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Density and Size of Lymphatic Vessels are Reduced in Cancer of the Pancreatic Head despite Expression of VEGF–C and –D

S.J. Cartland¹, K.V. Menon², S. Rahman², C.S. Verbeke¹
Departments of ¹Histopathology and ²Surgery, The Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Lymph node metastasis is common in pancreatic head cancer and adversely affects prognosis. The aim of this study is to determine if pancreatic head cancers are associated with lymphangiogenesis, and whether this correlates with VEGF-C/-D expression by the tumours.

Methods: Paraffin-embedded tissue from normal pancreas, ampulla, common bile duct (CBD) and each of 15 cases of adenocarcinoma of the pancreas (PC), ampulla (AC) and distal common bile duct (CC) was immunostained with D2–40 (lymphatic endothelial marker), VEGF-C and -D antibodies. Lymphatic vessel size (vascular area), shape (largest/smallest diameter) and lymphatic vessel density (LVD) in the centre and at the periphery of each tumour were assessed on digitized images.

Results: LVD was higher (p < 0.02) and vessel size smaller (p < 0.001) in normal ampulla and CBD compared to pancreas. LVD in the centre and periphery of PC did not differ from the low LVD found in normal tissue. In CC, central and peripheral LVD were similar to that in PC, and significantly lower than in normal CBD (p < 0.001). LVD in AC was higher than in PC and CC (p < 0.03), but significantly reduced compared to that in normal ampulla (p < 0.001). In AC, central LVD was lower than peripheral LVD (p < 0.04), but no such difference was seen in PC or CC. LVD was inhomogeneous in individual tumours and highest where cancer infiltrated the ampulla and duodenum. In all cases, lymphatics were of similar size in normal tissue and tumour periphery, but significantly smaller in the tumour centre (p < 0.001). No difference in vessel shape existed between cancers and normal tissue. Immunohistochemical staining with VEGF-C was stronger than for VEGF-D, and expression of both factors was higher in AC than in PC or CC (p ≤ 0.05) but did not correlate with LVD.

Rather than inducing lymphangiogenesis, pancreatic head cancers seem to destroy and constrict lymphatic channels, despite expression of VEGF-C and -D. LVD varies within individual tumours, reflecting differences in LVD of the normal tissue compartments within the pancreatic head.
Mitochondrial Ca\textsuperscript{2+} Overload is the Principal Mechanism of Injury to Pancreatic Acinar Cells from Bile Salts

J.A. Murphy, D.N. Criddle, J.P. Neoptolemos, O.V. Gerasimenko, A.V. Tepikin, O.H. Petersen, R. Sutton

MRC Group, Physiological Laboratory and Division of Surgery and Oncology, University of Liverpool, UK

Bile salts induce prolonged, global elevations of the free cytosolic ionised Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]\textsubscript{c}) that are toxic to pancreatic acinar cells, but the mechanism of injury has remained unclear. We sought to determine the contribution of mitochondrial Ca\textsuperscript{2+} overload to pancreatic acinar cell injury from the bile salt taurolithocholic-3-sulphate (TLCS).

Isolated mouse pancreatic acinar cells were examined by confocal microscopy to measure changes in [Ca\textsuperscript{2+}]\textsubscript{c} (Fluo4-AM), mitochondrial function (NADH autofluorescence), ATP concentration (Mg Green) and cell fate(propidium iodide, PI). TLCS (200 mM) was perfused externally while whole-cell recordings of Ca\textsuperscript{2+}-dependent Cl\textsuperscript{-} currents were made. All experiments were repeated at least six times, and in some experiments, supplementary ATP was added to the internal pipette solution.

Results: TLCS induced prolonged (>30 s), global [Ca\textsuperscript{2+}]\textsubscript{c} elevations accompanied by NADH and ATP depletion, inducing necrosis. Caffeine (20 mM), an inhibitor of inositol-trisphosphate-elicited Ca\textsuperscript{2+} release, inhibited these elevations. Supplementary ATP (4 mM) in the internal pipette solution reduced the period of globalisation associated with each [Ca\textsuperscript{2+}]\textsubscript{c} elevation and prevented necrosis, as did removal of Ca\textsuperscript{2+} from the external medium. Control experiments demonstrated that neither pipette application nor absence of supplementary ATP (0 mM) in the internal pipette solution induced necrosis.

Bile salts induce pancreatic acinar cell injury through mitochondrial inhibition, prevented by removal of Ca\textsuperscript{2+} from the cell exterior. These data indicate the principal mechanism of pancreatic acinar cell injury from bile salts is mitochondrial Ca\textsuperscript{2+} overload from excessive inositol-trisphosphate receptor Ca\textsuperscript{2+} channel release.

The Prognostic Relevance of ‘Equivocal’ Resection Margins in Peri-ampullary Cancer

J. Tang\textsuperscript{1}, G. Powell\textsuperscript{2}, R. Smith\textsuperscript{2}, L. Bosonnet\textsuperscript{2}, F. Campbell\textsuperscript{2}, M. Ratay\textsuperscript{2}, R. Sutton\textsuperscript{2}, J.P. Neoptolemos\textsuperscript{2}, P. Ghaneh\textsuperscript{2}

\textsuperscript{1}Medical student; \textsuperscript{2}Division of Surgery and Oncology, Royal Liverpool University Hospital

Microscopic resection margin status (ie. R0 vs R1 resection) is an important survival determinant following pancreatoduodenectomy (PD) for periampullary cancer. Equivocal R1 cases exist with evidence of tumour extension within 1 mm of (but not breaching) a resection margin. Royal College of Pathologists guidelines recommend that these R1a resections should be considered synonymous with margin positive cases (R1b) but there is a lack of objective evidence for this recommendation.

Methods: Clinical and pathological data were retrieved from a prospectively maintained database. 236 consecutive patients with histologically confirmed periampullary adenocarcinoma underwent PD over a ten year period. No R2 resections were included in this patient group.

Results: Of the 236 resected periampullary cancers, 150 (63.6\%) were R1 resections of which 54 were R1a and 96 were R1b. There was no significant difference in median survival between R1a resections and R1b resections in pancreatic ductal adenocarcinoma (PDAC) patients (15.4 vs 12.6 months respectively – log rank, \(p = 0.376\)). Similar findings were identified for ampullary and intra-pancreatic bile duct adenocarcinoma (p = 0.291 and 0.941 respectively). Both R1a and R1b cases were grouped together for subsequent analyses. When considering only PDAC cases with an R1 resection (n = 91), an involved pancreatic transection margin was found to confer a poorer survival outcome when compared with other involved margins (log rank, \(p = 0.036\)). As the number of involved margins in a single specimen increased, a trend towards poorer survival was exhibited (Cox, \(p = 0.045\)). Logistic regression demonstrated that increasing tumour size (p < 0.001), poor tumour differentiation (p = 0.005) and nodal status (p = 0.013) were all associated with an increased likelihood of a R1 resection for PDAC cases.

The findings from this study support the Royal College of Pathologists recommendations for classifying resection margin involvement in periampullary cancer. The results highlight the importance of standardised criteria for histopathology reporting when comparing the outcomes of surgery between individual centres.

Long-Term Efficacy of Minimally Invasive Stented Pancreatico cystgastrostomy


Department of Hepatobiliary and Pancreatic Surgery, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW

Introduction: Minimally invasive methods for draining pancreatic pseudocysts are numerous and have replaced surgery as a first-line treatment option. However, little is known regarding the long-term efficacy of minimally invasive approaches. The aim of this study was to evaluate long-term outcomes following minimally invasive stented pancreatico cystgastrostomy.

