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Abstracts

Guest Editor
Ross Carter, Glasgow

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Oral Presentations

1

Open Surgery Should No Longer Be Offered as Primary Treatment for Infected Pancreatic Necrosis

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Since December 2005 we have only offered minimally invasive techniques as primary treatment for infected pancreatic necrosis. We have prospectively evaluated this policy.

Methods: Data was collected to compare APACHE2 score on admission, total hospital stay and mortality in patients with bacteriologically confirmed infected necrosis between 1995 and 2008. Comparison was made between 3 different time periods related to the techniques used: 1995-1999 (Group 1: open necrosectomy only); 1999-2005 (Group 2: open and minimally invasive [percutaneous and endoscopic] techniques); 2005-2008 (Group 3: only minimally invasive techniques offered).

Results: Total number of patients was 146 (m:f=88:58). Analysis of variance revealed a significant ($p=0.002$) progressive increase in severity of illness as measured by the mean APACHE2 score [Group 1: 11.19; Group 2: 13.29; Group 3: 16.25]. Overall mortality in the 3 time periods was Group 1: 12/33 (36%); Group 2 31/90 (34%); Group 3 2/23 (8.6%), $p=0.03$. Hospital stay was Group 1: 73 days; Group 2: 56 days; Group 3: 82 days, $p=0.041$. Two patients in Group 3 had open surgery following open procedures at other hospitals.

Conclusion: The effect of not offering open necrosectomy as primary treatment for infected necrosis has resulted in a dramatic reduction in mortality despite increased severity of disease. This has been achieved at the expense of increased hospital stay.

Data to be presented at AUGIS and APA

2

Evidence of Improving Outcome from Acute Pancreatitis in Scotland 2002-2006

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Acute pancreatitis was studied in the Scottish population over a 12 year period between 1984 and 1995. Incidence was rising and mortality falling over this period. Early deaths are recognised to be deaths from multi-organ failure and late deaths, from sepsis. The proportion of early deaths was 54%. It has been suggested that improvements in survival are related to changes in critical care management. Surgical sub-specialisation and advances in intensive care medicine over the last 12 years may have altered these figures and the aim of this study was to assess this.

Methods: Patient details of those dying from acute pancreatitis in surgical wards were obtained from the Scottish Audit of Surgical Mortality which has a compliance rate in excess of 98%. Population data and admissions with pancreatitis were obtained from Information and Statistics Division, NHS Scotland.

Results: In the 5 year period from 2002 to 2006, the incidence of pancreatitis each year was approximately 45 per 100 000 population. There were 392 deaths in this period with a mortality of between 2.85 and 3.41% per year. 86% of deaths from acute pancreatitis were in patients over the age of 60. The proportion of early deaths was unchanged from the previous study period at 55%. Incidence AP Mortality AP % Early Deaths 1984-1995 31.8/ 100 000 7.5% 54% 2002-2006 45.5/ 100 000 3.1% 55%

The trend to an increased incidence of acute pancreatitis in Scotland previously reported in the 1980s and 1990s has continued and was up to 46/100 000 in 2006. Mortality appears to have decreased which may be a reflection on improvements in or access to critical care. Decreases in numbers of early and late deaths indicate improvements in organ support and surgical care and not solely to improvements in critical care management.

3

Clinical Islet Autotransplantation; Is Acinar Tissue Well Tolerated?

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Since the advent of islet transplantation the importance of islet purity before transplantation has always been stressed. Many of the assumptions that led to this advice are based on animal and cell culture models. This retrospective case series compares the peri-opera-

tive outcomes and long-term graft function of patient's auto transplanted with either purified or un-purified islet preparations.

Total pancreatectomy was carried out on 39 patients for intractable pain associated severe chronic pancreatitis. Concomitant intra-portal islet auto transplantation was then carried out to abrogate the onset of surgically induced diabetes. A comparison of un-purified islets (n=28) vs. purified islets (n=11) revealed no differences in hepatic portal pressure (15mmHg (range 12-34) vs. 17mmHg (10-33), $p=0.6428$) or central venous pressure (9 mmHg (range 8-10) vs. 8mmHg (6-15)) at the time of transplant. Annual patient follow-up data revealed that transplantation of un-purified islets was associated with superior fasting glucose levels compared with pure islets (7.05 ± 0.73 vs. 10.94 ± 1.57 , $p=0.049$) and also improved stimulated c-peptide (3.58 ± 0.98 vs. 0.85 ± 0.18) at year 2 post transplant. Moreover, with the exception of one value, un-purified digest was associated with lower glucose values (fasting and stimulated), higher c-peptide values (fasting and stimulated), lower HbA1c % and lower daily insulin requirements year on year for the entire 5 follow-up period.

