection ($P<0.001$), age <60 years ($P<0.001$), low malignancy grade ($P=0.02$), lipomatous histomorphology ($P=0.003$), non-invasive growth ($P<0.001$), and the absence of distant metastasis ($P=0.005$) were associated with favourable outcome. Malignancy grade, distant metastasis and the extent of surgical treatment remained independent prognosticators in a multivariate context. The level of experience was associated wth a higher rate of radical resections, but did not affect outcome.
Conclusion: Survival of patients with RSTS was determined independently by the extent of surgery, distant metastasis and malignancy grade. The level of experience, although influencing the result of surgery, did not affect long-term outcome.

101. Clinical detection of soft tissue sarcomas—how specific are the four cardinal features?

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Introduction: The four most common features of a soft tissue sarcoma are: size >5 cm; pain; increasing size; deep to the deep fascia.
We have assessed the reliability of these simple clinical criteria in diagnosing soft tissue sarcomas.
Method: The cases of 590 soft tissue lesions presenting to a specialized tumour unit over 2 years were reviewed to assess the sensitivity and specificity of the above four factors in diagnosing malignancy. The presence of each of the factors was noted along with the eventual diagnosis confirmed histologically.
Results: In isolation none of the above four factors were diagnostic of malignancy, the best being 'increasing size' which had a positive predictive value of 69%, followed by both 'pain' and 'size >5 cm' both of which had

PPV of 60%. More importantly the opposites were much more diagnostic of benignancy in that tumours superficial to the deep fascia were benign in 85% of cases and lumps not increasing in size were benign in 80% of cases. The cumulative predictive values of having one, two, three or all four of the cardinal features present were 15%, 24%, 67% and 85% respectively. Importantly there was no case of malignancy in any lump which was smaller than 5 cm, painfree, static in size and superficial to the deep fascia. We found that any combination of three or more of the above factors had a positive predictive value for malignancy of 73%.
Conclusion: The above four criteria are useful in indicating a lesion which needs to be investigated for potential malignancy. Even patients with just one of the above features had a one in six chance of having a malignancy. All suspicious soft tissue lumps should be treated as malignant until proved otherwise.

102. A biopsy of a suspected soft tissue sarcoma in the retroperitoneal area: the diagnostic yield and the risk of contamination of the different procedures

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Introduction: A biopsy is important to clarify the nature of a retroperitoneal mass, but its value in case of a suspected retroperitoneal soft tissue sarcoma (RSTS) is unclear. The diagnostic accuracy and the influence on the occurrence of local tumour spread of the different biopsy procedures was assessed.
Methods: Data were collected on 143 patients (64 males and 79 females, median age 60 years) in the Netherlands in whom a RSTS was confirmed histologically between 1/1/1989 and 1/1/1994. Biopsies were done during clinical work-up in 85 patients (59%), and in them the yield was assessed of fine-needle aspiration (FNA), core needle biopsy (CNB), and surgical biopsy (SB). The risk of developing local tumour spread was evaluated by comparison of the biopsied patients to those who had had no biopsies prior to surgery ($n=58$).
Results: A total number of 122 biopsies was performed: FNA ($n=46$), CNB ($n=61$) and SB ($n=25$). The proportion of affirmative biopsies was 22% for FNA, 54% for CNB, and 72% for SB (FNA *vs* CNB, $P=0.001$; FNA *vs* SB, $P<0.001$; CNB *vs* SB, $P=$ns). At the time of surgical treatment ($n=123$), no significant differences in the presence of local tumour spread were seen following pre-operative SB (4/16 = 25%), needle biopsies (8/49 = 16%), or when pre-operative biopsies weren't taken (11/58 = 19%; $P=0.74$). Following complete tumour resection ($n=78$), no significant differences were seen in 5-year local disease free proportional survival (SB, 50%; needle biopsy, 52%, no biopsy, 45%; $P=0.91$).
Conclusion: The yield of a biopsy in case of a RSTS was limited for all three techniques, being lowest for FNA. No effect of needle and open surgical biopsies was found on the occurrence of loco–regional tumour spread.

PARALLEL SESSION XI—TWO WEEK RULE

103. Is there any difference between routinely and urgently referred cancers?

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Introduction: In April 1999 a national directive was introduced which stated that 'all urgent breast referrals must be seen within 2 weeks of the General Practitioner's (GP) decision to refer'. There is mounting evidence that this directive has resulted in routine referrals waiting longer, whilst a significant minority of cancers are found in this group.
Methods: The aim of our study was to identify all cancers referred routinely and compare them with an age matched cohort of urgently referred cancers.
Results:

	Routine $n=44$	Urgent $n=44$
Size of tumour (mm)		
median ± IQR*	20 ± 9.5	25 ± 10
range	7–45	9–90
Grade of tumour (No of cases)		
1	6	7
2	25	22
3	13	15
Nodal status (No of cases)		
positive	21	23
negative	21	19
Nottingham Prognostic Index		
median ± IQR	4.35 ± 2.07	4.42 ± 1.9
range	2.2–46.54	2.34–7.4

* Mann–Whitney $P<0.01$.

Conclusion: The vast majority of patients presenting with breast cancer have a painless lump in the breast, without palpable axillary nodes. GPs are dependent purely on their clinical skills to accurately diagnose. It is perhaps nott surprising, therefore, that cancers referred routinely are significantly smaller than those referred urgently, though other prognostic factors show no difference.

104. Prioritization of referrals to a breast clinic: how do clinicians compare with general practitioners?

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Introduction: The 'two week' target aims to ensure that patients whom the general practitioner (GP) suspects may have breast cancer (SBC) are assessed rapidly by specialist teams. This study compares outcomes for patients prioritized by clinicians in 1997 with patients referred as SBC by GPs in 1999.
Methods: A retrospective audit of referrals between 1 April 1997 and 30 October 1997. Referrals were prioritized by the clinicians from the referral letter, and correlated with outcome. This was compared to a retrospective audit of referrals between 1 August and 31 December 1999, of patients referred as SBC by GPs.
Results: In the first audit period 779 referrals were received. One hundred and ninety (24%) were allocated high priority by the clinicians, of which 44/190 (22%) were carcinoma. Five hundred and eighty-nine referrals were given lower priority, of which 14 (2.3%) were carcinoma. In the second audit period 1159 referrals were received. Two hundred and fifty-two (21.6%) were referred as SBC, of which 66/252 (26%) were carcinoma. Nine hundred and seven patients were referred less urgently. Of these 19 (2%) were carcinoma. (Chi-squared; no significant differences).
Conclusion: Transferring responsibility for prioritization of referrals to primary care has not produced a significant change for patients. A small proportion of patients allocated lower priority prove to have breast cancer, and prioritization by the examining GP has not improved this.

105. Prioritization of breast referrals: is age the safest criterion?

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Introduction: Government guidelines require that when a general practitioner refers a patient with suspected breast cancer that she be seen within 2 weeks. Proforma referral letters have been recommended to aid prioritization by GPs but several centres have subsequently reported a high proportion of breast cancers with non-urgent referral.
Methods: The age distribution of patients who present with breast cancer at a DGH Breast clinic was reviewed. The age profile, urgency of referral and

diagnosis were reviewed for each GP referral between April and December 1999.
Results: Of 2100 patients with breast cancer on the database only 14 (0.7%) were aged 30 or less. Five patients were aged 26 or less. There were 1176 GP referrals in nine months of which 115 had breast cancer. There were 54 cancers in 249 urgent referrals (22%) but there were 61 cancers in the 927 referrals rated as routine (7%). One hundred and fifty-two (13%) of referrals were aged 30 or less of which 21 were rated urgent. Only one patient aged 30 or less (27 years) had breast cancer whose referral was rated routine. Ninety-three (8%) of referrals were aged 26 or less of which 11 were urgent.
Conclusion: Prioritization by general practitioners is unsafe. The risk of prioritization by age alone would be much less but would save very few urgent referrals. Prioritization of referral of women over 30 carries a risk of delay if there is consequent increase in the waiting times for non-urgent referrals.

106. The impact of colorectal cancer awareness week

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Introduction: The aim of this study was to identify knowledge of bowel cancer awareness week and to determine whether this affected knowledge of colorectal cancer symptoms.
Method: A questionnaire was given to all non-emergency patients attending their GP surgery during the week following bowel cancer awareness week. The questionnaire examined knowledge of colorectal cancer symptoms, sources of information and awareness of bowel cancer awareness week. This was compared to knowledge of breast cancer since the two diseases have a similar incidence.
Results: Seventy-seven patients responded (96% response rate). Median age was 42 (40% male). Eighty-five per cent could name a breast cancer symptom compared to 41% who could name a symptom of colorectal cancer ($P<0.0001$ McNemar's chi-squared). Only 21% had heard of bowel cancer awareness week and none could name its symbol whereas 70% had heard of breast cancer awareness week and 28% knew the symbol for it ($P<0.0001$ McNemar's chi-squared). Twenty-five per cent of those who had heard of bowel cancer awareness week and 42% of those with a family history of bowel cancer could not name a symptom of the disease. The main sources of information for both diseases were television/radio and magazines/newspapers but respondents identified more sources of information for breast cancer (mean = 2) than bowel cancer (mean = 1).
Conclusion: Despite the similar incidence of colon and breast cancer, knowledge of colorectal cancer is significantly less than breast cancer. In part this may be due to the greater publicity given to breast cancer. Currently, bowel cancer awareness week has not impacted on the general public in the same way as breast cancer awareness week and is failing to educate the public on colorectal cancer symptoms.