Methods: A retrospective study of patients undergoing combined endoscopic/ultrasound guided percutaneous stenting between 1994 and 2007. Data was extracted from case records and our computerised radiology database.

Results: 37 combined endoscopic/ultrasound guided procedures were undertaken. Median patient age was 52 years (range 26 to 84 years). 19 pseudocysts were secondary to acute pancreatitis and 18 were secondary to chronic pancreatitis. The maximum diameter of pseudocysts on pre-procedure imaging ranged from 4 to 21 cm (median 11 cm). Median length of hospital stay was 7 days (range 1

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to 44 days) and 30-day mortality was 0%. The technical success rate of stent insertion was 70.3% (n = 26). Of those patients stented during the combined procedure 3 developed infection of the pseudocyst necessitating open cystgastrostomy within the first month. During a mean follow-up period of 41 months 2 patients developed recurrent pseudocysts which were successfully drained by a further combined procedure (16 and 43 months). Repeat imaging in the remainder of patients (n = 21) failed to show any evidence of a persistent/recurrent pseudocyst beyond 2 months.

Conclusions: Minimally invasive stented pancreaticocystgastrostomy is safe and highly efficient in preventing recurrent pseudocyst formation in the long-term. Recent data suggest endoscopic-ultrasound sphincterotomy is safe and highly efficient in preventing recurrent pseudocyst formation for- }

Is There a Role for Prophylactic Antibiotics in Necrotising Acute Pancreatitis?

E.A. Villatoro\(^1\), M. Mulla\(^2\), R.I. Hall\(^2\), M. Larvin\(^1\)

\(^1\)Division of GI Surgery, University of Nottingham School of Graduate Entry Medicine and Health, Derby UK;
\(^2\)Derby Hospitals NHS Trust, Derby City General Hospital, Derby UK

A series of randomised controlled trials (RCTs) has produced conflicting evidence as to the role of antibacterial prophylaxis against infection of pancreatic necrosis in acute pancreatitis. The quality of RCTs has varied, and different therapeutic regimens have been employed. Not surprisingly, the quality of RCTs has increased over time. However even the most recent high-quality double-blinded RCTs were underpowered, and the results have left clinicians confused over the best clinical management of patients with proven pancreatic necrosis. The aim of the study was to determine whether antibiotics are effective in this group of patients, and if so, to seek an explanation.

We sought RCTs which compared antibacterial therapy against placebo in patients with significant necrosis proven by CT. Six relevant RCTs were identified with regimens falling into two groups: four evaluated beta-lactams (n = 292), and two quinolone/trimidazole (n = 102). None was adequately powered, and only two were double-blinded. Meta-analysis was performed using ‘RevMan’ software (Update, Oxon UK). Analysis from 394 subjects demonstrated significantly less mortality with therapy (6.5%) versus controls (14.4%), odds ratio 0.43 (95% CI 0.22, 0.84). However, rates for infected necrosis were not significantly different. Non-pancreatic infections were significantly lower in the antibiotic group, with a 24.2% incidence in antibiotic treated patients versus 35% in controls, odds ratio 0.55 (95% CI 0.33, 0.91), although only four studies offered data for this evaluation (n = 308). Sub-group analysis showed that beta-lactam usage was associated with significantly less overall mortality (6.8%) than controls (15%), odds ratio 0.42 (95% CI 0.19, 0.92), but no significant difference between quinolone/trimidazole and controls. Beta-lactam treatment appeared to be associated with a lower incidence of infected necrosis (16.4%) versus controls (23.3%), but this was statistically non-significant, odds ratio 0.62 (95% CI 0.34, 1.12).

There was a non significant increase in cases of infected necrosis in the treatment group of the quinolone/trimidazole studies. Other infections were significantly lower in those patients treated with beta-lactams, with an incidence of 22.4% versus 35.3% in the control group, odds ratio 0.48 (95% CI 0.27, 0.87). Only one study in the quinolone group reported the incidence of non-pancreatic infections, with no significant difference between the groups.

The results confirm previous meta-analyses demonstrating that antibacterial prophylaxis does not significantly influence whether pancreatic necrosis becomes infected. However antibacterial therapy does significantly reduce mortality and the mechanism remains unclear. Given the apparent stronger contribution of beta-lactams to reduced mortality, which may have a broader effect on non-enteric organisms than a quinolone/trimidazole combination, we speculate that antibiotics reduce mortality by preventing serious non-pancreatic infections alone. This effect is well described in general intensive care patients. Concerns persist about poor quality of studies and lack of data on adverse effects. Further, adequately powered, double-blinded studies, perhaps now targeting beta-lactam agents, are required to confirm efficacy, safety, and elucidation of the mechanism.

Potential Markers for Pancreatic Cancer Identified by Gene Expression Profiling

A. Rogers, J. Murphy, E. Manahan, D.P. Toomey, K.C. Conlon

The Professorial Surgical Unit, Trinity College Dublin, The Trinity Centre for Health Sciences, The Adelaide and Meath Hospital Inc, The National Children’s Hospital, Tallaght, Dublin 24

Current management of pancreatic cancer is mired by late presentation and lack of effective adjuvant therapy. New methods of genome-wide expression analysis allow identification of novel targets. This study investigated the expression profiles of pancreatic cancer cell lines, BxPC-3 and AsPC-1, to identify diagnostic markers and therapeutic targets for this disease.

Methods: Confluent cells were treated with Camptothecin (pro-apoptotic agent) or phorbol 12-myristate 13-acetate (PMA – pro-inflammatory mediator). Non-treated cells were used as control. RNA was extracted and hybridised to Affymetrix GeneChip\(^®\) U133 oligonucleotide arrays. Differentially expressed genes were identified using ArrayAssist\(^®\). Significantly interacting genes were linked and their pathways mapped using Pathway studio\(^®\). Multiple differentially expressed genes were selected based on pathway significance and fold change for validation by RT-PCR.

Results: Separate gene sets for each condition were generated that displayed a 1.5 fold differential expression with a p value <0.02. Pathway analysis revealed that camptothecin was primarily involved in signal transduction via MAP kinase pathways. PMA induced apoptotic signalling through a family of receptors known collectively as ‘death receptors’ including Fas, DR3 and DR4–5. Quantitative RT-PCR analysis confirmed the microarray results for selected genes. Genes selected included those already implicated in pancreatic cancer (SMAD3, BRCA2, MMP-1) and also several not previously reported. Although camptothecin and PMA had distinct expression profiles, 3 genes (ATF3, PLA2 and SOD2) were ≥ 10 fold up- and down-regulated in AsPC-1 and BxPC-3, respectively.
Novel genes have been identified in pancreatic cancer for evaluation as screening and therapeutic targets. Three genes (ATF3, PLAU and SOD2) are involved in early stage invasion and cell dissociation, thus demonstrating potential as specific tumour markers or molecular targets in pancreatic cancer.

Hyponatraemia in Chronic Pancreatitis is Associated with an Increased Inflammatory Response and Hyperglycaemia

E.J. Dickson, G. Wilson, N. Jamieson, C. Perry, C.J. McKay, C.R. Carter
West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow, Scotland, UK

The relationship between glycaemic control, electrolyte disturbance and inflammatory response in chronic pancreatitis is not fully understood. This study examined the influence of blood glucose level and the degree of inflammation on serum sodium concentration at the time of hospital admission in patients with an established diagnosis of chronic pancreatitis.

