Method: A prospective study of 212 patients undergoing laparoscopic cholecystectomy was performed. A detailed postal symptom questionnaire was designed and piloted. Patients completed these preoperatively and at three and 12 months postoperatively.

Results: 169 patients were female. The median age of patients was 57 years (range 21–81). Complete data was available on 68% (145 patients). 34 patients (23%) continued to be symptomatic. Only one patient (0.06%) reported their abdominal pain/discomfort had become worse. Of the symptomatic patients with continuing abdominal pain, 15 (44%) claimed their pain was identical to that pre-operatively. 55% (26) of the symptomatic patients consulted their GPs during the one year follow up period.

Conclusion: A significant number of patients are dissatisfied one year after laparoscopic cholecystectomy. All patients should be pre-operatively counselled about the risk of persistence of some pain symptoms after laparoscopic cholecystectomy. There should be a high index of suspicion for upper GI conditions and more patients should undergo diagnostic endoscopy before subjecting them to surgery.

NEOPLASIA POSTERS 392–409

392 CURRENT MANAGEMENT OF IRON DEFICIENCY ANAEMIA BY GENERAL PHYSICIANS DOES NOT COMPLY WITH BRITISH SOCIETY OF GASTROENTEROLOGY GUIDELINES

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Introduction: Iron deficiency anaemia is a common problem encountered in all medical specialties. In men and post menopausal women common causes are gastrointestinal blood loss or malabsorption. The British Society of Gastroenterology (BSG) recently produced guidelines on the management of this condition.

Aim: To establish current practice in the investigation of iron deficiency anaemia.

Methods: The laboratory identified all patients with a haemoglobin and mean cell volume below the normal range, for the six month period between January and July 2001. The charts of those patients under the care of consultant physicians were reviewed. Data collected included details of history taking, examination, investigations performed, treatment and follow up.

Results: 74 patients were identified with both a low haemoglobin and mean cell volume (age range 15–90 years). 70% were female. A rectal examination was performed in 16%. 13 patients (18%) had antiendomysial antibodies tested. 27 patients (36%) had colonoscopy or barium enema performed, planned, or were unsuitable for investigation. 25 (34%) had an OGD or barium meal performed, planned or were unsuitable. One patient had duodenal biopsy. A reason for anaemia was found in 24 patients (32%). In this group five had colonic or gastric carcinoma, and no diagnosis of coeliac disease was made. 38 patients (52%) were placed on iron supplements. Excluding four patients who were unsuitable for follow up, 49 (70%) had a hospital review arranged.

Conclusion: A low proportion of patients underwent full upper and lower GI tract investigation although five patients were diagnosed with carcinoma. No cases of coeliac disease were detected, but only 18% had antiendomysial antibodies tested, and one duodenal biopsy was performed. We have produced a summary of the BSG guidelines to improve management of these patients and encourage early referral for endoscopy.

393 SPEED OF DIAGNOSIS OF UPPER GASTROINTESTINAL CANCER: DOES THE METHOD OF REFERRAL MATTER?

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All cases of upper gastrointestinal (GI) cancer diagnosed at two district general hospitals in south Wales between 1/7/93 and 30/6/99 have been reviewed. Cases were identified from pathology, endoscopy and clinical information systems and data extracted from hospital and primary care records, using a structured proforma. Case finding was cross checked with the local cancer registry and data held in central returns. The data extracted were validated on a randomly identified 10% sample. Four hundred and thirty-nine cases were identified and data obtained on 418. Median age was 73, range 36–96 years, male:female 258:160, cancer site oesophagus (150), stomach (265), duodenum (2), lung primary (1).

Over the six years of the study, during which open access services (OAG) and a "one stop" Rapid Opinion Clinic (ROC) were introduced, there was an overall decrease in the median interval from first presentation to the General Practitioner to diagnosis by histology (from 68 to 17 days, $p<0.001$, when first and last six months compared). This overall NHS delay was significantly longer for those patients referred through outpatients (173 cases; mean interval 111.3; median 70; range 5–956 days) compared with admission (144 cases; mean 34.6; median 13, range 0–546 days), OAG (89 cases; mean 56; median 27; range 3–335 days), and the ROC (12 cases; mean 43.2; median 13; range 4–185 days; $p<0.05$ for all methods compared with outpatients). The main reason for this delay was the time taken to reach the diagnosis after the initial contact in hospital (mean 61.3 days for outpatients versus 26.7; 12.8; and 22.8 for admission, OAG, and ROC respectively; $p<0.05$ for all methods compared with outpatients). Most patients presented with a combination of symptoms which included loss of appetite or weight, but isolated dysphagia occurred in 14 patients (youngest 52 years) and isolated abdominal pain or dyspepsia was noted in eight (youngest 63 years).