107. Preliminary evaluation of UK national referral guidelines for lower gastrointestinal tract cancers

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Introduction: From July 2000 all patients suspected of having lower GI tract cancer by their GP must be seen within two weeks of referral. Guidelines have been developed to help GPs identify those patients requiring urgent assessment. The aim of this ongoing, prospective study is to evaluate the criteria used in the guidelines.
Methods: Consecutive patients aged 50+ referred with lower GI tract symptoms were given urgent, soon or routine outpatient appointments according to information in the referral letter. The clinical information obtained during the outpatient consultation was used to identify those patients that satisfied the guideline criteria for urgent referral. Patients were investigated and the findings recorded.
Results: Between September 1999 and March 2000, 166 referrals were seen. Fourteen patients had no investigations and are excluded from the analysis. Lower GI tract cancer was diagnosed in nine of the remaining 152 patients. Urgent outpatient appointments were given to 57 patients of whom six had cancer ($\chi^2 = 3.47$, $P>0.05$). If the referral guidelines had been used to prioritize these cases, 71 patients would have required urgent appointments and all nine patients with cancer would have been identified for assessment within two weeks of referral ($\chi^2 = 10.92$, $P<0.001$).
Conclusion: The guidelines can be an effective method for prioritizing referrals.

PARALLEL SESSION XII—OESOPHAGO-GASTRIC CANCER

108. Prospective evaluation of possum methodology in the audit of oesophageal carcinoma including unresected cases

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Introduction: The aim of this study was to evaluate POSSUM methodology in auditing results of oesophagectomy for oesophageal cancer and investigate the physiological score as a measure of patient fitness.
Method: Data required to calculate the physiological and operative scores for all oesophageal cancer patients were collected prospectively. The scores and POSSUM estimated morbidity and mortality risks were calculated after surgery. The pre-operative FEV_1 was recorded. Predicted morbidity and mortality was compared to the observed rates. The physiological scores for patients deemed unfit by the consultant surgeon were compared to those under going surgical resection.
Results: Ninety-nine patients entered the study. Of these 23 were assessed by the consultant surgeon as being unfit for surgery, 27 had advanced disease that precluded resection and 49 had oesophagectomy. Crude mortality and morbidity rates were 7 (14%) and 23 (47%) respectively. The percent predicted FEV_1 for the unfit was significantly less than for patients having resection with ($P = 0.02$) and without post-operative complication ($P = 0.009$) but there was no difference between the FEV_1 in the unfit and those who died post-operatively ($P = 0.2$) or those who died and those who survived surgery ($n = 0.9$). POSSUM risk estimation for post-operative morbidity and mortality agreed with the observed rates with overall observed/expected ratios of 0.99 and 1.3 respectively. POSSUM physiological scores were significantly greater in the unfit than the resected patients ($P<0.001$) and between those dying post-operatively and those surviving with ($P = 0.01$) and without complication ($P = 0.04$). There was no difference in the physiological scores for those with or without complications ($P = 0.37$).
Conclusion: POSSUM satisfactorily estimates risk for morbidity and mortality in patients having oesophagectomy for carcinoma and the physiological score correlates with the consultant surgeons impression for fitness for resection and the risk of post-operative mortality. FEV_1 correlates with the impression of fitness for surgery but not the risk of death. POSSUM methodology may be useful in comparative audit of oesophagectomy between units including the selection policy used for patient fitness for resection.

109. Positive truncal nodes for oesophageal carcinoma: not always a dismal prognosis

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Introduction: Nodal involvement of the truncal area is considered metastatic disease (M1a) in the 1997 pTNM classification for mid- and distal oesophageal neoplasms. Patients with pre-operatively diagnosed stage IV (M1) tumours are generally not considered candidates for potentially curative oesophagectomy. With the development of advanced pre-operative staging techniques, e.g. endoscopic ultrasonography with the fine needle aspiration

(EUS-guided FNA), the possibilities of diagnosing small positive coeliac lymph nodes are improving. In this study we evaluate whether it is justified to exclude all patients with nodal involvement of the truncal area, from curative surgery.
Methods: Survival data of 112 patients who underwent subtotal oesophageal resection for a mid-/distal oesophageal carcinoma between 1993 and 1997 were analysed. All patients underwent transhiatal resection with routine dissection of lymph nodes near the origin of the left gastric artery. The other nodes near the celiac trunc were dissected only when clinically suspect.
Results: Eighty-seven men and 25 women (mean age 63±11 years) were included. There were 16, 29, 11, 38 and 18 patients with pTNM stages I, IIa, IIb, III and IV (M1a) respectively. Conventional pre-operative staging had not been able to identify positive truncal nodes in the 18 patients with stage IV disease (16.1%). On multivariate analysis radicality and lymph node status were significant independent prognostic factors for survival (HR 3.2; 95% CI 1.8–5.7 and HR 3.1; 95% CI 1.7–5.9 resp.). However, there was no significant difference between stage III and IV tumours: for stage III tumours median survival was 1.54 years IV (95% CI 0.60–2.48) versus 1.46 years (95% CI 0.55–2.53) for stage IV tumours ($P=0.91$). At the end of follow-up 5/18 patients with stage IV disease were still alive.
Conclusion: Survival of patients with tumours of the oesophagus after oesophagectomy is related to radicality and lymph node status. The presence of malignant cells in small, resectable lymph nodes near the coelic trunc (not detected pre-operatively by conventional staging procedures) does not imply a dismal prognosis in patients who undergo intended curative surgery. With the current possibility of more accurate subtle staging of truncal lymph node involvement by EUS-guided FNA, more tumours might be classified as stage IV pre-operatively. However, these new endosonographic cytologic findings should be interpreted with caution, until firm criteria for irresectability/incurability of positive truncal nodes are established.

110. Proximal and distal gastric cancer. The influence of extent of resection and tumour subsite on survival

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Introduction: The extent of resection required for gastric cancer and the influence of tumour subsite on prognosis remain controversial. This study aimed to compare the outcome following radical total gastrectomy (T-G) versus subtotal gastrectomy (St-G) with specific reference to primary tumour sub-site.
Methods: A consecutive series of 149 patients (median age 68 years, M:F ratio 2:1) undergoing absolute curative (R0) primary radical gastrectomy from May 1989 to Oct 1999 were studied. Distal third tumours underwent St-G whereas middle or proximal third tumours were subjected to T-G.
Results: In hospital mortality was 4% for T-G and 4.2% for St-G. Both groups were comparable in terms of age, M:F ratio, extent of lymphadenectomy and disease stage (UICC 5th edition). 1, 3 and 5-year survival in relation to extent of resection and tumour subsite are shown below:

	n	1-year	3-year	5-year	Median (months)
St-G	48	90%	67%	53%	>60
T-G	101	72%	45%	33%	29.3*
Lower 1/3	48	90%	67%	53%	>60
Middle 1/3	26	69%	52%	47%	55.6
Upper 1/3	75	73%	40%	26%	27.4†

* Log rank = 5.6; 1 df; $P=0.018$; † Log rank = 7.2; 2 df; $P=0.028$.

Conclusion: Proximal gastric cancers have a significantly worse prognosis compared to distal tumours, despite the greater extent of associated resection. Whilst good long-term survival is achievable with radical surgery alone for antral cancer, the dismal outlook for proximal tumours demands further assessment of multi-modality therapy.

111. Pure gastric or duodenal reflux is associated with increased risk of Barrett's oesophagus

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Introduction: The aetiology of the lower oesophageal columnar metaplasia (Barrett's oesophagus—BO) is not clearly understood. The aim of this study was to determine the nature and constituents of the gastrointestinal refluxate that induce BO.
Methods: *In vitro* BO models were established surgically in Sprague–Dawley rats by physiological refluxate of pure gastric, bile, duodenal secretions; and gastric + bile, gastric + duodenal, gastric + pancreatic, duodenopancreatico-biliary and duodenogastroesophageal reflux. After 4 months the lower oesophagus was examined with H&E stains for length and intensity of columnar change and severity of inflammation by an experienced pathologist blinded for the procedure.
Results: The columnar metaplasia of the lower oesophagus was seen in all the groups. Length of columnar change in pure gastric reflux (PGR) and pure duodenal reflux (PDR) was significantly longer than all other groups (PGR (length in cm ± SEM) (1.12±0.10) (all $P<0.05$), PDR (0.93±0.06) ($P<0.001$)). The severity of inflammation and metaplastic change was higher in the gastric and duodenal groups as compared to the other groups.
Conclusion:
(1) Reflux of pure gastric, pure duodenal, pure biliary secretions or mixed refluxates can produce columnar metaplasia in oesophagus.
(2) Reflux of pure gastric or pure duodenal contents produced metaplasia of much greater intensity and extent compared to other groups.

112. Omeprazole is ineffective in Barrett's oesophagus caused by pure duodenal reflux

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Introduction: The role of proton pump inhibitor omeprazole in columnar metaplasia of the lower oesophagus (Barrett's oesophagus) is not completely understood. Our aim was to assess the therapeutic role of omeprazole in preventing Barrett's oesophagus.
Methods: Oesophago-intestinal anastomosis were performed to achieve pure gastric, pure duodenal, pure biliary and various combination of refluxes in 10 groups of Sprague–Dawley rats. Omeprazole elixir was administered to half of each group during 4 months of the post-operative period. Histological examination for columnar change and severity of metaplasia was performed using H&E staining by an experienced pathologist blinded to the experiment.
Results: Inflammation and columnar metaplasia was seen in all groups. In pure duodenal reflux group, Omeprazole treatment caused longer columnar change in oesophagus compared to untreated group ((length in cm ± SEM) (1.08±0.08) ($P<0.001$)) and similar changes were seen in groups with dominant duodenal contents. In pure gastric reflux group Omeprazole treatment had significantly decreased columnar length than untreated group (1.04±0.12) ($P<0.005$) and the groups with dominant gastric contents had similar trend.
Conclusion:
(1) Omeprazole increased columnar metaplasia in pure duodenal reflux group, and decreased in pure gastric reflux group.
(2) Duodenal reflux may be the cause of ineffectiveness of Omeprazole in a significant number of Barrett's oesophagus patients.