Although transplantation of purified islets is regarded as the gold standard, purification is often associated with loss of islet mass and possibly islet potency. The present study suggests the auto transplantation of purified islets provides no advantage to the patient peri-operatively and within this series is associated with inferior graft function.

4

Risk Stratification in Familial Pancreatic Cancer Kindreds Using a Mathematical Model

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Background: Screening for pancreatic cancer is being trialled in high risk groups and improved risk stratification will increase positive predictive value, minimise harm and reduce financial costs.

Methods: 1251 individuals (total affected 297) from 85 families with ≥ 3 pancreatic cancers were divided into training and test sets. Data were used to create and validate a hazard model estimating the likelihood that an individual belongs to a high risk family, is a gene carrier and will develop cancer in a fixed period. The results were tested with Hosmer-Lemeshow statistics and Harrell's C index (modified ROC). An internet compatible interface was developed for data entry.

Results: The model was accurate in terms of both discrimination [area under curve = 0.72 (CI 0.68-0.76), remaining >0.7 up to 69 years] and calibration [no significant difference between estimated and observed events e.g. at 60-64 years $p=0.935$, (ideal $p=1.0$), goodness of fit $R^2=0.83$]. Accurate calibration was maintained to age 79 years.

Discussion: This model gives an individual probability of developing cancer within a set period. The online user interface will permit data to be entered and the probability calculation to be com-

pleted during a clinical consultation. It is relevant in both patient counselling and selection for secondary screening. As screening progresses it should be possible to determine values at which screening is both clinically justifiable and cost effective.

5

Quantitative Characterisation of Ductal Cells, PDX-1 Positive Cells and Intermediate Cells in the Normal and Chronic Pancreatic Pancreas

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The treatment of chronic pancreatitis by total pancreatectomy and islet autotransplantation requires intra-portal transplantation of whole pancreatic digest. We speculate that non islet cell types may contribute to insulin secretion in-vivo and therefore influence the clinical outcome. Such data may explain why metabolic outcomes post transplant are not strictly related to IEQ of islets transplanted.

Specimens of CP pancreas (n=30) and normal pancreata (n=9) were fixed in formalin and immunohistochemical staining using a range of antibodies was performed including insulin, glucagon, somatostatin, cytokeratin 19, cytokeratin 7 and PDX-1. Quantification of stained cells was carried out using Axiovision digital image processing software. PDX-1 and cytokeratin 19 expression was significantly up-regulated in CP tissue compared with control pancreata (18.944 ± 1.251 vs. 10.144 ± 1.262 , $p<0.0007$ and 36.335 ± 2.745 vs. 17.333 ± 0.781 , $p<0.0001$ respectively). Similarly, cytokeratin 7 was up-regulated but this did not reach significance (24.333 ± 1.575 to 18.411 ± 2.867 $p=0.0934$). Interestingly, the occurrence of insulin intermediate cells (acinar cells that express hormone) was noted and was found to occur more frequently in the CP pancreas than control tissue (1.093 ± 0.1815 vs. 0.331 ± 0.03413 , $p=0.0014$). When comparing results with clinical graft outcome, it was found that cytokeratin 19 expression positively correlated with basal C-peptide ($r=0.598$, $p=0.0112$, $n=17$) as did stimulated C-peptide secretion, although this did not reach significance ($r=0.4500$, $p=0.0803$, $n=16$). Notable correlations were also found between increased PDX-1 and intermediate cell occurrence and low fasting glucose values, although again this did not reach significance.

In conclusion, the acinar parenchyma of the CP pancreas boasts an up-regulation of both endocrine and pre-endocrine cell types. Additionally, correlation studies suggest that these cells may contribute to the insulin secreting capacity of an islet autograft.

Is There a Role for EUS with FNA in the Assessment of Small Pancreatic Cystic Lesions?

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Small pancreatic cystic lesions (PCL) are increasingly diagnosed as incidental findings. It has been suggested that the risk of malignancy is low in small cysts (≤ 3 cm).

Aim: To assess the role of EUS with FNA in assessment of small PCL

Methods: Review of consecutive patients referred with PCL between June 2003 and December 2007. All patients had linear EUS examination and FNA. Cyst sizes were recorded and aspirates sent for cytology and tumour markers.

The decision to operate was guided by worrying features on cross-sectional imaging and/or EUS with FNA.