Consecutive patients with chronic pancreatitis (n = 162) admitted to a tertiary referral pancreatic unit were analysed. Serum sodium and formal laboratory blood glucose concentrations were determined at the time of admission, and prior to administration of intravenous fluids. The magnitude of the inflammatory response was assessed by measuring the C-Reactive Protein (CRP) concentration. The patients were subdivided according to the serum sodium concentration with respect to the laboratory reference range. Three patients had a serum sodium greater than the reference range (135–145 mmol/l). Patients with hyponatraemia (n = 41, sodium < 135 mmol/l) had a significantly greater inflammatory response than those with a normal or high serum sodium (mean CRP 115.2 versus 64.3 respectively, p = 0.011, Student’s T Test). In addition, hyponatraemia was significantly associated with higher blood glucose levels when compared to patients with normal or high serum sodium concentrations (mean blood glucose 12.0 versus 7.8 respectively, p < 0.0001, Student’s T Test).

Our data demonstrate that patients admitted to hospital with chronic pancreatitis are significantly more likely to be hyponatraemic if they have a marked inflammatory response or hyperglycaemia. The underlying pathophysiology of a low serum sodium concentration in these patients is not clear. The degree of metabolic disturbance as a consequence of chronic inflammation may influence the transmembrane sodium pump at a cellular level. Further work is in progress to elucidate this, and to determine the prognostic significance of hyponatraemia in chronic pancreatitis.

CCK-8 Directly Evokes Exocytosis in Human Pancreatic Acinar Cells

E. McLaughlin1,2, J. Murphy1,2, D. Cridde1, M. Sherwood1, M. Chvanov1, J. Gerasimenko2, O.V. Gerasimenko2, M. Raraty2, P. Ghaneh2, J.P. Neoptolemos2, A.V. Tepikin1, O.H. Petersen3, R. Sutton3
1Physiological Laboratory, 2Division of Surgery and Oncology, University of Liverpool and Royal Liverpool University Hospital, Liverpool, UK

CCK and its analogues are used extensively in experimental models of pancreatitis in rodents, both in isolated cells and in vivo work. There is debate as to whether CCK acts only indirectly on human pancreatic acinar cells, via vagal nerve stimulation, or by
direct CCK receptor activation, which could limit the applicability of rodent studies. We have investigated whether CCK-8 directly elicits exocytosis in isolated human pancreatic acinar cells, as occurs in isolated murine pancreatic acinar cells.

**Methods:** Freshly isolated, perfused human or murine pancreatic acinar cells were loaded with fluorescent dyes including quinacrine, an acidophilic dye preferentially taken up by secretory granules, that has been widely used to detect and quantify exocytosis from a variety of isolated cell types, including pancreatic acinar cells. Confocal microscopy was employed to measure spatiotemporal changes in quinacrine fluorescence, when perfused with physiological (2 pm, 10 pm) and hyperstimulatory (10 nM) concentrations of CCK-8.

**Results:** A prompt drop in quinacrine fluorescence was seen when murine pancreatic acinar cells were perfused with physiological concentrations of CCK-8 2 pm (n = 12) and 10 pm (n = 9). Similar decreases in quinacrine fluorescence were seen in isolated human pancreatic acinar cells, with a similar time course, in response to similar concentrations of CCK-8. These responses were accompanied by similar calcium signaling patterns. The responses occurred in the presence of atropine (to prevent possible stimulation via cholinergic nerve endings) and tetrodotoxin (to prevent non-cholinergic nerve stimulation). In both cell types responses to hyperstimulation with 10 nM CCK-8 were less pronounced than at physiological concentrations, in keeping with the reduction of secretion seen in rodent pancreatic acinar cells following hyperstimulation with secretagogues.

Our results show that when CCK-8 is applied to human and murine pancreatic acinar cells at physiological concentrations, both cell types display similar calcium signaling and subsequent prompt secretion of secretory granules. At supramaximal concentrations, however, secretion is reduced. These data underline the relevance of rodent models for human pancreatic disease.

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Pancreatic Carcinoma Occurring in Chronic Calcific Pancreatitis of the Tropics

S. Iype¹,², M.L. Arunkumar³, N.S. Lai³, A.P. Kuruvilla¹, M. Anandakumar³, H.M. Kocher²

¹Department of Surgical Gastroenterology, Medical College Hospital, Trivandrum, India; ²Barts and The London HPB Centre, The Royal London Hospital, London, UK

Carcinoma developing in chronic calcific pancreatitis of tropics has been hypothesized since last 3 decades without adequate cohort studies to define the clinical presentation of the disease or its assessment in comparison to pancreatic cancer occurring de novo.

**Methods:** We reviewed 2 cohorts of patients in a single tertiary referral centre: CCPT with malignancy (n = 90) and de novo pancreatic ductal adenocarcinoma (n = 195) during a 9-year period from March 1998 to October 2006.

**Results:** Salient clinical difference in the two groups are listed in table De novo Pancreatic cancer Ca in CCPT Age (median, range) 62 (43–81) years 42 (26–77) years M:F 140:55 (2.54:1) 66:24 (2.75:1) Location of tumour Head 88.22% 74.70% Body 10.25% 22.80% Tail 1.53% 2.50% Operation types Biliary bypass 20 (10.3%) 19 (21.2%) Biliary bypass + GJ ± Other procedures 87 (44.6%) 13 (14.4%) Classical Whipple 21 (10.7%) 4 (4.4%) PPPD (Pylorus Preserving Pancreatoduodenectomy) 45 (23.1%) 28 (31.2%) Distal pancreatectomy 9 (4.6%) 4 (4.4%) Others 13 (6.7%) 22 (24.4%) Location of tumour Head 88.22% 74.70% Body 10.25% 22.80% Tail 1.53% 2.50% Operation types Biliary bypass + GJ ± Other procedures 87 (44.6%) 13 (14.4%) Classical Whipple 21 (10.7%) 4 (4.4%) PPPD (Pylorus Preserving Pancreatoduodenectomy) 45 (23.1%) 28 (31.2%) Distal pancreatectomy 9 (4.6%) 4 (4.4%) Others 13 (6.7%) 22 (24.4%)

Carcinoma occur at younger age in CCPT patients, as compared to de novo pancreatic cancer suggesting the pre-malignant state of the CCPT. Also carcinoma in CCPT tended to occur twice more commonly in the head and generally tumours were of the worse grade and less likely to be resectable.

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Inhibition of the Mitochondrial Membrane Permeability Transition Pore Affects Murine Pancreatic Acinar Cell Responses to Bile Acids

R. Mukherjee¹,², D.N. Criddle¹, O.H. Petersen¹, R. Sutton²

MRC Group, ¹Physiological Laboratory and ²Division of Surgery and Oncology, University of Liverpool, Liverpool, UK

Increasing evidence implicates mitochondrial inhibition from calcium overload as an important early component of pancreatitis. Toxins or hypoxia cause the inner mitochondrial membrane to become permeable to solutes <1,500 Da through the mitochondrial permeability transition pore (MPTP), which may be important in pancreatic acinar cell necrosis. We have investigated the role of the MPTP in pancreatic acinar cell responses to bile acids known to cause pancreatitis.

**Methods:** Confocal fluorescence microscopy of freshly isolated, perfused murine pancreatic acinar cells was undertaken to measure changes of cytosolic calcium ([Ca²⁺]c). Fluo-4, NAD(P)H autofluorescence, a measure of mitochondrial ATP production and mitochondrial membrane potential (ΔΨm: TMRM). Cells were exposed to the bile acid tauroliotholic acid 3-sulphate (TLC-S) with or without pretreatment using 50 μM bongkrekic acid, known to inhibit the MPTP.