113. Early distant recurrence after oesophagectomy—a failure of staging

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Introduction: Despite stringent staging investigations, including spiral CT and endoscopic ultrasound, many patients present with distant recurrence within 12 months of apparently curative radical surgery for oesophageal carcinoma. The aim of this study was to identify potential prognostic clinico-pathological characteristics in these patients in order to clarify the failure of current pre-operative staging.
Methods: Two hundred and one consecutive patients (median age 64 years, M:F ratio 2.6:1) discharged from hospital after potentially curative (R0) subtotal oesophagectomy with two-field lymphadenectomy for oesophageal carcinoma between 1/5/90 and 1/5/99 were followed up for evidence of distant recurrence in the first post-operative year. Investigations were performed for symptoms or clinical signs of recurrence.
Results: The ratio of adenocarcinoma (ACA) to squamous carcinoma was 2:1. Fourteen per cent (28 patients) developed proven distant recurrence within 12 months of surgery (bone 5.5%, liver 5.5%, lung 1%, brain 1%, peritoneal 1%) with a median time to recurrence of 9 months (1.5–12) and a median survival thereafter of only 1.5 months (0–13.9). In these patients adenocarcinoma was the predominant histological subtype (79%). Depth of tumour invasion ≥ pT3 ($P<0.05$), nodal involvement ($P=0.02$), poor tumour differentiation ($P=0.02$) and lymphatic or vascular invasion ($P<0.01$) were all significantly associated with early distant recurrence. Twenty-five per cent (17/69) of patients with pT3N1 ACA developed distant metastases including 10% (7/69) with bone metastases and 7% (5/69) with liver metastases.
Conclusion: A high proportion of patients with pT3N1 oesophageal ACA develop bony or hepatic metastases within 12 months of curative surgery. Pre-operative bone scintigraphy and liver MRI for patients staged as T3N1 by current investigations may identify patients who would be more appropriately managed by non-surgical palliation.

PARALLEL SESSION XIII—BREAST ADJUVANT THERAPY

114. A novel grading system assessing the pathological response to primary chemotherapy in breast cancer predicts survival

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Introduction: Primary chemotherapy is used to treat large breast cancers. However, at present there is no reliable method of assessing the degree of pathological response to primary chemotherapy in breast cancers. A novel grading system for assessing pathological response to chemotherapy and its role as a prognostic indicator for survival has been examined.
Methods: Patients with large primary breast cancers (>4 cm) received six pulses of chemotherapy. Pathological response was assessed in the resected breast tissue using a novel five-point graded scale according to the degree and appearances of tumour cells (1 = no response to 5 = complete response). All patients were followed up for 5 years. Survival and disease free intervals were calculated and compared to pathological response using Kaplan–Meier and the log-rank test.
Results: One hundred and seventy-six patients have been recruited into this study. Overall 5-year survival for all patients was 76%. Survival according to response grade is shown below.

Response grade	5-year survival (%)
1	60
2	65
3	78
4	82
5	100

Log-rank test: 0.022.

Conclusion: This novel method of assessing pathological response can be used to predict survival and disease-free interval in patients receiving primary chemotherapy for breast cancer.

115. Improvements in response and disease-free interval in patients receiving primary chemotherapy with taxotere for breast cancer

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Introduction: Primary chemotherapy is commonly used to treat breast cancer. The most efficacious drug regimens utilize anthracyclines, but many cancers fail to respond. The aim of this study was to determine the efficacy of primary taxotere in patients with breast cancer.
Methods: Patients with breast cancer received four pulses of CVAP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy. Clinical response was then assessed. Those with a partial (PR) or complete clinical response (CR) were randomized to receive either four further pulses of CVAP or four pulses of taxotere. All patients, whose tumours failed to respond, received four further pulses of taxotere. Following this chemotherapy regimen, clinical response was assessed and surgery was carried out. Pathological response was assessed in the resected breast tissue.
Results: One hundred and seventy patients have been enrolled into the study; 105 were suitable for randomization. In randomized patients, after chemotherapy completion, the clinical PR or CR rate was 67% in the CVAP group and 96% in the taxotere group ($\chi^2 = 12.57$, $P<0.001$). Non-randomized patients had a clinical PR or CR of 43%. Pathological response in randomized patients was 43% with CVAP and 78% with CVAP plus taxotere ($\chi^2 = 2.05$, $P = 0.15$); in non-randomized patients it was 42%. In addition, patients receiving taxotere had a significantly increased disease-free interval ($P<0.05$).
Conclusion: Primary treatment with taxotere resulted in substantial and significantly increased responses and disease-free interval.

116. Clinical and biological factors that predict response of operable breast cancer to neoadjuvant chemotherapy

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Introduction: Neoadjuvant therapy allows great rates of conservative surgery when response occurs.
Method: Women with primary operable large breast carcinoma treated by neoadjuvant chemotherapy between January 1993 and December 1998 were studied. All of them had performed core biopsy before starting chemotherapy for 4–6 cycles of combined AC, CMF, EFC or MMM. All core biopsies were assessed for the following tumour biological markers: oestrogen (ER), progesterone (PR), Ki_{67}, epithelial growth factor receptors (EGFR) and Cerb-B_2.
Results: Sixty-three women (mean age: 46; range: 32–65 years) who had operable breast cancer (mean size: 6.4; range: 3–12 cm) had been included in this study. Fifty-two patients (83.3%) of them showed response to neoadjuvant treatment (9.6% complete, 72.7% partial). Although the size of a breast tumour observed at the start of preoperative therapy was unrelated to a tumour response to primary chemotherapy ($P = 0.33$), initial size was a predictor of complete tumour response ($P<0.001$). Excluding the tumours which were eligible to breast conservative surgery from the start (primary tumour <4 cm, $n = 12$), we have found that primary chemotherapy had saved the breast of 21 (52.5%) patients out of 40 who were initially going to have mastectomy. The mean of ER, PR, Ki_{67} were 20.3, 23.8, 33.1 in responders compared with 26.2, 24.9, 19.3 in non-responders (statistically significant with Ki67 only, Mann–Whitney test = 0.136, 0779, 0.001 respectively). Seventy-one per cent of Cerb-B_2 negative and 64% of EGFR negative tumours were responders but that was not statistically significant (Chi-square = 0.127, 0.743 respectively).
Conclusion: Initial size <2 cm could predictor of complete tumour response. Ki_{67} could be used as single predictive value of the response of cancer breast to neoadjuvant chemotherapy.

117. *Targ*eted *i*ntra-operative radio*t*herapy (*TARGIT*): a novel approach for local treatment of breast cancer

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Introduction: We believe that conservative treatment of breast cancer may not require radiotherapy that encompasses the whole breast. We present here the clinico–pathological basis for this belief and a novel therapeutic approach that allows intra-operative radiotherapy to be safely and accurately delivered to the target tissues in a standard operating theatre.
Methods: Whole-organ analysis of mastectomy specimens reveals that 80% of occult cancer foci are situated remote from the index quadrant. In contrast, over 90% of local recurrences after breast conservative therapy occur near the original tumour—even when radiotherapy is not given. Therefore, these occult cancer foci may be clinically irrelevant and radiotherapy to the index quadrant alone might be enough.

The Photon Radiosurgery System (PRS) is an ingenious portable electron-beam driven device that can typically deliver, intra-operatively, 5–20 Gy, respectively, to 1 cm and 0.2 cm from the tumour bed over about 22 min. The pliable breast tissue—the target—wraps around the source providing perfect conformal radiotherapy. Being soft X-rays, the dose attenuates rapidly ($\alpha \sim 1/r^3$), reducing distant damage.
Results: In our pilot study of 25 patients (age 30–80 years, T = 0.42–3.5 cm), we replaced the routine post-operative tumour bed boost with *targ*et *i*ntra-operative radio*t*herapy. There have been no major complications. The cosmetic outcome has been good to excellent and no patient has developed local recurrence at the median follow-up of 12 months.
Conclusion: It is safe and feasible to deliver *targ*eted *i*ntra-operative radio*t*herapy (*Targit*) for early breast cancer. We have now begun a randomised trial of *Targit vs* post-operative radiotherapy—with a potential elimination of the conventional 6-week course of radiotherapy.

118. Pre-treatment predictors of survival in locally advanced breast cancer treated with multi-modality therapy

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Introduction: Multi-modality therapy for locally advanced breast cancer has improved survival rates. However, many patients still have a poor prognosis. This study aimed to detect which patients were likely to have a poorer prognosis prior to commencing treatment by assessing a range of factors related to the patient, tumour, acute phase response and indices of immune function (natural cytotoxicity).
Methods: Eighty patients with locally advanced breast cancer were treated with primary chemotherapy, surgery, radiotherapy and tamoxifen. They were followed up for 5 years. The following factors were entered into a survival analysis: age, menopausal status, albumin level, CRP, CD56, natural killer cell activity, clinical tumour size and axillary node status.
Results: Five-year survival rate was 72%. Results of a multivariate (Cox's proportional hazard) analysis of these factors revealed that reduced CD56 count ($P=0.04$), increased clinical axillary nodal stage ($P=0.04$) and a lower serum albumin level ($P=0.002$) independently predicted patients with a poorer survival.
Conclusion: Pre-treatment albumin levels, CD56 counts and clinical axillary nodal assessment were independent predictors of survival in patients with breast cancer treated with multi-modality therapy.