Results: 149 individuals underwent investigation of PCL, 64 (43%) of whom had lesions ≤ 3 cm. Histological diagnosis was reached in 56 patients forming the study group. Average age was 60 years (range 19-82). Female to Male ratio, 1.7:1. Cyst size ranged from 0.9cm to 14cm (mean 4.8cm). 18 patients had malignant cysts (12% of total, 32% of study group). 6 (33%) malignant cysts were ≤ 3 cm and 3 (17%) were ≤ 2 cm. EUS with FNA identified suspicious features in all the malignant cysts ≤ 3 cm while CT identified suspicious features in 3 (50%) of malignant lesions.

Conclusion: Cyst size ≤ 3 cm or indeed 2cm does not predict benign histology. In our series 4 % of all cysts ≤ 3 cm were malignant as were 2 % of cysts ≤ 2 cm. Our data supports careful assessment of all pancreatic cysts irrespective of size in individuals fit for surgery. EUS with FNA plays an important role and adds diagnostic information over cross sectional imaging.

A More Favourable Early Survival Is Observed Following Resection of Pancreatic Ductal Adenocarcinoma if Clinical Jaundice Is Resolved Preoperatively

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Numerous studies have investigated the relationship between preoperative biliary stenting and postoperative morbidity in patients undergoing pancreatoduodenectomy. There is no general consensus regarding whether biliary drainage represents a superior management approach over early surgery in these cases. The aim of this study was to investigate the relationship between preoperative biliary drainage,

resolution of obstructive jaundice and early survival in patients with resected pancreatic cancer.

155 patients undergoing pancreatoduodenectomy for pancreatic ductal adenocarcinoma between January 1997 and August 2007 were identified from a prospectively maintained database. 130 patients (84%) of patients underwent preoperative biliary drainage. There was no significant difference in survival between patients who did or did not undergo biliary drainage (log rank, $p=0.981$). The presence of jaundice (ie. bilirubin $>35 \mu\text{mol/l}$) at the time of surgery was associated with a trend towards less favourable early survival (Breslow-Wilcoxon, $p=0.013$) but not overall survival on Kaplan-Meier analysis (log rank, $p=0.116$). A Cox multivariate model was used to investigate which prognostic variables were specifically associated with early post-operative survival by censoring all patients who survived beyond six months. This demonstrated that the association between residual jaundice at the time of resection and poorer early survival was independent of other prognostic factors ($p=0.017$) as was tumour size ($p=0.029$) and serum albumin ($p=0.043$).

The results of the present study suggest that the presence of jaundice at the time of pancreatoduodenectomy for pancreatic cancer has an adverse impact on early, but not overall, postoperative survival in patients undergoing preoperative biliary drainage.

A Comparative Analysis of Safety and Efficacy of Different Methods of Enteral Feeding Following Major Pancreatic Resection? A Non-Randomized Study

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Postoperative enteral nutrition (EN) is thought to reduce complications and speed recovery after pancreatic resection. There is little evidence on the best route for delivery of EN. Currently we use percutaneous transperitoneal jejunostomy (PTJ) or percutaneous transperitoneal gastrojejunostomy (PTGJ), or the nasojejunal (NJ) route to deliver EN, according to surgeon preference. We have reviewed recent cases to compare morbidity, efficiency, and safety of these three routes for EN following pancreaticoduodenectomy

Method: Data were obtained from a prospectively maintained database of all patients undergoing pancreatic resection between January 2007 and June 2008 ($n=100$; 93 Whipple's operation, 7 total pancreatectomy). Information collected included demographic details, duration of feeding, any tube-related and non-tube related complications. EN was delivered by agreed protocol, starting within 24h of operation and increasing over 2-3 days to meet full nutritional requirement. Standard feed solutions were used with all tubes.

Results: Delivery route of EN was PTJ in 25 (25%), PTGJ in 32 (32%) and NJ in 43 (43%). The incidence of catheter-related complications was significantly high in percutaneous techniques ? PTJ (29%), PTGJ (40%) as compared to NJ technique (11%) [$p=0.02$]. Median time to complete establishment of oral intake was 14.4, 14 and 10.5 days in PTJ, PTGJ and NJ groups respectively. NJ tubes were removed at median 11 (mean 11.5) days compared to 5-6 weeks

for PTJ and PTGJ. Commonest catheter-related complication in the PTJ and PTGJ was pain following removal of feeding tube at 5-6 weeks (n=5) followed by blockage (n=3), whereas in the NJ group it was blockage (n=3), followed by displacement (n=2). Altogether, 7 patients underwent re-operation, but no operations were performed for catheter-related complications. Two patients died postoperatively in this cohort, however, there were no catheter-related mortalities.