**Results:** 500 μM TLC-S induced a partial fall in [Ca²⁺]c (n = 14) that was further fully depolarised with 10 μM carbonyl cyanide-m-chlorophenylhydrazone (CCCP), a protonophore that uncouples the mitochondrial permeability transition pore (MPTP) and suggests the pre-malignant state of the CCPT. Also carcinoma in CCPT tended to occur twice more commonly in the head and generally tumours were of the worse grade and less likely to be resectable.
Infected Pancreatic Necrosis – Favourable Outcome Associated with Wide-Bore Percutaneous CT-Guided Drainage, Critical Care Management and Delayed Necrosectomy

J.B. Conneely, S. Shine, H. Fenlon, M. MacNicholas, F. Colreavy, D. Phelan, G.P. McEntee

Mater Misericordiae University Hospital, Eccles St., Dublin 7, Ireland

The role and timing of surgery in severe acute pancreatitis remains controversial. Despite the development of minimally invasive surgical techniques, multiple procedures are commonly required and morbidity and mortality rates remain high. We postulated that control of sepsis facilitating a delay in surgery would lead to improved outcomes.

From January 1999 to December 2006 all patients with infected pancreatic necrosis (IPN) were managed with wide-bore radiologic drainage and critical care management. Disease severity and progress was assessed using APACHE II, Sequential Organ Failure Assessment and CT Severity Index scoring systems. Necrosectomy was performed when there was radiological and clinical evidence of resolution of disease. 47 patients were admitted with severe acute pancreatitis. Six patients had sterile necrosis and were managed conservatively and 41 developed IPN. Critical Care management and wide-bore radiologic drainage yielded a significant reduction in disease severity indices; APACHE II: peak 12 (range 8–22) vs. pre-op 6 (range 1–15) (p < 0.001); SOFA: 4 (0–11) vs. 1 (0–7) (p = 0.01); Modified CT Severity Index: 10 vs. 8 (p < 0.001). Necrosectomy was delayed to a median of 42 days (range 31–98) post onset of symptoms. There was conversion to sterile necrosis with resolution of sepsis in 8/41 (19.5%) of IPN patients. 3 patients (7.3%) died post-operatively. One enteric fistula was encountered requiring reoperation. 2 patients with IPN were managed entirely conservatively and did not require necrosectomy.

Our results demonstrate that wide-bore percutaneous drainage, coupled with critical care management in patients with infected pancreatic necrosis achieved a significant improvement in physiological and radiological parameters, facilitating delayed surgery which was associated with reduced morbidity and mortality (7.3%). Non-operative clearance of infection and successful conservative management associated with reduced morbidity and mortality (7.3%). Non-operative clearance of infection and successful conservative management associated with reduced morbidity and mortality (7.3%).

An Audit of Pancreatic Enzyme Replacement Therapy (PERT) after Pancreatic Surgery

L. Lewis, M. Abu Hilal, N. Pearce, C.D. Johnson

Southampton General Hospital, Southampton, UK

After pancreatic resection, impaired pancreatic function may contribute to postoperative malnutrition and failure to gain weight. Our practice is to prescribe a small dose of pancreatic enzymes routinely, and adjust dose as required; all patients receive a proton pump inhibitor to prevent stomal ulcer. We have audited this practice to identify the dosing schedule most often associated with weight gain and normal stools.

Methods: 45 patients with no evidence of recurrence were interviewed in clinic at least 3 months after pancreatic surgery. Dose, timing and frequency of PERT (Creon, Solvay) were recorded, as well as weight change, bowel function.

Results: 40 patients had had a formal pancreatectomy (Whipple’s 33, Beger 2, left resection 5). Six were not taking PERT. Most patients were taking either 25,000 u (21) or 50,000 u (5) lipase TDS and only 4 were taking a higher dose. Over half the patients (12/21) taking 25,000 u TDS had lost weight, 3 of 5 on 50,000 u TDS had gained weight. Weight gain was associated with enzymes taken before meals (9/12): 16 of 23 taking enzymes during a meal had lost weight. Bowel function was recorded in 32 patients: 21 reported soft or solid stool; of these 8 were taking PERT before meals, 6 during and 3 after meals and 4 were not using PERT. Of 5 patients with loose or liquid stool one took PERT before meals and 3 during.

Conclusion: This audit suggests that most patients offered PERT after pancreatic surgery will continue to take the medication but that the desirable aims of normal bowel function and adequate weight gain are not achieved in many patients. Taking PERT before meals was associated with weight gain: this dosing schedule may be preferable for most patients.

This study was supported by an educational grant from Solvay.

Importance of Reactive Oxygen Species Generation by Bile Acids to Murine Pancreatic Acinar Cell Fate

D.N. Criddle1, D. Booth1, R. Mukherjee1,2, O.H. Petersen1, R. Sutton2

1Physiological Laboratory, 2Division of Surgery and Oncology, University of Liverpool

Oxidative stress has been implicated as an important determinant in the severity of acute pancreatitis, although this remains controversial. We have investigated the acute generation of reactive oxygen species (ROS) by bile acids, recognised precipitants of acute pancreatitis, in pancreatic acinar cells and a possible modulatory role of the endogenous detoxifying enzyme NAD(P)H quinone oxidoreductase (NQO1) in determining pancreatic acinar cell fate.

Methods: Confocal fluorescence microscopy of freshly isolated, perfused murine pancreatic acinar cells was undertaken to measure
spatiotemporal changes of ROS (5-chloromethyl-2,7-dichlorodihydrofluorescein diacetate acetyl ester; CM-H2DCFDA), cytosolic calcium ([Ca2+]c: Fluo4), NAD(P)H (autofluorescence), mitochondrial membrane potential (∆ψm: TMRM) and caspase activation (R110-aspartic acid amide) induced by the bile acid tauroliotholic acid 3-sulphate (TLC-S).

**Results:** Lower concentrations of TLC-S (10–200 μM), which evoked predominantly oscillatory [Ca2+]c elevations, did not generate ROS. In contrast 500 μM TLC-S, which induced a sustained rise of [Ca2+]c and concomitant decrease of NAD(P)H, caused a significant increase of ROS, as shown by a rise in CM-H2DCFDA fluorescence. This rise was completely blocked by the antioxidant N-acetyl-L-cysteine (NAC; 10 mM), whereas [Ca2+]c and NAD(P)H signals were unaffected. ROS generation induced by 500 μM TLC-S was blocked by the calcium chelator BAPTA-AM, indicating a dependence on [Ca2+]c elevation. A partial depolarisation of ∆ψm was induced by 500 μM TLC-S, whereas this remained stable in the presence of lower concentrations of TLC-S. Inhibition of NQO1 with 1,4-dimethoxy-2-methylnapthalene (DMN: 30 μM), which did not induce ROS per se, unmasked ROS generation by 200 μM TLC-S. This rise of ROS was not inhibited by the antioxidant N-acetyl-L-cysteine (NAC; 10 mM), indicating that ROS generation was responsible for induction of the intrinsic mitochondrial apoptotic cell death pathway.

Our results show that the bile acid TLC-S induces acute production of ROS, especially when endogenous defence mechanisms are compromised, which may contribute to pancreatic acinar cell death. These data suggest that abnormal sustained elevations of [Ca2+]c induced by high levels of bile acids, which compromise mitochondrial function, are likely to be a crucial trigger for ROS generation.