119. Prognostic indicators in locally advanced breast cancer treated with primary chemotherapy

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Introduction: Primary chemotherapy for locally advanced breast cancer has been shown to downstage tumours and may prolong survival. This study aimed to detect whether a variety of factors related to the primary tumour, nodal metastasis and response to chemotherapy, predict survival.
Methods: One hundred and seventy-five patients with locally advanced breast cancer were treated with primary chemotherapy followed by surgical resection of residual tumour. They were followed up for a mean of 70 months (38–120 months). Clinical and pathological responses were assessed after completion of chemotherapy.
Results: Three-year survival was 82% and disease free three-year survival 75%. Results of a univariate (log-rank test) and multivariate (Cox's proportional hazard) analysis for a variety of prognostic factors are summarised below.

Univariate	*P*	Multivariate	*P*
ER status	<0.001	Clinical response	0.04
Clinical response	0.04	% nodes with tumour	0.04
Path response	0.04		
Node status	<0.001		

Conclusions: Axillary node positivity following chemotherapy and clinical response to chemotherapy are independent predictors of survival following primary chemotherapy for breast cancer.

POSTERS

120. Do p53, TGFβ and FAS-L play a role in the development of post-transplant dermal neoplasia?—Immunohistochemical assessment of serial skin biopsies

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Introduction: The relative risk for the development of skin neoplasia in the transplant population is up to 100 times that of the general population. Although the increased incidence of skin tumours is attributed to immunosuppressive therapy, the actual molecular mechanism of tumourogenesis has not been explored. The aim of this study was to determine expression of three molecules associated with dermal tumourogenesis—p53, TGFβ and Fas-L—in sequential skin biopsies obtained from renal transplant recipients.
Methods: Four sequential skin punch biopsies (0, 3, 6 and 12 months) were obtained from 40 cadaveric renal transplant recipients, using the dorsum of the non-dominant hand. Serial paraffin sections were stained for elastin and for p53, TGFβ and Fas-L using immunohistochemistry. The intensity of staining for each individual waas compared with their peritransplant biopsy stain intensity.
Results: Although no focal points of malignancy were identified, increased expression of proteins occurred in 12/40 patients as shown below. These changes were over and above background variation.

Time of onset	p53 ($n=2$)	TGFβ ($n=6$)	Fas-L ($n=6$)
3 months	1	2	2
6 months	0	3	3
12 months	1	1	1

Conclusion: This preliminary study will be extended to include 2, 3 and 5 years follow-up biopsies to determine if the early increases in protein expression are progressive. Long-term follow-up should also determine whether these changes predispose to the development of skin neoplasia and if so whether they could be subsequently used as a predictive marker of the risk of developing skin malignancies.

121. A quantitative, microsphere based cytotoxic drug targeting assay for human breast cancer cells using laser flow and scanning cytometry

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Introduction: The drug treatment of aggressive breast and other cancers is handicapped by systemic toxicity and lack of drug specific targeting assays. One approach to better use of existing drugs is with microsphere based delivery systems such as using human serum albumin as a vector (Cytocaps). Anthracyclines such as doxorubicin exhibit intrinsic fluorescence, which is a valuable marker for quantitative studies of drug distribution and metabolism using laser cytometry.
Methods: Flow (FCM) and laser scanning (LSC) cytometry were used to study the uptake and binding of Cytocaps–doxorubicin, albumin-TRITC and free drug is a series of time course experiments on MCF-7 Wild Type (WT) and drug resistant (R) breast cancer cells. Drug effect on cell viability was assessed by trypan blue assay and evidence of apoptosis. The passage of Cytocaps into cells was also observed by image analysis.
Resuts: *In vitro* studies showed Cytocaps bound to the surface of 80% of WT cancer cells within 1 hour of incubation and was still present on the surface at 24 hours. They were endocytosed by 48 hours and drug release into the cytoplasm was observed up to 120 hours. Only 50% of MCF-7/R cells showed Cytocaps binding by 72 hours. TRITC-AM bound similarly to cells as Cytocaps, suggesting the binding phenomenon was doxorubicin-independent. Free doxorubicin passed directly to cell nuclei within 24 hours of incubation and thereafter migrated back into the cytoplasm. The cytotoxic effects of free drug and cytocaps in MCF-7/WT cells were cytostatic and were identical at comparable concentrations (0.5 μM).
Conclusion: Microsphere based drug delivery systems such as Cytocaps are an effective way of sequestering and delivering a cytotoxic agent *in vitro*, suggesting a method for reducing systemic toxicity *in vivo*. Laser scanning cytometry advances quantitative and qualitative studies of drug delivery to target cancer cells.

122. Expression of renin in human breast tissue and correlation with prognostic factors

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Introduction: Angiotensin II (AII) is the biologically active peptide of the renin angiotensin system. Most of the known physiologic actions of AII are mediated via its type I (ATI) receptor. AII in the context of a local renin angiotensin system (LRAS) regulates growth and development of tissues and thus may be an important factor in tumour progression. Using a specific monoclonal antibody (6313/G2) and cDNA primers for the AT1 receptor we have previously shown its protein expression and mRNA transcription in breast tissue. The aim of this study was to determine the cellular location of renin at protein and mRNA levels, correlate these with factors that affect prognosis of breast cancer.
Methods: Formalin fixed paraffin embedded breast tissue sections cut at 5 μm were subjected to immuno-histochemistry using the streptavidin–biotin complex labelling technique. The specific monoclonal antibody for human renin (2D12) was used. mRNA location was investigated by *in situ* hybridization using a single-stranded digoxigenin-labelled ribo probe.
Results: Of the 102 patients with primary breast cancer, 35 (34.4%) had axillary lymph node involvement, the remainder were node negative. Using the 2D12 monoclonal antibody renin was mainly cytoplasmic in its location. The cells stained include the myoepithelium, epithelium and fibrous tissue stroma. There was significantly more immunoreactive renin in myoepithelium compared to the other sites ($P<0.0001$). Renin mRNA was transcribed mainly around the stromal and myoepithelial cells in the normal non-diseased tissue. Whilst in primary breast cancer there was a disruption of this band of positively stained cells mainly in the myoepithelium.
There was a positive correlation of stromal renin expression with node positive disease ($P<0.02$). Furthermore increased immunoreactive renin was associated with vascular invasion ($P<0.01$). Larger tumours had a greater expression of renin compared with smaller tumours but no relationship was observed with histological tumour grade.
Conclusion: Overall these results suggest a higher content of immunoreactive renin in poorer prognostic tumours, furthermore that renin acting within a LRAS may be involved in the progression of primary breast cancer.

123. Integrin β1 expression and long-term oestrogen deprivation

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Introduction: Integrins are transmembrane proteins that are involved in a diverse array of cellular processes including cell adhesion migration and growth. The mechanisms involved in the transition of breast tumours to steroid hormone-independent growth remain poorly understood. The aim of this study was to assess the effects of oestrogen deprivation on integrin β1 expression.
Method: MCF-7 cells were cultured in oestrogen deficient medium (phenol red free RPMI-1640 containing 10% charcoal stripped serum) for over 100 weeks. Integrin β1 expression of these long-term oestrogen-deprived (LTED) cells, was established at regular intervals by Western blot.
Results: Integrin β1 expression of the LTED cells was compared to that of wild-type MCF-7 cells grown in RPMI-1640 supplemented with 10% fetal bovine serum. Integrin expression was significantly upregulated during weeks 1 to 25 of oestrogen deprivation. During this time the cells were noticeably more difficult to trypsinise during passage. The peak effect was during weeks 20–25 with a 2.8 fold induction of integrin β1 expression. After 25 weeks the cells appeared to adapt to oestrogen deprivation with little or no change

in expression between weeks 26 to 109 compared to control wild-type cells.
Conclusion: We have demonstrated that integrin β1 is significantly upregulated during weeks 1 to 25 of oestrogen deprivation. Our data suggests that integrins may play an integral role in the adaptive changes of tumours of steroid-independent growth. Modulation of integrin function may provide a functional approach of preventing the evolution of tumours to a hormone insensitive state.

124. Conjugated linoleic acid reduces breast tumour growth

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Introduction: Dietary fatty acids play an important role in carcinogenesis. Oleic acid (present in olive oil), eicosapentanoic acid and docosahexanioc acid (both present in fish oil) may have anti-tumour effects. Recently attention has focused on the fatty acid conjugated linoleic acid (CLA). This study has evaluated the anti-tumour effects of CLA on breast cancer cells (oestrogen receptor positive and negative).
Methods: Breast cancer cell lines (MCF7, MDA-MBA-231) were grown to subconfluence and incubated with the above fatty acids in concentrations of 0 to 200 μM. After 24 hours and 48 hours culture cell growth was assessed using an MTT assay. All experiments were carried out in triplicate.
Results: EPA elicited an inhibitory effect on both cells only at high concentrations (>100 μM, $P<0.01$) but no effect was observed at lower levels. However, exposure to CLA resulted in a dose dependent reduction in growth in MCF7 cells—20% reduction at 6.25 μM, 50% at 100 μM and 65% at 200 μM of CLA ($P<0.01$). Similar results were obtained for the oestrogen receptor negative MDA-MBA-231 cells (reductions up to 39% at 200 μM of CLA ($P<0.01$).
Conclusion: CLA had the most potent action of the fatty acids assessed in reducing cell growth and its effects were more marked in oestrogen receptor positive cell lines. Further studies are now indicated to determine if these effects will occur *in vivo*.