We conclude that if upper GI cancer is suspected patients should be referred for "one-stop" assessment, or admission, rather than outpatients. Cancer may present as isolated abdominal pain or dyspepsia.

394 THE ROLE OF FDG-PET IN THE EARLY DETECTION OF RESPONSE OF COLORECTAL LIVER METASTASES TO CHEMOTHERAPY

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Aim: To determine if 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-Positron Emission Tomography (PET) could detect early response to combination chemotherapy in patients with liver metastases from colorectal primary cancers.

Methods: Seventeen patients were imaged immediately prior to the first cycle of 5-Fluorouracil (5FU)/ leucovorin using FDG-PET. Thirteen patients had follow up scans at 14 days. Tumour / Liver Ratios (TLRs) were used to quantify the PET images. Computed Tomography (CT), serum Carcinoembryonic Antigen (CEA) levels and survival figures were used as comparative evidence of response.

Results: Areas of enhanced FDG uptake in comparison to adjacent normal liver tissue were seen in all patients on pre chemotherapy scans. Thirty-four liver metastases were assessed for evidence of response in the thirteen patients completing both scans. A change in tumour/liver ratio of less than 20% was seen in 25 of 34 lesions. Non-uniform changes in activity were seen in five patients. Two patients with uniform reductions in FDG uptake greater than 20% had prolonged survival.

Discussion: FDG PET is reliable in the detection of metastatic colorectal cancer including those patients with low CEA levels. The changes seen in tumour FDG uptake at two weeks were small and often not uniform within patients. Sizable uniform reductions in activity, suggestive of response, were seen in only two of 13 patients both of who had longer than median survival. It is possible that these two patients were the only genuine early responders and that PET has the ability to identify this small group of patients

395 P53 MUTATION DOES NOT INFLUENCE COX-2 IMMUNOREACTIVITY IN GASTRIC ADENOCARCINOMA

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Both COX 2 over-expression and p53 mutation are common findings in gastric adenocarcinoma, being seen in 60% and 40% of cancers respectively. Recently, it has been suggested that wild type p53 expression suppresses COX-2 mRNA transcription by competing for the COX-2 promoter site. If this is the case, COX-2 expression should be markedly increased in tumours with mutated p53 compared with those with wild type p53.

Abstract 395

	p53 positive	p53 negative	
COX-2 positive	**14**	**18**	*32*
COX-2 negative	**6**	**7**	*13*
	20	*25*	***45***

Method: Paraffin embedded tissue sections from gastric adenocarcinomas (n=45) were sectioned and immunohistochemistry carried out utilizing a polyclonal antibody raised against human COX-2 (Cayman) or the DO-7 clone of mutated p53 (DAKO). An avidin-biotin detection system and a DAB chromagen (Vector laboratories) were used. Positive controls slide derived from an oesophageal adenocarcinoma (DAKO) and negative controls comprising serum from the host animal were utilized. COX-2 antibody specificity was determined by western blotting of purified COX-1 and COX-2. COX-2 and p53 positivity was determined as expression by at least 50% of malignant cells in the section. Results were analyzed using a 2×2 table and Chi^2 testing.

Results: COX-2 and p53 positivity was 71% and 44% respectively. The results are shown in the table below. Chi^2 analysis demonstrated that the frequency of COX-2 positivity was unchanged between p53 positive and negative tumours (Chi^2 value = 0.88).

Conclusion: The rate of COX-2 dysregulation is not altered by p53 gene mutation in gastric carcinoma.

396 A SYSTEMATIC EVALUATION OF THE SIGNIFICANCE OF IMMUNOHISTOCHEMICALLY DETECTED LYMPH NODE MICROMETASTASIS IN LOCALISED COLORECTAL CANCER

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Background: Regional lymph node metastasis in colorectal resections is routinely detected by examination of H & E stained tissue sections. There is no consensus regarding the clinical significance of lymph node micrometastasis detected solely by immunohistochemistry.