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**Toxic Globalisation of Secretagogue-Elicited Acinar Cell Ca2+ Signalling and Prevention by ATP or Removal of Ca2+ from the Cell Exterior**

J.A. Murphy, D.N. Criddle, J.P. Neoptolemos, O.V. Gerasimenko, A.V. Tepikin, O.H. Petersen, R. Sutton

MRC Secretory Control Group, Physiological Laboratory and Division of Surgery and Oncology, University of Liverpool, UK

We have previously demonstrated that low concentrations of the pancreatic acinar cell toxins tauroliotholic-3-sulphate (TLCs) or palmatolic acid ethyl ester (POAEE) induce toxic globalisation of inositol trisphosphate (IP3)-mediated signaling increases in the cytosolic calcium ion concentration ([Ca2+]c, IP3 applied via patch pipette). We sought to determine whether toxic globalisation of [Ca2+]c can occur with physiological secretagogues, and how it can be prevented.

Isolated mouse pancreatic acinar cells were examined by confocal microscopy to measure changes in [Ca2+]c (Fluo4-AM), mitochondrial function (NADH autofluorescence), ATP concentration (Mg Green) and cell fate (propidium iodide, PI). Cholecystokinin (CCK, 1–20 μM) or acetylcholine (ACh, 50 nM) were perfused extracellularly and low concentrations (10 μM) of TLCs or POAEE added, while whole-cell recordings of Ca2+-dependent Cl– currents were made. In some experiments, supplementary ATP was added to the internal pipette solution.

**Results:** CCK and ACh elicited typical [Ca2+]c signals in the granule pole with stimulus-metabolism coupling (NADH). Extracellular TLCs or POAEE (10 μM) transformed these signals into prolonged (>30 s), global [Ca2+]c increases accompanied by NADH and ATP depletion, inducing necrosis. Supplementary ATP reduced the period of globalisation associated with each elevation of [Ca2+]c and prevented necrosis, as did removal of Ca2+ from the external medium, and in the case of POAEE, hydroxide inhibition, preventing POA formation.

Physiological Ca2+ signals elicited by secretagogues can undergo toxic globalisation from low concentrations of acinar cell toxins, resulting in mitochondrial Ca2+ overload, inhibition of ATP production and cell death. Cell injury could be prevented by blockade of Ca2+ entry.

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**Epidemiology of Acute Pancreatitis — A Prospective Observational Study**

M.P. Ellis, J.J. French, J.J.S. Brown, R.M. Chamley

HPB Surgical Unit, Freeman Hospital, Newcastle upon Tyne, NE7 7DN, UK

The aetiology and mortality of acute pancreatitis (AP) are known to be related to lifestyle factors such as alcohol, smoking and obesity. The role of social deprivation has however not previously been reported.

**Methods:** All patients with a clinical and biochemical diagnosis of AP were identified. Clinical casenotes were reviewed to confirm the diagnosis, aetiology and outcome of confirmed cases. Age standardised incidence (ASI) and mortality (ASM) were calculated using 2001 census data and the European standard population. To study social deprivation patients were stratified into five quintiles of deprivation based on the index of multiple deprivation (IMD) score.

**Results:** AP was confirmed in 963 episodes during the study period. ASI was 55.6 per 105 per year. Case mortality was 4.98% (48/963) for all patients and 17.16% (46/228) for patients with severe AP as defined by the Atlanta criteria. ASM was 2.19 per 105 per year. The aetiology of AP was gallstones in 409 (42.5%), alcohol in 277 (28.8%), idiopathic in 137 (14.2%) and other aetiology in 140 (14.5%). A significant trend was observed of increasing ASI with increasing levels of deprivation (Pearson correlation, R = 0.943, p = 0.012). There was also a significant trend of increasing proportion of AP secondary to alcohol excess with increasing level of deprivation (R = 0.981, p = 0.003). This trend however was also seen in patients with aetiology other than alcohol or gallstones.

A higher incidence of AP was observed than has previously been reported in the UK. A moderate decline in case based mortality is observed compared to previous studies although patients with severe AP remain at significant risk of death. Socially deprived individuals have a significantly increased incidence and alcohol aetiology.
18 Percutaneous Feeding Jejunostomy and Naso-Jejunal Tubes as Nutrition Delivery Systems in Patients following Pancreatic Head Resection

J.J. French1, S. Lobaz1, I. Iqbal1, B. Davidson2, L. Fletcher2, S.A. White1, B.C. Jaques1, D.M. Manas1, R.M. Charnley1
1Departments of HPB Surgery and 2Dietetics, Freeman Hospital, Newcastle upon Tyne, NE7 7DN, UK

Delivery of nutrition is thought to be an important part of the recovery of patients following pancreatic head resection. We have routinely used naso-jejunal (NJ) or percutaneous feeding jejunostomy (PFJ) delivery systems.

Methods: Using a set proforma, data was prospectively collected on all patients undergoing pancreatic head resection over a 6 month period Jan – June 07. There were no exclusion criteria. Method of feeding was according to consultant preference.

Results: 28 pancreatic head resections were performed (20 pylorus preserving, 8 classical Whipples). Mean patient age was 58 years (range 18–80). Thirteen were male. NJ tubes were inserted in 12 patients (9 pylorus preserving, 3 classical Whipples). PFJ was used in 16 patients (11 pylorus preserving, 5 classical Whipples). Tube/feed related complications occurred in 9/12 NJ cases (displacement, bloating/discomfort, diarrhoea and reflux) and 4/16 PFJ cases (displacement, blockage, tube damage, bloating/discomfort, diarrhoea and reflux). Other operative complications were comparable in each group. The mean amount of feed received (and as a percentage of that prescribed) was 4,007 mls (35.5%) and 6,402 mls (50.2%) for NJ and PFJ respectively. The mean time from operation to commencement of a normal diet was 6 days in NJ patients and 8 days in PFJ patients. The mean length of hospital stay was 17 days (NJ patients) and 20 days (PFJ patients).

NJ had a higher tube related complication rate than PFJ, but both systems failed to achieve delivery of the prescribed feed volume. Commencement of normal oral diet was successful at an early post-operative stage and questions the need for either NJ or PFJ systems.

to investigate factors that delay or preclude the delivery of chemotherapy in patients with pancreatic cancer detected to have inoperable disease following surgical workup.

Methods: Patients referred to the regional cancer treatment centre with pancreatic cancer found to have inoperable disease following surgical work-up in the year 2005 were identified from the HPB unit database. Following audit approval a data collection tool was developed and relevant patient information gathered using multiple sources.

Results: 39 patients were identified from the HPB database. Overall only 12/39 (30%) of these patients received chemotherapy. The remaining 27 patients did not receive chemotherapy due to death before tissue diagnosis obtained (n = 12 (31%)), low performance status (n = 11 (28%)), patient choice not to have chemotherapy (n = 2 (5%)), refractory biliary obstruction (n = 1 (3%)), unknown (n = 1 (3%)). The median time from referral to first chemotherapy delivery was 75 days (SD 93 days). Delay before commencement of chemotherapy was due to achieving biliary drainage (11 days (SD 36 days)) and obtaining a tissue diagnosis (25 days (SD 34 days)).

Multiple procedures were needed in 16 patients Interruption of chemotherapy delivery due to plastic and metal stent occlusion was seen in 3 patients and 0 patients respectively (p = 0.24).

A disappointingly low percentage (30%) of patients in this investigated group received chemotherapy. Reducing the time taken to achieve biliary drainage and tissue diagnosis and the use of metal stents where possible is likely to improve chemotherapy delivery.