125. Interleukin (IL)-10 as a possible mediator of the defective immune response in human breast cancer

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Introduction: We have shown that the main source of the immunosuppressant cytokine IL-10 in human breast carcinoma is tumour-associated mononuclear (TAM) phagocytes (unpublished data). The functional consequences of IL-10 produced by these mononuclear phagocytes, on putative anti-tumour immune mechanisms, are unclear. The aim of this study, therefore, was to define more clearly the possible inhibitory effects.
Methods: We determined the effects of supernatants from U937 monocytic cells, following culture with breast cancer cell (MDA-MB231, MCF-7) conditioned media (CM), on lymphokine-activated killer (LAK) cytotoxicity and proliferation capacity of peripheral blood mononuclear cells (PBMCs), using standard *in vitro* ^{51}Cr release assays (4 hours) and PHA-dependent proliferation ($[^3H]$ thymidine) of PBMCs (72 hours), respectively.
Results: While no significant change of LAK cytotoxic activity was observed, a dose-dependent inhibition of $[^3H]$ thynidine uptake was demonstrated, as compared with controls. Neutralizing antibodies to IL-10 significantly, although not completely, reversed the PBMCs growth-inhibitory activity produced by the supernatants.
Conclusion: These results show that the inhibition of PBMC proliferative activity was primarily due to IL-10 produced by the monocytic cells following culture with breast cancer cell CM. By contrast, no significant effects on LAK cell activity were observed. This is consistent with earlier observations that IL-10 only weakly inhibits LAK cytotoxicity. Taken together, these results suggest that IL-10 produced by TAM phagocytes may have important regulatory effects on anti-tumour immune responses by inhibiting the expansion of immune effector cells.

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126. Breast cancer in elderly and infirm. Does radiotherapy after excision under local anaesthetic help?

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Introduction: Since 1991, elderly and infirm patients over 70 years have been treated with surgery under local anaesthetic in our unit. Between February 1991 to April 1994 42 of these patients received tamoxifen as adjuvant treatment and then from then on till May 2000 radiotherapy was added to the adjuvant treatment. We have audited our data to determine whether radiotherapy offers any additional advantage in terms of local recurrence or survival.
Methods: A total of 90 breast cancer patients from 1991 to 2000 have been treated with primary surgical resection under local anaesthetic with the mean age of 81.9 years (range 70 to 96 years) and a mean follow-up of 79 weeks (range 1 to 352 weeks). All patients are followed at 1, 12, 24, and 52 weeks and then yearly. Data are recorded on tumour size (clinical and histological), grade, margins and vascular invasion.
Results: Five patients in each group developed local recurrence, which were treated with re-excision under local anaesthetic. Seven patients (16%) in surgery and tamoxifen only group and five patients (10.9%) in surgery + tamoxifen + radiotherapy group developed generalised or bony metastasis. Mortality in surgery and tamoxifen group was 18/42 (42.8%) with the mean survival of 21.4 months and in surgery, tamoxifen and radiotherapy group 7/48 (14.6%) died with mean survival period of 17 months.
Conclusion: We conclude that addition of radiotherapy to surgery and tamoxifen in these elderly and infirm patients is of questionable value in terms of local recurrence or survival.

127. Surgery after neoadjuvant therapy for locally advanced breast cancer may be reserved for residual or recurrent disease

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Introduction: A significant number of patients with locally advanced breast cancer (LABC) treated by primary chemoradiotherapy (C/RT) or radiotherapy alone (RT) will have complete clinical and radiological resolution of the tumour. The aim was to evaluate a conservative policy to salvage surgery after neoadjuvant therapy for LABC.
Methods: Patients presenting with LABC between 1979 and 1997 were treated with RT alone in the early part of the study and subsequently with C/RT. Patients treated by primary surgery, metastatic disease at presentation or by primary tamoxifen therapy were excluded. Post-treatment surgery was reserved for patients with residual disease. Local recurrent disease was treated with surgery or further chemotherapy. Life table analysis was used to compare disease free and overall survival in the two groups.
Results: One hundred and ten (110) patients with LABC were included. The mean age in the RT alone group was 62 *vs* 50 in the C/RT group. In the RT alone group there were 34 patients *vs* 76 patients in the C/RT group. Additional tamoxifen was given to 89 patients (81%). Eighty-four per cent of patients had complete response to the therapy. Twenty patients (18%) had surgery for residual disease. The mean follow-up was 68 months in the RT alone group *vs* 38 months in the C/RT group. On follow-up 21 patients (19%) had local recurrence and 52 patients (47%) have died. There were four patients with local recurrence at the time of death and two of these had had a previous mastectomy. Life table analysis showed a non-significant trend to improved recurrence free and overall survival in the C/RT group, $P=0.5$ and $P=0.2$ respectively (log-rank test).
Conclusion: Salvage surgery after neoadjuvant therapy can be safely reserved for residual or recurrent disease in patients with locally advanced breast cancer.

128. Prevention of chemotherapy-induced premature ovarian failure with goserelin

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Introduction: The aim of this study was to determine whether temporary interruption of the hypothalamic–pituitary axis by administration of a luteinizing hormone releasing hormone analogue, goserelin, during cytotoxic chemotherapy, would diminish the incidence of chemotherapy-induced premature ovarian failure in pre-menopausal women with breast cancer.
Methods: A retrospective analysis was carried out on women selected from the Cancer Research Campaign Adjuvant Breast Trial for women under fifty years old. Twelve patients were evaluated at a mean interval of 2.4 years after completion of treatment. Six had been treated with goserelin during their course of adjuvant chemotherapy and the other six, who served as controls, had received only chemotherapy. The mean age at diagnosis was 43.3 years in the goserelin-treated group and 38.8 years in the control

group. Chemotherapy consisted of cyclophosphamide, methotrexate and 5-fluorouracil in both groups. At interview, patients completed questionnaires on their menstrual and reproductive history. Serum oestradiol, follicle-stimulating hormone (FSH) and luteinizing hormone levels were measured in all patients. Ovulation was assessed by mid-luteal phase serum progesterone.
Results: Eight patients, three in the control and five in the study group, developed evidence of ovarian failure with permanent amenorrhoea, low serum oestradiol and high FSH levels. Of the four patients who retained their menstrual cycles and had normal oestradiol and FSH measurements, only three showed positive ovulation tests.
Conclusion: Goserelin did not prevent chemotherapy-induced ovarian failure. However the results were inconclusive as patients in the goserelin group were perimenopausal. The study should be repeated prospectively in women below 40 years old.

129. Is breast MRI superior to clinical examination in the assessment of response to primary medical therapy?

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Introduction: The role of breast MRI in defining the extent of residual disease both during and on completion of primary medical therapy, was evaluated and compared to clinical and histological assessments.
Methods: Over 18 months, 15 newly diagnosed breast cancer patients (16 tumours) with locally advanced breast cancer (T3–4, N0–2) were recruited prospectively. At presentation, 4–6 weeks and on completion of chemotherapy (18 weeks), patients were assessed clinically and by MRI.
Results: Mean tumour bidimensional product by clinical assessment was three times greater than by MRI ($P<0.000$) and two times greater than by mammography ($P<0.003$). There was a statistically significant correlation between clinical and MRI assessments of tumour bidimensional product at presentation ($r=0.67$; $P=0.007$), on completion ($r=0.63$; $P=0.012$) but not at 4–6 weeks ($r=0.27$; $P=0.429$). All patients underwent nipple preserving breast conservation surgery and only two patients had close or positive resection margins. Patients were followed up for 31.2 ± 10.7 months (mean $\pm$ SD), 1/16 had residual disease 2/16 died of metastatic disease and 13/16 are alive and free of recurrence.
Conclusion: MRI is more accurate than clinical examination both in assessing tumour size at presentation and in assessing the extent of residual disease during neoadjuvant chemotherapy.

130. Is tamoxifen alone in the treatment of elderly patients with breast cancer justified?

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Introduction: A third of breast cancers occur in women over 70. It is a widely held view that the cancers in these women are less aggressive and tamoxifen alone is sufficient. However, more recent papers refute this and advise surgery even in frail patients under a local anesthetic.
Methods: We identified elderly patients who were judged to be frail and not ideal candidates for surgery, treated with tamoxifen alone from the years 1997 and 1998. The notes of these patients were reviewed and data extracted.
Results: One hundred and ninety-eight patients presented with breast carcinoma of which 24 were treated with tamoxifen alone initially. Over the follow-up period only 2 (8.6%) of these patients had poor local control and needed further treatment and three (13.04%) developed distant metastasis. There were seven deaths in the series and only four (16.6%) of these were due to cancer.
Conclusion: The preliminary results from the study indicate that tamoxifen alone in this group of frail patients is adequate treatment and does not decrease survival rates significantly.

131. Tubular, lobular and other low-grade carcinomas are difficult to diagnose on FNA cytology requiring core biopsy for definitive pre-operative diagnosis of malignancy

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Introduction: While FNA cytology is now in widespread use in breast screening many units now use combined FNA/core biopsy for preoperative diagnosis of breast lesions.
Methods: A retrospective review was performed of all screening and symptomatic disease core biopsies performed in our unit prior to the introduction of combined FNA/core biopsy. The 34 core biopsies included in this study were all required to show sufficient invasive carcinoma to assess tumour type and grade on the core biopsy alone, with direct comparison with prior FNA cytology results.
Results: At least half of the carcinomas diagnosed on core biopsy could not be graded as less than 10 high power fields of tumour were available for examination. Of the remaining 34 cases grade 1 carcinoma was seen on core biopsy in 28 of 33 cases and grade 2 carcinoma in the remaining five cases. No grade 3 cases were identified. While there was no significant association with the Nottingham Modified Bloom and Richardson tubule score (1–3), mitotic score (1–3) or pleomorphism score and FNA category (C1–C5), there was a significant association of overall Nottingham grade and cytology category (C1–C5) ($P=0.036$). There was also a large excess of carcinomas of tubular or classical lobular morphology.
Conclusion: If FNA cytology is used alone without combination core biopsy low-grade cancers may be difficult to diagnose with certainty. Accurate assessment of histological grade requires several needle cores of tissue to ensure that adequate tissue is available for histological assessment of tumour grade. The results of this study suggest that the same combinations of histological features that are applicable to histological grading of breast carcinoma may also be directly relevant to the understanding of the reasons for difficulty in conclusive cytodiagnosis of malignancy in breast FNA.