Design: Formalin fixed, paraffin embedded tissue sections of all pericolic lymph nodes dissected from 155 patients with Duke's A/B colorectal cancer who had undergone a curative resection were immunostained using cytokeratin antibodies (Pan cytokeratin and AE1/AE3). Pre-operative and follow up information was sought by review of case notes and death registration where appropriate. Study end points (adverse outcome) were tumour recurrence and cancer related death. Five patients who died in the immediate post-operative period and 41 patients who received pre-/post-operative radio/chemotherapy were excluded from adverse outcome analysis.

Results: Eight hundred and ninety eight lymph nodes (range 1–20, median 5) were identified in the 155 resection specimens. Immunohistochemically detected micrometastasis, generally as single cells in the subcapsular sinus, was present in 155 (17.3%) lymph nodes (range 1 to 10, median 2) from 67 (43.2%) of patients (7/24 Duke's A, 58/115 Duke's B, 2/16 Duke's A/B with history of pre-operative radiotherapy).

Adverse outcome was recorded in eight (15 %) of 52 patients with micrometastasis detected by immunohistochemistry in comparison with twelve (20%) of 60 patients without immunohistochemically detected micrometastasis. No significant association could be found between immunohistochemically detected lymph node micrometastasis and adverse outcome in both univariate (p=0.316) and multivariate (p=0.414) Cox regression analysis.

Conclusion: Immunohistochemically detected micrometastasis in morphologically benign lymph nodes from resections for colorectal cancer is a common phenomenon but appears to be of no clinical significance.

397 EXPRESSION OF HEPARIN BINDING EPIDERMAL GROWTH FACTOR (HBEGF) IN TUMOUR AND EMBRYONIC CELL LINES

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Background: HBEGF binds to the epidermal growth factor receptor (EGFR) with high affinity and has increased mitogenic potential compared to other EGF ligands. Many solid tumours overexpress the EGF receptor. Co-expression of HBEGF by tumour cells would thus provide a powerful autocrine mechanism for tumour cell growth.

Aim: To assess expression of HBEGF in tumour and embryonic cell lines Method: Using an anti-HBEGF antibody (Santa Cruz, USA),with immunoblotting, we examined lysates from 6 tumour and embryonic cell lines for expression of HBEGF; HepG2 (human hepatocyte carcinoma), WRL68 (human liver embryonic), C170HM2 (liver metastasizing human colon carcinoma), HTC (rat hepatoma), PLC/PRF/5 (human liver hepatoma) and MCA RH7777 (rat hepatoma).

Results: We found immunodetectable HBEGF in WRL68, C170HM2, PLC/PRF/5 cells but not in HTC, HepG2, or MCA RH 7777 cells. In the three positive cell lines there was a band of ~30 kD which was not present when anti-HBEGF antibody preabsorbed with the immunizing peptide was used. In the C170HM2 cells only there was also a specific band present at ~51 kD.

Conclusion: These results suggest that HBEGF is present in human cell tumour and embryonic cell lines and may be important as an autocrine growth factor.

398 THE IMPACT AND CLINICAL APPROPRIATENESS OF THE TWO WEEK WAIT SCHEME FOR SUSPECTED CANCER

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Introduction: The two week wait scheme for patients with suspected cancer was introduced in April 2000. Guidelines as to which patients are suitable for this scheme have been produced. The evidence base that the scheme will produce clinical benefit is limited.

Methods: all patients referred to the two week cancer wait scheme in its first year with suspected gastro-oesophageal cancer (GOC) or colo-rectal cancer (CRC) were audited. After taking the history and examining the patient, the consulting doctor was asked to assess the indication for and appropriateness of the referral. The eventual diagnosis was recorded and correlated to the indication for referral. The out-patient (OP) waiting times for non-urgent cases during the year were documented.

Results: 394 patients were referred with suspected CRC and 280 with suspected GOC. The table shows the commonest referral indications, defined by the guidelines, and the pick up rate for cancer. 27 cases of GOC and 46 cases of CRC were detected in patients referred via the scheme. During the same period 49 cases of GOC and 77 cases of CRC were detected in patients referred out with the scheme. The OP waiting times for non-urgent cases increased from 9 to 16 weeks during the year.

Discussion: The guidelines are inadequate for detecting patients with cancer and are not adhered to for many referrals. The majority of cancers do not present through the scheme. It is likely that the scheme is having an adverse effect on non-urgent waiting times.