19 Factors affecting Delivery of Chemotherapy in Patients with Inoperable Pancreatic Cancer

M. Lown1, J.J. French1, F. Caxon2, K. Sumpter2, P. Atherton2, U. Mullick2, K. Oppong3, R.M. Charnley1
1Department of Hepato-Pancreato-Biliary Surgery, Freeman Hospital, Newcastle upon Tyne, UK; 2Northern Centre for Cancer Treatment, Newcastle upon Tyne, UK; 3Department of Gastroenterology, Freeman Hospital, Newcastle upon Tyne, UK

Pancreatic cancer is an increasingly common disease that frequently presents with obstructive jaundice. Chemotherapy is the only therapeutic option in inoperable cases. Tissue diagnosis, relief of biliary obstruction, and an adequate patient performance status are prerequisites prior to chemotherapy delivery. The aim of this study was to investigate factors that delay or preclude the delivery of chemotherapy in patients with pancreatic cancer detected to have inoperable disease following surgical workup.

Methods: In all cancer groups, the distance between cancer cells in large bowel cancer (LBC) has been established as tumour cells within 1 mm to the margin. This R1 definition is also used for the reporting of pancreatic head cancer specimens, but has never been validated. The Minimum Spanning Tree algorithm (MSTA) is a computer generated method that analyzes the topology of cancer growth patterns by determining the minimum distance between tumour cells. The aim of this study is to determine, using the MSTA, whether a similar growth pattern in LBC and cancer arising in the pancreatic head justifies the current R1 definition for reporting of the latter.

Methods: In 10 cases of each LBC, pancreatic (PC), ampullary (AC) and distal bile duct cancer (DBC) a 200× picture was taken in the centre and periphery (at the invasive front) of the tumour as well as half way between both. For each picture, the distances between cancer cells were determined using the MSTA. The average minimum distance was compared between the 3 zones in the 4 cancer groups, as was the tumour cell density.

Results: In all cancer groups, the distance between cancer cells was comparable in the central zone, and larger in the periphery than to investigate factors that delay or preclude the delivery of chemotherapy in patients with pancreatic cancer detected to have inoperable disease following surgical workup.

Methods: In all cancer groups, the distance between cancer cells was comparable in the central zone, and larger in the periphery than
in the centre of the tumour ($p \leq 0.02$). However, this difference between centre and periphery was smaller in LBC than in PC, DBC and AC ($p \leq 0.03$). Results were similar for PC and DBC, but differed from those of AC ($p \leq 0.03$). On average, the tumour cell density dropped in the periphery of PC to 30% of that in the tumour centre, and only to 83% in LBC ($p < 0.0001$), 62% in AC and 40% in DBC ($p \leq 0.01$).

Tumour cell growth in PC, DBC and – to a lesser extent – AC is less dense than in LBC. Particularly in the periphery, tumour growth is more dispersed in PC, DBC and AD, and tumour cell density drops to as little as 30% at the invasive tumour front. This difference in tumour growth demands revision of the R1 definition for pancreatic head cancer. The MST algorithm is a useful tool to assess the topology of cancer growth patterns.

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**21**

*Can Pre-Operative Imaging Predict the Site of Origin of Peri-Ampullary Neoplasms?*

G. Morris-Stiff⁴, C.S. Verbeke³, D. Gomez¹, A.Z. Khan¹, A. Guthrie³, M. Sheridan⁶, K. Menon¹, A.M. Smith¹

¹Departments of Pancreaticobiliary Surgery, ²Histopathology, ³Radiology, St James’s University Hospital, Leeds

It is well accepted that there is a significant difference in survival between carcinomas of the head of the pancreas (HOP), ampulla (AMP) and distal common bile duct (CBD). Given the current advancements in neoadjuvant protocols which differ according to histopathology, it is now increasingly important to obtain an accurate preoperative diagnosis. To evaluate the accuracy of radiological imaging, and the relative roles of each modality, in distinguishing between HOP, AMP and CBD cancers. The results of overall and final radiology were compared with the definitive histopathology.

The histopathology and preoperative radiology of all patients undergoing pancreatoduodenectomy (PD) during the period 2001–2006 were reviewed. Imaging modalities assessed included CT, MRCP and ERCP. Endoscopic ultrasound was not included as it was not widely available during the interval covered by the study. The degree of agreement between the modalities and final pathology was assessed using Kappa statistic. During the period of the study 101 PDs were performed, of which, 1 was an emergency performed without pre-operative imaging, leaving 100 patients for analysis. The final pathology was: AMP; n = 32; CBD; n = 37; HOP; n = 31. The overall agreement between first radiological imaging and final pathology was poor with a Kappa statistic of 0.26, whilst the final pre-surgery radiology showed a moderate agreement with histopathology with a Kappa statistic of 0.43. The most accurate primary investigation was MRCP (56%) followed by CT (38%) and ERCP (32%). The accuracy according to histopathology was better for HOP both with initial (56%) and final radiology (76%). For AMP the figures were comparable at 50% and 68% but were worse for CBD at only 19% and 29%.

Preoperative imaging using CT, MRCP and ERCP shows only a moderate correlation with final histopathology in terms of correct attribution of the cancer origin site. MRCP would appear to be the most accurate single investigation and should be considered the primary tool. Whilst the preoperative diagnosis of HOP and AMP is reasonably accurate, that of CBD is poor.

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**22**

*Ultrasound Changes in the Liver Post Total Pancreatectomy and Islet Cell Auto-Transplantation*


Department of Hepatobiliary and Pancreatic Surgery, Leicester General Hospital

Intra-hepatic infusion is the commonest method of islet auto-transplantation. Structural and functional changes within the liver may result from a number of factors, including embolisation of terminal branches of the portal vein or effects of high insulin concentration on surrounding hepatocytes. It is important to be aware of potential changes in the appearance of the liver on ultrasonography (US), which combined with hepatic function allows appropriate post-operative surveillance of these patients.

**Methods:** We retrospectively reviewed post-operative US findings and liver function tests from 30 patients who underwent total pancreatectomy and islet auto-transplantation at the Leicester General Hospital, between 1993 and 2003. The islets were infused into the left hepatic lobe via the transverse mesocolic or recanalated umbilical vein. All patients underwent six-monthly ultrasound scan of their liver post-operatively for post hepaticojejunostomy surveillance.

**Results:** Echogenic areas were noted within the left lobe of the liver in 17 (56%) patients during their follow-up ultrasound scans, 3 (10%) had changes consistent with fatty liver, 4 (13%) had evidence of air within the biliary tree. Only 6 (20%) patients had a completely normal liver on ultrasound scan. None of the patients with echogenic changes in the liver had any significant loss of liver function. These changes occurred from 6 to 12 months following auto-transplantation.

Focal echogenicity is a common ultrasonographic finding in the liver following intra-hepatic islet auto-transplantation. These changes do not appear to adversely affect liver function. Appreciating these changes is important to avoid over-interpretation of post-operative US images.

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**23**

*IgG4 Positive Sclerosing Cholangitis Following Autoimmune Pancreatitis*


Department of Hepatobiliary and Pancreatic Surgery, Leicester General Hospital

Sclerosing cholangitis is an autoimmune condition characterised by lymphocytic infiltration within the biliary epithelium leading to multifocal stricturing of the biliary tree. Primary sclerosing cholangitis (PSC) is the commonest type encountered clinically. However, a
similar process may occur in conjunction with autoimmune pancreatitis (AIP), known as AIP-associated sclerosing cholangitis (AIP-SC). This subtype is associated with an elevated IgG4 level and the presence of a number of auto-antibodies. AIP-SC shows good response to steroid treatment, distinguishing it clinically from PSC.