132. The outcome of C1 fine needle aspiration cytology of breast lumps

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Introduction: The aim of this study was to test the hypothesis that acellular fine needle aspirate cytology (FNAC) (C1) of breast lumps not suspected as being malignant on the basis of clinical examination or mammography indicates benign pathology.
Methods: During a 41-month period, from July 1994 to December 1997, of the 687 patients who were referred to the breast clinic with a breast lump and who underwent FNAC, 138 (20.1%) were reported as C1. Their case notes were retrospectively reviewed.
Results: Of these six cases (4.3%) finally proved to be malignant. In five patients the diagnosis of malignancy was suspected on both clinical grounds and imaging. In the sixth patient, malignancy was confirmed on imaging, although it was not suspected clinically. To date, out of the initial 138 patients with C1 FNAC, excluding the six malignant cases, only 16 patients presented again to the breast clinic. The majority of them were complaining of the same lump, and after further investigations, including repeat FNAC, none were found to have malignancy.
Conclusion: In the absence of clinical or mammographic suspicion of malignancy, C1 cytology generally equates to benign breast pathology.

133. Factors determining inadequate FNA cytology in patients with palpable breast cancers

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Introduction: Fine needle aspiration (FNA) cytology is an essential component in the triple assessment of breast lesions. This study retrospectively analysed factors contributing to inadequate (C1) cytological specimens in patients with invasive breast cancer.
Methods: Patients with palpable breast cancers ($n=396$) were identified from data prospectively collected between January 1996 and December 1998. FNA specimens were taken by surgeons using a hand-held 20 ml syringe with a 23G needle. Cytological smears were prepared using the Cytospin method. Patients with inadequate (C1; $n=98$) and adequate (C2–C5; $n=298$) cytological specimens at their first clinic visit were compared. The experience of the aspirator and the pathology of the tumour were obtained. Statistical analyses were by the chi-squared and Mann–Whitney *U*-tests.
Results: There was no difference in the proportion of C1 samples taken by consultants or trainees (82/345 (24%) *vs* 16/51 (31%); $\chi^2=1.00$, df = 1, $P=0.32$). There were no differences in the median (mm; range) tumour diameters (C1 = 20; (7–110) *vs* C2–C5 = 18; (2–70). $P=0.48$) or grades ($\chi^2=4.98$, df = 2, $P=0.08$) between the two groups. A greater proportion of lobular compared to ductal tumours had initial C1 cytology (20/44 (45%) *vs* 55/273 (20%); $\chi^2=12.1$, df = 1, $P=0.005$).
Conclusion: Neither the experience of the clinician taking the FNA sample nor the size and grade of the tumour appeared to influence the cytological result. The histological type of the tumour was the most important factor that determined the rate of inadequate cytology.

134. Palpable breast cancer which is mammographically invisible

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Introduction: We have evaluated tumour characteristics, local recurrence rates and prognostic markers in 40 women with symptomatic palpable breast cancer proven by cytology, but in whom routine two-view mammography failed to detect a radiological abnormality. We believe that this is the most comprehensive study on women with mammographically invisible breast cancer, as well as being the first European study to examine the success of breast conservation therapy (BCT) in treating these patients.
Methods: This was a retrospective study based on mammograms performed at the Royal Victoria Infirmary during the period 1995–1999, as well as records from the pathology department at the same institution. All mammograms were performed within 6 months of pathological diagnosis of malignancy. The median follow-up period was 18 months after the pathological diagnosis of malignancy.
Results: The average age was 48 years. There were 35 invasive ductal carcinomas and one tubular, lobular, medullary, clear cell and invasive adenocarcinoma. The average tumour size was 24 mm, and there were nine Grade I, 16 Grade II tumours and 15 Grade III tumours. Lymphovascular invasion was seen in 18 on histology. Eighteen out of 38 patients receiving an axillary dissection had involved lymph nodes and in six patients distant metastases were present at presentation. Of those patients treated by conservation therapy in only one was there a local recurrence, with a median follow-up of 18 months. This patient is clear of disease, but five others have died.
Conclusion: We conclude that mammographically invisible tumours are of common histological type, frequently of high grade and node positive, and frequently occur in the younger age group. However, these tumours may be satisfactorily treated by wide local excision in appropriate cases.

135. Mammographic patterns and breast cancer risk

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Introduction: The aim of this study was to evaluate the risk of breast cancer with respect to mammographic density as described by Wolfe who classified the mammograms into N1, P1 codes (less density) and P2 and DY codes (increased density).
Methods: In 1980 a prospective study of symptomatic breast clinic, was set up to determine whether patients with Wolfe code P2 or DY had a higher risk of developing breast cancer than those with N1 or P1 codes. A total of 5021 women between 1980 and 1985 had their mammograms coded according to Wolfe classification. We present our interim results of the analysis of this cohort. From the pathology records of the hospital and crematorium records form district crematorium, we have matched the cases that had a diagnosis of breast cancer with our cohort to identify patients that developed interval breast cancer.
Results: We have identified a total of 280 patients in the initial cohort who have developed breast cancer. The distribution of these patients according to Wolfe coding was as follows: N1 = 42, P1 = 51, P2 = 143, DY = 44. The overall proportion of low-risk codes (N1 and P1) was 33% and that of high-risk codes (P2 and DY) was 67%. The proportion of these codes in the overall sample of 5001 evaluable patients was 51% and 49% respectively. This difference was statistically significant.
Conclusion: The interim results are in line with the earlier reports that high density Wolfe coding increased the risk of breast cancer.

136. Use of the Internet to provide information for patients attending breast clinics

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Introduction: Patients attending breast clinics are anxious and if diagnosed with breast cancer may fail to recall information provided in the clinic. The Internet is an exciting new tool for providing information to such patients, but there is little data relating to its use in this context. This study investigated whether patients referred to a specialist breast clinic in Glasgow had access to the Internet, and whether they would make use of a breast disease information website.
Methods: Three hundred and forty-seven patients attending the specialist breast clinic completed a questionnaire which included questions on their age, PC ownership, and Internet access and what features they would want on a breast disease information website. We also asked patients if they had previously sought information relating to breast disease and from what source.
Results: Median age was 48 years (range 13–91). On the DEPCAT score for social class, patients were from all seven deprivation categories with a median DEPCAT score of three. Thirty-seven per cent of patients had a computer at home and 32% had Internet access. Forty-four per cent of patients had previously sought information about breast disease, from sources including GP (57%), magazines (44%) and family and friends (43%). Seven per cent had looked for information on breast disease via the Internet. Fifty per cent of patients said they would use an Internet-based breast disease website for information. Most commonly requested features were breast cancer (85%), investigations used in diagnosis (76%) and benign breast disease (74%).
Conclusion: Access to and usage of the Internet by the general population is growing rapidly. Patients attending breast clinics already seek information from a variety of sources, and will increasingly search the Internet. Breast specialists have the opportunity to provide accurate and relevant information to their patients via the Internet, and should make use of this by providing hospital-base web sites.

137. Meeting the two week wait for breast cancer in a district general hospital

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Introduction: This prospective study was carried out to determine whether specific changes in the referral process of patients with suspected breast cancer made it possible to meet the 2 week waiting time in a district general hospital. In addition, it is desirable that patients diagnosed with breast cancer receive surgical treatment within four weeks, and we prospectively studied whether the provision of designated theatre time achieved this target.
Methods: A breast referral proforma sheet was designed for use by local generaal practitioners for patients suspected of having breast cancer. A dedicated facsimile line was instituted, and all referrals seen and assigned clinic dates by a senior clinical nurse specialist. All patients were seen in a 'one-stop' breast clinic. Data was prospectively collected over a seven month period, starting on 1 April 1999.
Results:

Month	Number of urgent referrals received	Number seen in two weeks (%)	Number of breast cancers (%)	% receiving surgery in 4 weeks
April	80	80 (100)	7 (9)	83
May	38	38 (100)	3 (8)	100
June	31	31 (100)	9 (29)	100
July	47	47 (100)	10 (21)	100
Aug	43	43 (100)	13 (30)	100
Sep	61	61 (100)	7 (11)	100
Oct	50	50 (100)	8 (16)	100

All cases of breast cancer detected during this 7 month period were referred as urgent cases, as identified by accepted Guidelines, and seen within 2 weeks. Within 1 month of provision of designated theatre time, all patients with breast cancer received surgery, where appropriate, within 4 weeks.
Conclusion: It is possible to meet the 2 week waiting time for patients suspected of having breast cancer and also for patients diagnosed with cancer to receive definitive surgery within four weeks in a district general hospital.