EN following pancreatic resection can be delivered in different ways. NJ feeding was associated with fewest complications but was frequently blocked and displaced. On current evidence surgeon preference is a reasonable way to decide EN.

9

Posterior Margin Involvement Does Not Influence Survival in Operable Pancreatic Cancer

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Pancreato-duodenectomy for ductal adenocarcinoma of the pancreas (CaP) results in resection margin involvement in around 75% of specimens. The significance of which margins are involved has not been previously studied. The posterior margin is a mobilisation rather than transaction margin, and it was felt that this margin was less likely to influence survival. The aim of the present study was to assess correlation of posterior margin involvement with survival.

Methods: Patient and tumour characteristics were extracted from a prospective database. Patients who died within 30 days were excluded from the analysis. Margin involvement was defined as positive if tumour was present within 1mm of circumferential or transection margin. Margins were defined as anterior, posterior, medial and transection margin as per Verbeke.

Results: 134 consecutive patients undergoing pancreato-duodenectomy for CaP were studied. 34 were defined as R0 and 100 as R1, with median survival 27.5 months and 15.1 months respectively ($p=0.011$). In 16 patients, posterior margin only was involved and survival in this group compared with R0 resections was not significantly different ($p=0.680$). The survival of patients with posterior margin only involvement was significantly longer than those with any other margin involved ($p=0.01$). Modifying the R0 resection group (R0m) to include patients with R1 involvement of the posterior margin allowed comparison with the R1m group as shown in the table below. Survival months (median) R0 vs R1 ($n=34/100$) 27.5/15.1mths; $p=0.011$ R0m vs R1m ($n=53/81$) 26.5/13.7mths; $p<0.001$

Redefinition of R0 to include those who are only posterior R1 positive increases the discrimination of survival. Further work in a larger cohort of patients is required to corroborate these results, however our results suggest that an isolated positive(R1) posterior margin should be considered to have a similar prognosis to an R0 resection.

10

Dynamic Cardiopulmonary Exercise (CPX) Testing as a Means of Risk Stratification in Populations Undergoing Pancreatico-Duodenectomy. A Prospective Cohort Study

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Comparison of post operative mortality figures are often compromised by differences in the background co-morbidity within populations. Standard tests for the preoperative evaluation of patients prior to surgery are poor at predicting actual risk. Objective preoperative cardiopulmonary exercise testing (CPX) has been shown to provide an indication of individual risk. CPX has also been used to identify patients at high risk (with an anaerobic threshold $<11\text{ml/min/kg}$) who may benefit from enhanced postoperative monitoring in a critical care setting. Functional capacity can also be expressed as metabolic equivalents (MET, ml/kg/min of O_2 consumption). The aim of this study was to evaluate the use of formal preoperative CPX assessment in a tertiary referral pancreatobiliary centre.

In a 6 months period, 22 patients with a clinical diagnosis of pancreatic or peri-ampullary neoplasia, who were deemed suitable for resection on clinical and radiological staging, underwent formal CPX using a cycle ergometer. 10 patients were male and 12 female with a median age of 61.5 years (range 19-77). AT was unable to be measured in 5 patients; one due to arthritic pain, one due to significant ischaemic ECG changes and three due to abnormal breathing pattern. Median AT was 8.6 (8.9-12.5), 15 patients had $\text{AT}<11$ and 2 patients had $\text{AT}>11$. Functional capacity, as measure by peak VO_2 and converted into METs, was measured in 21/22; those with good functional capacity $n=11$ ($\text{MET}>4$) and those with poor functional capacity $n=10$ ($\text{MET}<4$). One patient was turned down for surgery on the basis of further cardiac evaluation. Twenty-one patients proceeded to exploration, 20 undergoing a pancreatobiliary-duodenectomy and one a palliative bypass. No patient had an elective post-operative admission to ITU. Ninety day mortality was 4%.

AT and MET scoring indicates a high level of background morbidity with associated high risk of perioperative morbidity in our population. If suggested guidelines were followed, $>80\%$ of patients should receive elective ITU admission. Given that current mortality is 4%, further evidence proving ITU admission reduces mortality in such groups would be required before implementing a policy with significant resource implications.

Current Indicators of Preload May Be Misleading during Fluid Resuscitation in Severe Acute Pancreatitis

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Optimal fluid resuscitation is fundamentally important during the immediate and early phases of severe acute pancreatitis (AP). The aim of this study was to conduct a detailed hour-by-hour analysis of fluid resuscitation in relation to preload, physiological derangement and outcome in patients with AP admitted to intensive care (ICU).