We report a case of AIP-SC in a patient who had previously undergone a biliary bypass for AIP-induced chronic pancreatitis. The presentation of jaundice and grossly elevated tumour marker, CA19.9, raised the concern of malignancy. The uncertainty of the diagnosis was resolved when AIP-SC was confirmed on liver biopsy, with a concomitantly elevated serum IgG4 level. The disease went into remission with steroid treatment.

Stricture may occur as a result of biliary tree involvement in the inflammatory process associated with AIP, causing jaundice. Recognition of this unique disease entity should lead to early commencement of steroid therapy and prevent unnecessary surgery. The role of long-term steroid in preventing disease recurrence requires further exploration.

24 Prognostic Value of Genome-Wide Array-Based Comparative Genomic Hybridization Analysis of Pancreatic Ductal Adenocarcinoma


West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, UK; Cancer Research UK Centre for Oncology and Applied Pharmacology, Beatson Laboratories, University of Glasgow, UK

Chromosomal instability is characteristic of pancreatic ductal adenocarcinoma and manifests as subchromosomal numerical aberrations resulting in amplification and deletion of specific oncogenes and tumour suppressor genes respectively.

To identify novel genetic subchromosomal aberrations and to discover underlying genes that reflect the clinical characteristics of this disease we screened a total of 20 surgically resected fresh frozen pancreatic ductal adenocarcinoma tumour samples using oligonucleotide array-based comparative genomic hybridization (array CGH) measuring 236,000 coding and non-coding human sequences (providing a resolution of 6.5 Kb). Using stringent statistical technique we identified sequences of non random genomic changes. A large number of small loci, as yet unidentified in pancreatic ductal adenocarcinoma, demonstrated non-random loss or gain. Frequent losses at 1q21, 1q22, 5p15, 6q25, 10p5, 10q26, 11q23.3, 13q13.12, 13q33.3, 14q22-33, 15q26, 18q21.1, 20p12.3, 20p12.3 and 21q22, and gains at 2p16.1, 2q14.3, 2q24.3, 5p14, 6q12-14, 7q21-22, 8q23-24, 9p23, 10q21, 11q14.3, 13q22, 14q31, 15q14-15, 18p11, 19q13.2, 19q13.32 were identified. A number of chromosomal aberrations were related to pathological phenotype and additionally we identified novel chromosomal alterations that were independently predictive of patient outcome. Overall survival was reduced (p = 0.036) for the cases with chromosomal loss of the 18q21.1 locus, while survival was significantly prolonged (p = 0.02) in those cases with loss of the 15q26 locus. Further investigation is underway to identify potential candidate genes within these loci.

25 Radiofrequency Ablation of Locally Advanced Pancreatic Cancer: A Pilot Study

J.A. Logue, E. Leen, S.J. Moug, C.R. Carter, C.J. McKay

West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow, Scotland, UK

Radiofrequency ablation has been demonstrated to be effective in the treatment of unresectable hepatic tumours and promising results have been obtained in other cancers. In pancreatic cancer, small series and case reports suggest that this technique is feasible and safe in selected patients. The aim of this study was primarily to assess the safety of radiofrequency ablation in patients with non-metastatic, locally advanced pancreatic cancer.

Methods: Full ethical approval was obtained from the Local Research Ethics Committee. Pre-operative consent was obtained from patients with tumours staged as being of borderline resectability. Five patients (3 female, 2 male) with unresectable but non-metastatic pancreatic tumours were recruited. If tumours were deemed inoperable after full laparotomy, radiofrequency ablation was performed using the Cool-tip TM ablation system with a single, cooled electrode. Accurate needle placement was confirmed by intra-operative ultrasound and the target temperature controlled by a thermo-sensor at the tip of the needle was 90°C.

Results: Three patients developed life-threatening complications; one of whom died. Significant gastrointestinal haemorrhage occurred in two of these patients requiring angiographic embolisation. The remaining patient developed a post-operative biliary leak, severe sepsis and died as a result of multi-organ failure. Given these initial complications, we believed that it would be unsafe to proceed and therefore after discussion with the local ethics committee the study was terminated.

The results of this pilot study suggest that radiofrequency ablation for locally advanced pancreatic cancer is not safe as a result of unacceptable, life-threatening post-ablation complications.
resection for ductal adenocarcinoma of the pancreas. The aim of this study was to prospectively evaluate the role of C-reactive protein (CRP) as a prognostic indicator in resectable pancreatic cancer in addition to examining for any association between serum levels of the regulatory cytokines interleukin-6, interleukin-8 and interleukin-10.

**Methods:** Pre-operative serum samples were collected prospectively from all patients undergoing Whipple resection between 2003 and 2006. Routine laboratory measurements of CRP were performed the day prior to surgery and recorded. Serum interleukin-6, interleukin-8 and interleukin-10 levels were measured by enzyme-linked immunosorbent assay (ELISA). Triplicate analysis was performed and the mean value was used as the final concentration.

**Results:** Sixty-four patients underwent Whipple resection for pancreatic or peri-ampullary tumours. Thirty-six patients had completed a minimum of 18 months of follow-up at the time of analysis. On follow-up, 22 patients had died of their disease. Elevated pre-operative CRP was confirmed as a predictor of poor survival (p = 0.04). Furthermore, Cox regression survival analysis demonstrated that those patients with elevated pre-operative serum interleukin-6 and interleukin-10 levels had significantly worse survival (p = 0.003 and p = 0.006 respectively). Serum interleukin-8 levels were not associated with survival differences. There was a significant correlation between serum interleukin-6 levels and CRP (r = 0.46, p < 0.01).

This is the first prospective study to demonstrate that elevated pre-operative CRP predicts poor survival in patients undergoing Whipple resection. This is associated with elevated interleukin-6 and interleukin-10 levels suggesting a relationship between dysregulation of the innate immune response and an adverse prognosis with pancreatic cancer. Confirmation in a larger cohort of patients may enable pre-operative CRP to aid in the selection of patients for potentially curative resection.

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**28**

Acute Pancreatitis. Are Funding Linked National Targets needed to Improve Management?

D. Dunne, M. Jha

James Cook University Hospital, Middlesbrough, UK

The aim of this study was to audit the management and outcome of patients with acute pancreatitis against the standards of practice in the British Society of Gastroenterology (BSG) guidelines, and use this to draw comparisons between recent work showing improved outcomes in tertiary referral centres where guidelines were being followed.

The study assessed all patients presenting with acute pancreatitis over a one year period. Audit targets were overall mortality below 10%, mortality for severe pancreatitis below 30%, correct diagnosis and severity stratification within 48h, use of ultrasound, CT, and ERCP when indicated, aetiology identification above 80%, definitive management of gallstones within 2 weeks, and overall compliance with guidelines. Of 57 patients with acute pancreatitis, 45.6% had severe acute pancreatitis (SAP). Overall mortality was 12.2%, and 25.9% of those with SAP. Acute pancreatitis was diagnosed within 48hrs of presentation in 96.4% of patients. Severity stratification occurred in 16% of patients. Only 23% of patients with SAP were admitted to HDU or ITU within 48h. Definitive management of biliary pancreatitis occurred within 2 weeks in 7%. Guidelines were adhered to in 9% of cases.