Abstract 398

Suspected GOC referrals			Suspected CRC referrals		
Indication	No.	% cancer	Indication	No.	% cancer
Inappropriate	61	5	Inappropriate	114	4
Appropriate, but not in guidelines	26	38	Appropriate, but not in guidelines	33	21
Dysphagia	79	27	Looser stool for >6 weeks	124	8
Dyspepsia + weight loss	49	10	Bleeding pr + change in bowels	46	22
Dyspepsia<12 months, age>55	33	3	Bleeding pr age >60 + no anal Sx	30	7

399 A SEVEN YEAR EXPERIENCE OF MANAGEMENT OF OESOPHAGEAL CANCER

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We conducted a retrospective review of all patients seen with oesophageal cancer at our institution over the last seven years. 225 patients were seen (mean age 49.6y, range 18-85y; 121 males).

Tumour site: 72 starting in upper 1/3 (69 squamous cell carcinoma [SCCA], three adenocarcinoma [ACA]), 67 mid 1/3 (64 SCCA, 2 ACA, one collision tumour), 86 lower 1/3 or G.O. junction (45 ACA, 34 SCCA, one lymphoma, six miscellaneous).

Results: 52 received no treatment (36 of these were lost to follow up during work up). 67 received purely palliative treatment, such as PEG/surgical gastrostomy, APC or other ablative techniques, radiation [DXT] or DXT/chemotherapy. Average age 51.8 yrs. 22 ACA, 43 SCCA, 2 others. 15 upper 1/3, 20 mid-1/3, 32 lower 1/3. 50 had surgery with curative intent, either alone or in combination with DXT/chemotherapy in adjuvant or neo-adjuvant setting. Average age 48 yrs. 35 SCCA, 13 ACA, two others. Four upper 1/3, 18 mid-1/3, 28 lower 1/3. 56 had treatment with either DXT or DXT/chemotherapy. Average age 46.4 yrs, 52 SCCA, 4 ACA. 37 upper 1/3, 12 mid-1/3, seven lower 1/3.

Outcome: 61 patients were lost to follow up during investigation. 14 patients alive (10 had surgery, three treated with palliative intent, one with primary DXT). Median survival 20 months. 34 definitely dead (3 had surgery, 13 treated with palliative intent, 10 DXT/chemotherapy, 8 had no treatment). Median survival 5.5 months. 116 patients lost to follow-up after median follow up of eight months.

Conclusions: (1) The average age of patients seen with oesophageal cancer is lower in our series than reported in the literature. (2) 25% of patients seen were younger than 40 yers old and may represent a subgroup for further study as to the aetiology of this cancer. (3) In our country, it is difficult to follow up patients, particularly those from rural areas and with limited means of communication, as evidenced by the large number of patients lost to follow up.

400 MATRIX METALLOPROTEINASE-2 CONCENTRATION CORRELATES POSITIVELY WITH PATHOLOGICAL TUMOUR STAGE IN PATIENTS WITH ADENOCARCINOMA OF THE OESOPHAGUS OR GASTRIC CARDIA

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Introduction: Matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9) facilitate tumour invasion and metastatic spread by degrading type IV collagen, the main structural component of the basement membrane. The aim of this study was to determine if these endopeptidases are markers of disease progression in adenocarcinoma of the oesophagus or gastric cardia.

Methods: Approval for this study was obtained from the local ethics committee and informed consent was given by each participating patient. Fresh tumour samples from neoplasms of the oesophagus or gastric cardia, obtained at the time of surgery, were homogenised, centrifuged and the supernatants analysed for expression of MMP-2 and -9 using matrix metalloproteinase activity assay systems (Biotrak RPN 2631 and 2634, Amersham Pharmacia Biotech, Buckinghamshire, UK). All tumours were assessed histologically by an independent pathologist. Tumour staging was based on the UICC guidelines (5th Edition). Correlation analysis was undertaken using Spearman's rank testing.

Results: Tumour samples were obtained from 33 patients with confirmed adenocarcinoma. Total and inactive MMP-2 concentrations correlated positively with overall pathological stage ($r^2 = 0.14$, $p < 0.05$; $r^2 = 0.15$, $p < 0.05$ respectively). There was no correlation between MMP-2 and histological parameters such as depth of invasion, vascular involvement, or lymph node metastasis. MMP-9 did not correlate with pathological stage or histological findings.

Conclusions: This study provides further evidence for the involvement of MMP-2 in tumour invasion and metastasis. MMP-2 concentration in diagnostic biopsies from oesophago-gastric cancers may therefore be of benefit in assisting the decision making process regarding the appropriateness of surgical resection.