138. The 'two week wait' for suspected breast cancer: its impact on a symptomatic breast unit and correlation of referrals with outcome

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Introduction: The 'two-week' target aims to ensure rapid assessment of patients suspected of having breast cancer (SBC) by specialist teams. This study assesses the impact on referrals in relation to outcome.
Methods: Referral numbers between 1 August and 30 November 1997, 1998 and 1999 were audited. Outcomes of SBC referrals for August to December 1999 were collected and correlated with all new breast cancers diagnosed during the same period.
Results: Total new referrals in these periods in 1997, 1998 and 1999 were 608, 853 and 958. SBC referrals for successive months from August to December 1999 were 37, 40, 62, 74 and 41. The numbers of new breast cancers in these referrals were 11/37 (29%), 7/40 (17.5%), 9/62 (14.5%), 21/74 (28%) and 14/41 (34%). Sixty-three per cent were received within 24 hours. Between 1 August and 31 December 1999, 100 new breast cancers were

diagnosed. Sixty-nine were referred as SBC, but 30 were allocated lower priority from their referral letter (one awaited).
Conclusion: Referrals have increased and the 'two week' rule means SBC referrals take urgent clinic spaces. A significant number of new breast cancers were not prioritised as SBC and appointments for these patients were delayed while some patients were seen urgently unnecessarily.

139. Assessment of grade and type of breast cancer on core biopsy: inter-observer variability and comparison with excision histology

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Introduction: Core needle biopsy is increasingly utilized in the pre-operative diagnosis of breast cancer. This technique has been shown to be as reliable surgical biopsy in diagnosing invasion. This study examines the accuracy of grade and type evaluation from core biopsies, by assessing interobserver variation between pathologists, and comparing their results to subsequent excision histology.
Method: Core biopsies of invasive breast cancers diagnosed at the Royal Hallamshire Hospital, between 1997 and 1999, were independently assessed by two specialist pathologies. The histological type and grade, assigned by each pathologist, were evaluated for inter-observer agreement and then compared to the history of the excised specimen. This was achieved by contingency table analysis and calculation of a Kappa statistic (<0.4 = poor, 0.4–0.6 = moderate and >0.6 = excellent).
Results: Between 1997 and 1999, 189 consecutive core biopsies from breast carcinomas were assessed. Concordance figures for type and grade of tumour are given below.

	Type—Kappa value (95% CI)	Grade —Kappa value (95% CI)
Core biopsy pathologist 1 *vs* 2	0.38 (0.22–0.53)	0.36 (0.28–0.5)
Core biopsy pathologist 1 *vs* final histology	0.54 (0.38–0.71)	0.27 (0.17–0.4)
Core biopsy pathologist 2 *vs* final histology	0.47 (0.33–0.60)	0.29 (0.15–0.38)

Conclusion: Concordance rates for the reporting of tumour grade and type on core biopsy specimens is moderate to poor. Results, pertaining to grade and type, from core biopsies should be interpreted with caution particularly when planning neoadjuvant therapies.

140. Is the 20 g standard for benign open biopsies in screen detected lesions too generous?

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Introduction: British Association of Surgical Oncology (BASO) guidelines for Breast Screening state '80% of biopsies which prove benign should weigh <20 g'. Nationally there has been continuing debate as to whether this directive is too strict, indeed, the national average for the screening period 1998/99 shows that only 51% were <20 g. In our unit we use combined image guidance (CIG) for such procedures i.e. standard wire localization is performed, but the tip of the wire is then located and marked on the skin using ultrasound.
Methods: Our results were audited prospectively and compared with a retrospective group prior to the introduction of this technique (control).
Results:

	No	Median (IQR)	Range	% <20 g	% <10 g
All diagnostic biopsies (control)	14	19.5 ± 14.5	4–77	50%	14%
All diagnostic biopsies (CIG)	9	5.5 ± 4.2	2.9–13.2	100%	89%
All diagnostic benign biopsies (control)	7	18 ± 18.5	7–77	71%	14%
All diagnostic benign biopsies (CIG)	7	5 ± 3.6	2.9–13.2	100%	86%

Conclusion: CIG is a simple and cheap technique, using equipment already available in the Breast Imaging Department. It provides an additional coordinate, which enables more accurate positioning of the skin incision in relation to the breast lesion. Although numbers are small, due to improved pre-operative diagnosis rates, we believe that this technique demonstrates that the 20 g target is easily achievable, and possibly too generous.

141. Predictors of positive margins after local excision of DCIS

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Introduction: This study aims to examine the association between positive margins after local excision of DCIS and clinico–pathological parameters.
Methods: We retrospectively reviewed the clinical, radiological and pathological data of 100 women who had undergone local excision of DCIS in our centre.
Results: Sixty-seven per cent of patients presented via breast screening and 55% of all cases were diagnosed preoperatively on FNA cytology (i.e. C5). Overall, 45% of patients had clear margins after initial local excision. Positive margins showed a non-significant trend of association with distribution of MCC, non-consultant operating surgeon, inconclusive pre-operative FNAC, presence of necrosis and low specimen weight. There was a highly significant association between low grade DCIS ($P = 0.003$) and incomplete excision. There was no significant association with age, associated invasive focus, morphology of MCC or with mode of presentation.
Conclusion: Positive margins after local excision of DCIS are significantly associated with low nuclear grade and pre-operative determination of nuclear grade by core biopsy may have surgical implications.

142. Development of a nurse led family history clinic in a district general hospital breast unit

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Introduction: There is increasing demand for family history assessment and advice. Previously patients were referred directly to the regional cancer genetics centre 90 miles away where there is a long wait to be seen or were seen in symptomatic clinics.
Methods: We established a nurse-led family history clinic in the local breast unit. A nurse was trained at the regional cancer genetics centre and set up a clinic to provide advice and risk assessment.
Results: Between June 1998 and April 2000 114 patients were seen. Ninety-eight were directly referred by their GP, 12 from breast clinic and four from the oncologists. Patients were assigned a risk category.

114 patients
↓

Low risk	Moderate risk	High risk
21 (18.4%)	64 (56.1%)	29 (25.5%)

The low-risk patients were counselled at length and discharged. The moderate-risk patients were offered local screening and 60/64 accepted this. The high-risk patients were offered referral to the regional centre and 21 accepted. Twenty-three of the high risk patients are currently being screened locally.
Conclusion: A nurse-led clinic is acceptable to patients and provides a prompt local service where there is time for discussion and reassurance. Patients can be advised about relevant trials and entered into them where appropriate. Seventy-four point five per cent of patients do not require onward tertiary referral and can be counselled and screened locally. This has reduced the workload in the busy symptomatic clinic and referral to the regional cancer genetics centre.

143. Graphical risk explanation as a new method of explaining risk to women with a family history of breast cancer

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Introduction: It has always been a matter of debate as to what is the best way to explain risk to women with a family history of cancer. A woman's accurate understanding of her risk is important to alleviate risk-related anxiety. However, it is not known whether risk has to be explained in a non-numerical or numerical format and, if numerical, whether it needs to be in the form of an odds ratio, relative risk or absolute risk. The most accurate method and also the most difficult to understand is absolute risk as it varies with age and different causes of mortality.

We believe that a visual depiction of risk in comparison with population risk can enhance understanding and help reduce risk-related anxiety. We have hence devised a graphical risk explanation method, which depicts absolute risk for differing family histories along with population risk at each age group. Absolute risk figures are shown for the remaining lifetime and for the next 10 years. The aim of this study was to compare the effectiveness of the graphical risk explanation method versus verbal risk explanation on subjective risk understanding and anxiety.
Methods: Out of 52 consecutive women who received counselling at our Breast Cancer Family History Clinic, 39 received graphical risk explanation and 11 received verbal risk explanation. All 52 were sent a questionnaire 2 months after counselling asking whether they thought that their understanding of their risk was better and if they felt any change in their risk-related anxiety. The replies were anonymous.
Results: Response to the questionnaire was 100%. Thirty-three of 39 of those having graphical risk explanation said they understood their risk better compared to only 4/11 having a verbal risk explanation. Twenty-one of 39 were less anxious following graphical risk explanation compared to none of the 11 following verbal risk explanation.
Conclusion: A graphical explanation of risk can help reduce risk-related anxiety levels, probably by enhancing the visual understanding of numerical risk.

144. Breast reconstruction in general surgical practice

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Introduction: Reconstruction following breast surgery is becoming increasingly requested. This work has traditionally been done in plastic surgical units or some larger breast units. We present a series of reconstructive breast procedures performed in a District General Hospital by a general surgeon with an interest in breast disease.
Method: Patients were identified from a prospectively compiled database. Their notes were then studied and the following details recorded; Age, Type and date of primary procedure, Pathology, Nottingham prognostic Index, Type and date of reconstruction, Numbers of procedures, Complications and Recurrence/Mortality.
Results: Eighteen women have undergone breast reconstruction, with an average age at operation of 49 years (Range 35–60). Sixteen had been treated for invasive carcinoma (NPI 2.24–7.5), 15 by mastectomy and one by wide local excision. One patient with DCIS had undergone mastectomy and one patient with persistent symptoms from duct ectasia had undergone bilateral subcutaneous mastectomy. During the same period 125 mastectomies and 244 wide local excisions have been done for breast cancer. Twelve patients had received radiotherapy to the chest wall or remaining breast and 10 patients had received chemotherapy.

Patients underwent reconstruction an average of 32 (Range 0–120) months after their primary procedure. One patient underwent immediate reconstruction.

Four techniques were utilized, tissue expander (two patients), gel/saline prosthesis (eight patients), TRAM flap (two patients) and latissimus dorsi flap (six patients, four with prostheses). Ten patients underwent contralateral reduction procedures and two patients whose tissue expanders were replaced with gel prostheses early in the series.