The BSG guidelines are not being used routinely outside of a tertiary referral setting. This confers a higher mortality rate. The BSG guidelines have been in existence for nearly a decade and have even been revised. Despite much work showing improved outcomes where guidelines are being followed it is not routine practice throughout the NHS. The authors ask the question, in light of their findings, do we need funding linked national targets to improve management?
The Analysis of Age Standardised Mortality Rates for Pancreatic Cancer across the World

D. Hariharan¹, A. Saied¹, J. Warwick², H.M. Kocher¹,³

¹Institute of Cancer and ²Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry and ³Barts and the London HPB centre, The Royal London Hospital, UK

Recent study has suggested that incidence and mortality of pancreatic cancer in the UK is falling. We investigated whether this trend was seen all over the world.

Age-standardized mortality (world) rate [ASR (W)] for pancreatic cancer were extracted separately for males and females from a data base maintained by International Agency for Research on Cancer for 51 countries across the world (Europe-33 countries, Americas-8 countries and Asia-10 countries) and logistic regression analysis was performed for the data available for each country for the last decade (1992–2002) to analyse trends in the last decade. The ASR(W) remained static across most countries for both sexes. The highest mortality rates (for both sexes) were seen in Central Europe [range: men (8–12), women (4.5–7)] with highly significant trends towards increasing mortality in Romania (p < 0.001) along with Albania, Spain and Croatia (p < 0.01). Korea in the Far East too demonstrated highly significant increasing mortality trends for both sexes (men p < 0.001, women p < 0.01). In France, a trend towards increasing mortality was observed amongst women (p < 0.001). In Canada there was a decline in mortality [men (7.5 to 6.4), women (5.9 to 5), p < 0.01] whilst for men there was a downward trend in Ireland, UK, Switzerland, Austria and Poland [p < 0.05].

The changes reflect standardisation and consolidation of diagnostic tests for pancreatic cancer in the westernised world.

Organotypic Culture Modelling of Pancreatic Cancer

T.A. Mirza¹, F. Froeling¹, J. Sandle¹, N.F. Li², I.R. Hart¹, H.M. Kocher¹,²

¹Centre for Tumour Biology, Institute of Cancer, Barts and the London School of Medicine and Dentistry, London and EC1M 6BQ, UK; ²Barts and The London HPB Centre, The Royal London Hospital, London E1 1BB, UK

Pancreatic cancer is characterized by an intense stromal reaction but, disappointingly, reproducible models for exploring any interaction of the stroma with transformed pancreatic epithelial cells have not previously been available. We describe the development of a organotypic culture model to study the effect of stromal elements on pancreatic cancer cells in an in vitro, yet physiologically relevant, three-dimensional environment.

Co-culture of CAPAN-1, PaCa-3 cells, or their spheroids, on the surface of collagen/Matrigel gels, either with or without hTERT immortalized MRC-5 fibroblasts, was performed. Paraffin embedded sections were immunostained with Ki67, active Caspase-3, E-Cadherin, p-ERM, ROCK and N-WASP antibodies.

Results: The growth of both cell types, as a monolayer, was suppressed significantly in the presence of fibroblasts (CAPAN-1, average cell count with MRC-5 on day 7 was 613.6 vs 901 without MRC-5, p < 0.05; PaCa-3: 399.3 vs 458 respectively, p < 0.05) whereas spheroid growth of both lines remained unaffected. Both cell lines rapidly formed luminal structures when cultured as monolayers, and these were more pronounced with the CAPAN-1 cells, which exhibited a central apoptotic core and a proliferating peripheral rim. Apoptotic events (range 0.94–12.28%, median 4.35%) remained dramatically lower than the proliferation rates (range 8.88–65.59%, median 41.38%) in these cultures. Luminal structures expressed p-ERM, principally at the margins, while E-Cadherin expression was concentrated at the intercellular junctions and absent at the margins with the cell-matrix and cell-medium interface. Conversely ROCK was located at the margins of cells adjacent to the matrix and the medium whereas N-WASP was expressed in the perinuclear region on day 4, later assuming a peripheral distribution, which linked the cell membrane, by day 7.

Pancreatic organotypic culture functions as a viable, reproducible, three-dimensional model, which can be used to explore different interactions between stromal elements and pancreatic cancer cells.

Role of Staging Laparoscopy/Laparoscopic Ultrasound in Resectable Pancreatic and Periampullary Cancers

D. Hariharan¹, M. Siddeshwarappa², S. Bhattacharya², A.T. Abraham², H.M. Kocher¹,²

¹Institute of Cancer, Barts and the London School of Medicine and Dentistry, London, UK; ²Barts and the London HPB centre, The Royal London Hospital, UK

The role of staging laparoscopy (SL) and laparoscopic ultrasound (LUS) remains controversial in the management of patients with pancreatic and peri-ampullary cancers (PAC). To determine the utility of SL/LUS in detecting unresectability in patients with PAC who were otherwise resectable based on conventional staging.

Publications (1995-to date) examining the role of SL/LUS in potentially resectable PAC were examined with respect to change in surgical management. Studies indirectly assessing the role of SL/LUS without actually performing laparoscopy as well as those where surgical outcome could not be determined were excluded. Operative evaluation was considered as gold standard for staging, when undertaken, while laparoscopy alone was considered as gold standard when it detected metastatic disease. Overall test characteristics and yield of SL/LUS in preventing unnecessary laparotomy were determined.

A total of 20 studies with 2,040 patients satisfied our inclusion criteria. However, as the definition of resectability varied, data were re-analysed with a specific algorithm to determine resectability. The test characteristics of SL/LUS for different sets of patients were as follows: Sensitivity Specificity PPV NPV Yield *Locally advanced disease (n = 316) 63.6 100 100 45.6 48.7 *Resectable disease (n = 1,724) 63.4 98.6 97.6 75.7 72.9 2 Combined (resectable + locally advanced disease) (n = 2,040) 63.4 98.7 98.2 72.1 32.3 *Metastatic
Pancreatic carcinoma remains almost uniformly lethal. Cyclooxygenase-2 (COX-2) is present in high levels in the majority of pancreatic carcinomas. This has been linked with Vascular Endothelial Growth Factor (VEGF) production and angiogenesis, implicating it in this disease’s aggressive phenotype. This study aimed to investigate COX-2 and endothelial cell (EC) proliferation – a crucial step in angiogenesis using an in vitro coculture model.

Two pancreatic cancer cell lines BxPC-3 and AsPC-1 were treated with Phorbol 12-myristate 13-acetate (PMA) or Camptothecin and western blot performed. Cells, with or without aspirin and NS398 (COX-2 inhibitor), were similarly treated and then saturated with arachadonic acid. Subsequent PGE2 ELISA determined maximum COX-2 activity. Tumour cells were cultured with EC using a coculture membrane system (4 μm pores). Giemsa staining and CD31 and WST assays, quantified EC proliferation which was correlated with Prostaglandin E2 (PGE2) and VEGF production. Western blot showed BxPC-3 and AsPC-1 to consistently produce high and minimal levels of COX-2 respectively. PGE2 assay following arachadonic acid treatment confirmed this. PGE2 and VEGF from BxPC-3 cocultures were 3.2 (p < 0.001) and 6.9 (p < 0.001) fold greater than that of AsPC-1 respectively. Giemsa staining showed increased proliferation of EC in BxPC-3 wells compared to AsPC-1. CD31 assay confirmed this (BxPC-3 v. AsPC-1: 1.18 v. 0.93 fold; p ≤ 0.01). WST assay indicate a 3.3 fold difference (p ≤ 0.01).

Effective inhibition of COX-2 did not impact on VEGF production or EC proliferation. This highlights the need for effective inhibitors to target EC proliferation and further investigation into the exact role of COX-2 in tumour angiogenesis to facilitate design of combination therapies.
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