401 CHANGES IN MUSCLE UNCOUPLING PROTEIN EXPRESSION IN HUMANS WITH GASTROINTESTINAL ADENOCARCOINOMA

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The mitochondrial uncoupling proteins-2 and-3 (UCP-2 and -3) are putative mediators of thermogenesis and energy expenditure in mammals. We obtained skeletal muscle from 12 gastrointestinal adenocarcinoma patients, of whom six had stable weight and six had lost 2–18 kg, and from six healthy controls undergoing elective surgery. We measured mRNA levels of UCP-2 and -3 using semi-quantitative RT-PCR.

UCP-3 mRNA levels were significantly higher in the muscle of cancer patients with weight loss (2.2 ±0.47 arbitrary units) compared both with controls (0.39 ±0.20) and with cancer patients who had not lost weight (0.47±0.23; $p<0.02$). UCP-2 mRNA levels did not differ significantly between groups, suggesting that UCP-2 is regulated by a different mechanism in human muscle and may have a different physiological role in this context. Elevations in muscle UCP-3 activity may enhance energy expenditure and contribute to the tissue catabolism seen in cancer associated cachexia. Manipulation of UCP expression may offer new therapeutic potential in combating the high morbidity and mortality associated with muscle wasting both in malignancy and other wasting conditions such as HIV.

402 PROLIFERATION ANTIGEN MIB–1 IN METASTATIC CARCINOID TUMOURS REMOVED AT LIVER TRANSPLANTATION: RELEVANCE TO PROGNOSIS

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Introduction: Metastatic carcinoid tumours are difficult to manage. Histopathology generally fails to provide prognostic information. In spite of multidisciplinary approach, including orthotopic liver transplantation (OLT), the recurrence rate is high with a poor prognosis.

Aim: To assess MIB–1 as a prognostic marker of early recurrence and death in a group of patients undergoing Orthotopic Liver Transplantation for Carcinoid/neuroendocrine tumours of the liver.

Results: 14 cases were studied with an average age of 47 years. The patients were divided into two groups, those having MIB–1 index of <2% and another group with MIB–1 of >2%. There was a trend for patients with MIB–1 index of < 2% to exhibit a late recurrence (>24 months) as compared to those with MIB–1 index >2%. The sensitivity as regard to recurrence was found to be 85.7% and specificity 71.4%. Those having MIB–1 <2% showed a longer survival than with MIB–1 >2% with a sensitivity of 83.3% and specificity of 62.5%.

Conclusion: MIB–1 antibody staining was found to be a useful method of predicting the prognosis of metastatic carcinoid/neuroendocrine tumours. Thus this method can provide an additional parameter for a rational approach to therapy. However this study is very small and a larger number of patients studied prospectively will be needed to confirm our findings.

403 METABOLIC THERAPY INHIBITS GENOTOXIC DAMAGE IN REGENERATING INTESTINAL EPITHELIUM

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Adverse effects of many dietary carcinogens are increased in conditions of tissue regeneration. This study tests the hypothesis that metabolic therapy may inhibit DNA damage from dietary carcinogens in regenerating human intestinal epithelium.

Methods: Metabolic therapy aimed at (i) inhibition of carcinogen bioactivating enzymes (CYP1A1/1A2) using ellipticine or furafylline and/or (ii) promotion of Glutathione –S transferase (GST) enzymes responsible for carcinogen detoxification, by ethoxyquin or oltipraz

treatment. A previously established model of regeneration, by subcutaneous transplantation of human fetal crypt cell aggregates was used. Regenerating intestinal epithelium was treated by metabolic therapy alone and in combination with the human dietary carcinogen Benzo[a]pyrene [BaP]. Endpoints included (i) western blot expression studies of CYP1A1/1A2 and GST enzymes (ii) EROD assay of CYP1A1/1A2 function and CDNB assay of GST function and (iii) BaP:DNA adduct formation in regenerating intestinal epithelium and normal tissue.

Results: All metabolic treatments induced CYP1A1 expression while antioxidants oltipraz and ethoxyquin induced GST expression. Ethoxyquin and Oltipraz promoted CDNB while furafylline inhibited EROD assays. Benzo[a]pyrene [BaP] alone induced 41.9 adducts/ 10^8 nucleotides in regenerating human epithelium vs 19.7 BaP + ethoxyquin vs 6.5 BaP + ethoxyquin + furafylline.

Conclusions: Metabolic therapy by antioxidants or CYP 450 inhibitors promote expression and function of P450s and GSTs and reduce adduct formation in regenerating intestinal epithelium.