There were a total of 13 complications. Five were managed conservatively and included, two seromas, a wound infection, a residual lateral fold and the need for a bra prosthesis. The remaining eight required surgical intervention and included, removal and replacement of prosthesis in five patients, repositioning of an inflation port, and umbilical necrosis and an incisional hernia in the same patient following a TRAM flap.

To date all patients are alive, apart from one who has died of widespread bony metastases. Another patient has recently been diagnosed with pulmonary metastases and is undergoing treatment.
Conclusion: As demand for breast reconstruction increases so will the need for surgeons able to offer this service. We believe our data demonstrates that good results can also be achieved in general surgical practice. Increased training opportunities in reconstruction should be made available to general surgical trainees. This may increase the attraction of breast surgery as a subspecialty and allow improved continuity of care, thus enhancing patient satisfaction.

145. Fibroblast growth factor 8, a breast oncogene, has protein expression in normal and lactational breast tissue

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Introduction: FGF8, is a member of the fibroblast growth factor family (FGFs). It has been identified as an oncogene in the development of mouse mammary tumours. In view of this, using a specific monoclonal antibody against FGF8, we investigated its expression in human breast tissue.
Methods: A total of 124 samples of breast tissue were analysed by immunohistochemistry.
Results: Immunoreactivity was seen in all tissues investigated, which included 85 malignant tissues, six cases of DCIS, 17 normal tissue from reduction mammoplasties, five fibroadenomas and 11 pregnant or lactational breast tissue. The staining pattern in the tissues was in the cytoplasmic component of epithelial cells. Highest expression of FGF8 was seen in normal breast tissue in different phases of pregnancy and lactation.
Conclusion: The presence of FGF8 in normal breast tissue including lactational tissue, along its presence in malignant tissue, indicates a dual role of this FGF8. In normal tissue, it may be involved in maintaining a state of differentiation. As FGFR4 is the only known receptor expressed in epithelial cells to which FGF8 binds to, a potential autocrine loop is possible in inducing neoplastic change. The trigger that results in FGF8 behaving as an oncogene could possibly come from the stroma and in a cross paracrine fashion with other growth factors that bind to epithelial receptors induces a neoplastic change.

146. Improved sentinel node localization by pre-operative assessment of node depth by lymphoscintigraphy and ultrasound

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Introduction: The aim of this study was to improve the localization of sentinel nodes in cancer patients.
Methods: Forty-three patients with malignant melanoma had sentinel node biopsies performed to stage metastatic spread. Dynamic lymphoscintigraphy using 99mTc-nanocolloid and ultrasonography of sentinel nodes was carried out, including depth measurements, on the morning of the sentinel node biopsy. During surgery the sentinel node was identified using both patent blue V dye injected around the site of the primary melanoma and gamma probe localization. The blinded surgeon measured the depth the node with a ruler.

Pre-operative and operative depth measurements were compared to assess the accuracy of the predicted depth.
Results: There was good correlation between the predicted and actual depth measurements. The error in depth was found to be 1.5 cm in the 92 nodes that were assessed using lymphoscintigraphy ($P<0.01$). The error on ultrasound was lower at 0.5 cm ($P<0.001$).
Conclusion: Pre-operative assessment of the depth of the sentinel node aids identification of the correct node, especially when there are multiple superimposed nodes or nodes in unexpected sites.

147. Hormone or surgery, local or general anaesthesia? A one year audit of treatment of carcinoma of breast in elderly patients

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Introduction: Presentation of carcinoma of breast in elderly patients is usually symptomatic. Because of the concern that these patients have increased anaesthetic risk, most are treated with primary hormonal therapy. Treatment failure leading to progressive local disease can mean more extensive surgery on an even older population. Many elderly patients are worried about the prospect of general anaesthesia and surgery. With suitable communication and discussion much breast surgery can be performed under local anaesthetic. We have retrospectively looked at 60 patients treated surgically during 12 months from January to December 1999 to identify feasibility of surgery under local anaesthesia and correlation between axillary dissection and further adjuvant therapy.
Method: Sixty patients with primary breast carcinoma were treated with wide local excision or mastectomy between January to December 1999. Axillary sampling was done only if the tumour waas >2 cm in size and clearance when there were palpable nodes present in axilla. Mean age of patients was 85.15 years (age range 70 to 98 years). Thirty-four patients had wide local excision and 26 were treated with mastectomy.
Results: Forty-eight per cent of patients (eight mastectomies and 21 wide local excision) had surgery under local anaesthesia. Twenty-one patients had axillary dissection done out of which another 35% needed axillary clearance. Ninety-seven per cent of patients were given hormonal treatment and 60% received radiotherapy. Two patients were entered in ATAC and START trial. Three per cent of patients were treated with radiotherapy only after surgery. Six patients during this period were treated with tamoxifen only.
Conclusion: We conclude that primary surgical treatment with selective axillary dissection for the carcinoma of breast is well tolerated in elderly

patients. It removes the bulk of the tumour and a complete response as compared to tamoxifen only. It provides accurate pathological assessment of tumour. Frail patients can easily be treated using anaesthesia with suitable adjuvant treatment. In our hand there has been no peri-operative mortality and minimal morbidity.

148. The role of gastrin in pancreatic and oesphageal tumour growth

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Introduction: The peptide hormone, gastrin, is thought to play a major role in the growth of pancreatic and oesophageal malignancy. The physiological actions of gastrin are mediated by the G-protein coupled 7 trans-membrane domain cholecystokinin B/gastrin receptor (CCKBR).

The classical CCKB receptor is activated by serum gastrin and a truncated splice variant (ΔCCFB), with no N-terminal extra-cellular tail, is thought to play an autocrine role. The aim of this study was to determine their presence in a panel of pancreatic and oesophageal cell lines.

Method: Lysates of three human pancreatic tumour cell lines Pan 1, MiaPaCa2 and BxPC3, and three oesophageal tumour cell lines, OE19 (moderately differentiated), OE21 (squamous) and OE33 (poorly differentiated) were assayed for CCKBR isoforms by Western blotting. The classical CCKBR and the ΔCCKBR were identified using rabbit polyclonal antibodies raised against an N-terminal epitope sequence (GRE1) and an epitope sequence found in the third extra-cellular loop (GRE4), respectively.

Results: Western blotting confirmed the presence of both receptor isoforms in all the pancreatic cell lines and two of the oesophageal cell lines. The squamous cell line OE21 did not present with the ΔCCKBR, aas shown in the table below.

	OE19	OE21	OE33	PAN	MiaPaCa2	BxPc3
GRE1	+	+	+	+	+	+
GRE4	+	−	+	+	+	+

Conclusion: This study indicates that the presence of ΔCCKBR may be an epithelial associated characteristic and that an autocrine pathway may be present in later stages of tumourigenesis. This study supports the potential use of anti-gastrin therapy in patients with pancreatic and oesophageal carcinoma.

149. Can p53 and Ki67 be useful in the clinical management of Paget's disease?

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Introduction: The aim of this study was to investigate the presence of p53 and Ki67 in mammary Paget's disease (MPD) and correlate any differences in the expression of these two markers between those cases with and without ductal carcinoma *in-situ* (DCIS) or invasive carcinoma.

Introduction: Since its first description in the nipple by Sir James Paget in 1874, MPD continues to stir debate as to its histogenesis. The p53 gene has been described as the most commonly mutated gene in human cancers. Once the gene is mutated the p53 protein becomes stabilized and is overexpressed, thus enabling its detection by immunohistochemistry. Loss of its function by mutation, deletion or binding of proteins has been implicated in a number of cancers and has been shown to be useful as a prognostic marker. Ki67 is a marker of cellular proliferation and useful marker of neoplastic development and prognosis.

Methods: Thirty-seven archival cases of MPD including, 20 with associated DCIS or invasive carcinomas, were evaluated immunohistochemically for the expression of p53 (clone DO-7) and Ki67 (clone MIB-1). Antigen retrieval from formalin-fixed tissue sections was performed using the method of microwaving. A section was scored positive for p53 if 10% or more cell nuclei were stained and Ki67 was expressed as a percentage of positive cells (staining index).

Results: p53 was expressed in 3/20 (15%) MPD cases with carcinoma and 1/17 (3%) cases without carcinoma. The Ki67 staining index for MPD associated with DCIS or invasion was 14.5% and for those without it was 6%.

Conclusion: Although the numbers are small, our data suggest that Ki67 may play a role as a potential prognostic marker in MPD, and its increased expression indicate the likelihood of associated DCIS or invasive carcinoma.

BREAST GROUP SYMPOSIUM LECTURE

Multi-disciplinary team working in breast cancer: variability and effectiveness

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This study of 83 breast teams (BTs) in England examined the variation in history, composition, team processes and selected measures of clinical performance in a random sample of BTs. The sample was stratified by NHS region and new cancer workload. The study used quantitative and qualitative research methods.

Three types of questionnaire were used, the first elicited baseline information including the names of BT members. The second, developed through a process of 'stakeholder' analysis, was sent to each core BT member asking a range of questions about that team member's experience. The third was to obtain selected clinical data. The response rates to all questionnaires were over 75%. A subset of 15 BTs were visited, their meetings observed, and BT members interviewed individually.

The study utilized the Input, Process and Output model of team effectiveness. Inputs include the health care environment, organization context, team task, and team composition. Group processes had eight dimensions (leadership, clarity of objectives, participation, task orientation, support for innovation, reflexivity, decision making, and communication). The main outputs were team effectiveness, self and externally rated, and specific measures of clinical quality of service.

Analysis was concentrated on those teams for which data was available from all core disciplines or when only one was missing. For studies relating inputs and processes to output analysis was based on those BTs above for which a clinical data questionnaire had also been completed.