404 FEW GASTRO-OESOPHAGEAL MALIGNANCIES ARE IDENTIFIED THROUGH TWO WEEK RULE

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Aim: To identify the proportion of patients diagnosed to have a gastro-oesophageal malignancy through Two Week Rule (TWR) referral.

Methods: All TWR referrals for a suspected gastro-oesophageal malignancy (GOM) were identified from the cancer audit office over a 14 month period (July 2000–August 2001). The number of patients eventually diagnosed to have a tumour through this referral mode was noted. During the same period, the total number of GOMs identified was recorded using a combination of coding and histopathology records. Time from referral to assessment in clinic and time to diagnosis and treatment were recorded for patients referred through TWR and conventional routes.

Results: 199 patients were referred through TWR during the study period. Only 11 patients were subsequently diagnosed to have a malignancy (5.5% of TWR referrals, 29% of total malignancies diagnosed). 27 patients were diagnosed to have a tumour through other modes of referral (emergency admission: 14 (37%), outpatient clinic: 6 (16%), direct access endoscopy: 7 (18%).

Conclusions: Only a minority of patients (5.5%) referred through TWR had a malignancy; the majority (94.5%) had alternative diagnoses. Possible reasons for this includes: (1) referral criteria used in TWR forms may be poor discriminators for GOM (2) over interpretation of alarm symptoms may lead to inappropriate referrals. There is no evidence that the TWR system has resulted in reduction in time to diagnosis and treatment of GOM. However, larger series are required to confirm these findings.

Abstract 404

	TWR	Non-TWR	*p*
Median age	67.5(55-96)	77 (43-89)	0.66
Median time to appointment	5 days (1-32)	20 (1-52)	0.09
Median time to diagnosis	13 days(7-65)	15 (2-565)	0.6
Median time to treatment	18 days (1-82)	16 (1-245)	0.9

Figures in brackets represent range

405 GASTRO-OESOPHAGEAL CANCER IN SCOTLAND

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The prospective population based Scottish Audit of Gastro-oesophageal Cancer identified 3293 consecutive patients between 1997 and 1999 with oesophageal or gastric cancer. Patient characteristics and details of presentation within Scotland, as a whole, and within different geographical regions were identified. The hospitals were divided into 4 bands according to the number of patients with gastro-oesophageal cancer seen each year: Band 1: <75 cases, band 2: 34–74 cases, band 3: 11–34 cases, and band 4: <10 cases.

In common with other western series oesophageal adenocarcinomas predominate over squamous cell carcinomas. All tumour types were most common in the 65–74 age group and were associated with significant co-morbid disease (40% ASA grades 3–5). The 3293 patients presented to a total of 53 different hospitals, only 1/3 of the patients initially presented to a hospital seeing in excess of 75 such cases per year. There were differences between regions in terms of the time between referral of cases and final diagnosis. A greater than four week delay occurred in between 13.7% of patients in the region with the shortest waiting times and 31.6% of patients in the longest. Delays were less common in patients initially presenting to band four hospitals—13% of patients waiting greater than four weeks compared with 22% in band one units. There were no differences between the size of the hospital of presentation and the time taken between diagnosis and commencement of treatment. Overall survival at one year was 29%, 32.7%, and 34.5% for oesophageal, gastro-oesophageal junctional, and gastric tumours and at two years: 13.8%, 16.6%, and 20.4% respectively. There was no difference between the size of the hospital of presentation and survival.

Any reorganisation of services must take cognisance of the fact that the majority of patients currently do not present to specialised centres. Patients are not disadvantaged by this and services in smaller units should be supported to ensure continued equity of access.

406 THE GASTRIC CANCER 5 (GC5) STUDY: ANTIBODY RESPONSE AND SIDE EFFECT PROFILE OF G17DT 500MCG IN POST GASTRIC CANCER RESECTION PATIENTS

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Aim: Gastrin has a trophic effect on gastrointestinal epithelium as part of its normal physiological function, and gastrin 17 in particular stimulates the growth of gastrointestinal (GI) cancer cell lines. The aims of the GC5 study were to determine the anti-gastrin antibody response to G17DT 500mcg (Aphton Corps) and to evaluate patient tolerance at this higher dose.

Methods: Gastrin 17 linked to the diphtheria toxoid (G17DT) was administered as a 500mcg intramuscular injection at weeks 0, 2, and 6 to seven patients who had previously undergone potentially curative gastric cancer resection. Approval was obtained from the local Ethics Committee. G17DT antibody titres were measured over the follow up period (median 419 days, range 391–463 days). Patients underwent CT scanning for assessment of tumour recurrence on three occasions.

Results: All seven patients achieved an antibody response (median 177.2 units, range 33.9–313.7 units) which remained quantifiable in five patients at the end of the follow up period, although the third dose was administered to one patient only. Four patients developed an abscess at the injection site and all seven patients reported minor to severe local side effects (pain, immobility, and tenderness). Based on CT scanning no patients had tumour recurrence during this period.

Conclusions: At this dosage schedule G17DT is an effective method of producing a sustained anti-gastrin antibody response at the expense of unacceptable tolerance. However the high dose of 500mcg may be utilised in conjunction with chemotherapy as combination therapy, as the chemotherapeutic agents are anti-inflammatory and may suppress injection site reactions.

407 NOVEL METHOD FOR MEASURING NITROSATION POTENTIAL WITHIN LOCALISED REGIONS OF UPPER GI TRACT

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Background: Luminal nitrosation may be important in the pathogenesis of adenocarcinoma at the gastro-oesophageal junction as swallowed saliva is the main source of nitrite entering the acid stomach. We have developed and validated a method employing microdialysis (MD) probes to measure nitrosation at this localised site.

Method: MD probes were perfused with distilled water at 0.15ml/hr. The recoveries of chemicals relevant to luminal nitrosation i.e. nitrite (NO_2^-), thiocyanate (SCN), ascorbic acid (AA) and total vitamin C (TVC) were studied at 37°C at different pH in aqueous solutions and/or gastric juice (GJ). Experiments simulating the gastric milieu, when NO_2^- intake was in excess of gastric AA secretion and vice versa were performed. For use in human subjects, four MD probes with 1metre inlet and outlet tubes were secured in individual recesses created in a nasogastric (NG) tube.

Abstract 407

	NO_2^-		SCN^-		AA		TVC	
pH	NA	A	NA	A	NA	A	NA	A
1.5	78±4	74±6	97+1	92±5	71±4	63±9	76±5	68±9
2.5	85±3	82±6	97±2	92±3	70±6	64±10	74±4	69±9
7	91±4	87±6	91±4	87±6	65±4	60±6	73±5	62±8

Results: The mean recovery (%±SD) for each analyte in aqueous solutions at pH1.5, 2.5, and 7 for probes not assembled in NG tube (NA) and probes assembled in NG tube (A) are shown in the table. The recoveries were independent of sample concentration. NO_2^- recovery was pH-dependent with lowest recovery at pH1.5 (78%) and highest at pH7 (91%). The results were similar in gastric juice.

The intra-probe coefficient of variation for recovery of NO_2^-, SCN^-, AA and TVC respectively were ±6, 5, 18, and 17% for unassembled probes; for assembled probes the respective recoveries were ±9, 8, 16, and 18%. The probes also proved to be reliable under dynamic conditions simulating the interaction between NO_2^- in swallowed saliva and AA secreted in GJ under the condition of NO_2^- > AA and AA> NO_2^-.

Conclusion: Multiple MD probes mounted on NG tube allows simultaneous measurement of nitrosation chemicals within different localised regions of the upper GI tract.

408 ENDOCYTOSIS OF GASTRIN ANALOGUE PEPTIDES BY TUMOUR CELL LINES

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Background: We have previously demonstrated the endocytosis of an antibody raised against an N-terminal fragment of the CCKB/gastrin receptor in tumour cells bearing the latter. This raised the possibility of using such an antibody in cancer therapy. However, for therapeutic purposes a peptide ligand may have greater potential

Aims: To assess endocytosis of gastrin analogue peptides. Methods: Cys-23-Phe-NH_2 (a Gastrin 34 analogue) and GRTL-1 (a Gastrin 17 analogue) were labelled with Alexa Fluor 488 dye (Molecular Probes, USA). These labelled peptides were exposed to PLC/PRF/5 (human liver hepatoma), WRL68 (human liver embryonic , AR42J (rat pancreatic adenocarcinoma), HepG2 (human hepatocyte carcinoma) and MCA RH *7777* (rat hepatoma) cells at a concentration of 20 µg/ml for 1 hour at 37°C. Endocytosis into the nucleus was confirmed by costaining with propidium iodide or diamidino-2-phenylindole.

Results: Endocytosis was demonstrated with Cys -23-Phe-NH_2 for AR42J, PLC/PRF/5 and WRL68 cells and with GRTL-1 in AR42J, MCA RH *7777* and HepG2 cells. GRTL-1 was found to undergo significant dimerization in aqueous solution. Addition of beta-mercaptoethanol to the labelled GRTL-1 (which increased the monomer:dimer ratio as confirmed by HPLC analysis) before addition to AR42J, MCA RH *7777* and HepG2 cells resulted in an increased number of cells displaying endocytosis.

Conclusions: Gastrin analogue peptides have potential to act as vehicles for cytotoxic substances in the therapy of CCKB/gastrin receptor positive tumours.

409 IMMUNOTHERPAY BOOSTER ADMINISTRATION FOR PATIENTS WITH PANCREATIC AND GASTRIC CARCINOMA

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Background: Gastrin is a growth factor for gastric and pancreatic malignancy. G17DT is an anti-gastrin immunogen that induces the production of gastrin neutralising antibodies. Patients with advancing age or stage of disease may have reduced immunological responsiveness and thus the aim of this study was to evaluate the effect of immunogen boosting to increase the longevity of the immune response to G17DT.

Methods: G17DT was administered by intra-muscular injection to 52 patients with gastric adenocarcinoma and 41 patients with pancreatic adenocarcinoma in phase II studies. 28 patients were followed-up and boosted when antibodies fell to <25% of peak values achieved during the main body of the study.

The antibody isotypes following booster administration were examined by an ELISA capture assay and compared to the antibody isotypes generated by the initial dosing schedule.

Results: One patient died of disease progression prior to booster administration and two boosted patients died prior to antibody analysis. Of the remaining patients, eight of the twelve (66.7%) patients with advanced pancreatic cancer and seven of the thirteen gastric cancer patients (53.85%) achieved a higher antibody response following boosting than after the primary three injections.

There was only one adverse event: induration at injection site of the booster that resolved completely within two months with conservative management. The antibody isotypes following booster administration changed from a IgG, IgM, and IgA mixture to a predominantly IgG response.

Conclusion: All boosted patients were able to mount an antibody response. This was at least as good as the one following the initial three doses in most patients, and, in a proportion of patients, was greater with few side effects.

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410 URINARY TAURINE AND HIPPURATE ARE USEFUL MARKERS OF ALCOHOLIC CIRRHOSIS

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Both taurine and hippurate are mainly produced by the liver and their excretion rate in the urine could provide us with markers in liver dysfunction. We aimed to evaluate the usefulness of urinary taurine and hippurate levels as markers of cirrhosis.

Materials and Methods: Urine was collected from 40 patients with alcoholic cirrhosis (18 males and 12 females) aged 37 -74 (mean age 52.9) and 20 controls (25 males and 15 females) aged 21–68 years old (mean age 49.9) with normal liver function. All patients had moderate to severe liver disease (mean Child's Pugh score 9.3) due to ethanol abuse. We used 1H NMR spectroscopy to quantify levels of taurine and hippurate in the patients urine. Both taurine and hippurate were expressed as excretion indexes relative to the amount of creatinine in each sample. ANOVA was applied to compare values between the groups.

Results: Taurine excretion index was significantly higher in cirrhotics than controls (0.27 ± 0.04 vs 0.046 ± 0.005) ($p<0.009$). Hippurate excretion index was significantly lower in patients with cirrhosis than controls (0.097 ± 0.016 vs 0.25 ± 0.06) ($p<0.014$). If the two values were combined then the results were again highly statistically significant ($p<0.000126$).

Conclusions: A combination of low hippurate and high taurine excretions is highly significant in alcoholic cirrhosis and can be a cheap non invasive marker of the disease.

411 HAZARDOUS DRINKING IN HOSPITAL INPATIENTS: STILL COMMON, STILL UNDER DIAGNOSED

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Introduction: Brief counselling for hazardous drinkers can lead to reduced alcohol consumption, hence detection is important.

Aims: a): To establish the prevalence and detection rate of hazardous drinking in unselected hospital inpatients and b) to ascertain whether, in patients who present with a first episode of decompensated alcoholic liver disease (ALD), opportunities to manage excessive drinking during previous admissions were exploited.

Methods and Results: a) On specific weekdays over a nine month period, all patients aged 30–60 years admitted to the admissions unit under the care of a general physician or surgeon were considered for screening using the Alcohol Use Disorders Identification Test (AUDIT)