We identified all ICU admissions between July 2004 and Jan 2008 with a diagnosis of AP. Individual casenotes, A&E shock charts, fluid balance sheets and ICU charts were hand-searched regarding vital signs and clinical course. The hourly amount and type of fluid administered during the first 72 hours after admission were tabulated against urine output, central venous pressure, inotrope/vasopressor therapy and shock index. Analysis was by one-way ANOVA (post hoc: Dunnett's T3).

Results: 63 consecutive admissions to ICU with a diagnosis of AP were identified. Inter-hospital transfers with established organ dysfunction (n=11) or where records had insufficient detail (n=22) were excluded. In the remaining 30 patients, in-hospital mortality was 23% (n=7). Admission to critical care occurred at a median of 15 (IQR: 6, 35) hours from presentation. Median length of ICU stay was 3.2 days (IQR: 1.2, 17.1) and mean hospital stay was 47.5 days (s.e.m: 10.8). When in-hospital survivors and non-survivors were compared, the cumulative volume of crystalloid given was similar during the first 6 hours, but at 48 hours was significantly less in patients who died (P<0.01). Non-survivors received a greater cumulative volume of colloid between 24 and 48 hours, had higher CVP, and received more inotropes/vasopressors. The cumulative volume of all fluids was less at 72 hours in non-survivors.

In severe AP-associated organ failure, it is possible that CVP as a crude indicator of adequate preload may lead to the use of inotropes/vasopressors in the inadequately-filled patient. Further study is needed to delineate an optimum fluid resuscitation regimen in AP.

Linear EUS and EUS-FNA in the Diagnosis of Pancreatic Cystic Lesions in a Single Tertiary Referral Centre

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Accurate classification of pancreatic cysts into malignant/ potentially malignant or benign would facilitate management decisions.

Aim: To assess EUS with EUS guided FNA in correctly classifying pancreatic cysts as malignant/ malignant potential or benign.

Methods: Inclusion of consecutive patients with suspected neoplastic pancreatic cysts between June 03 and December 06. Linear echoendoscope assessment of cyst appearance, fluid viscosity and FNA for cytology and fluid amylase, CEA and CA19-9 assays were done. Final diagnosis was positive cytology, histology or cyst resolution. Analysis was performed for the differentiation of malignant and potentially malignant from benign.

Results: 173 EUS-FNA were performed in 149 patients. Average age was 64 (19-94). Female to male ratio was 1.6:1. A final diagnosis was reached in 80 patients (93 procedures) forming the study group. 56 patients had malignant or premalignant lesions: Adenocarcinoma n=14, Mucinous Cystadenocarcinoma n=13, IPMN n=14, Mucinous Cystadenomas n=8, NET n=4, other n=3. 24 patients had benign lesions: Pseudocyst n=17, Serous Cystadenomas n=6, Other n=1. Identification of malignant/malignant potential Accuracy Sensitivity Specificity PPV NPV EUS Diagnosis 80% 86% 61% 88% 58% FNA Cytology 66% 56% 96% 97% 43% Fluid Appearance 68% 64% 68% 81% 47% CEA Cut-off >159 ng/ml 67% 51% 95% 95 51% Combination of Tests 82% 90% 62% 86% 70%

The global performance of EUS & EUS-FNA in our series compares favourably with previous studies. However, we have demonstrated an improved performance by combining the test results. Our data supports decision making based on results of linear EUS with EUS-FNA.

Poster Presentations

Is Strong Ion Difference Reliable for Prediction of ITU Admission in Acute Pancreatitis?

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High mortality and morbidity rates in acute pancreatitis require further measures to assess the patients and predict their need for early ITU admission and close monitoring and support. Electrolyte and acid-base disturbances occur frequently in acute pancreatitis, and it has been suggested that Strong Ion Difference (SID), which reflects disturbance of Acid- base balance in the extracellular fluid, can help in assessing the severity of pancreatitis and may predict the need for ITU admission.

SID was calculated in mmol per litre from observed plasma values within 24h of admission to hospital: $SID = (Na+K) - Cl$ mmol/L. SID was then correlated with fatal outcome and with the need for ITU admission. We reviewed retrospectively 43 patients admitted as direct referrals to our hospital with acute pancreatitis. We used a normal/ abnormal cut off as defined by the Glasgow group (EPC 2008) (1) to divide the patients into two groups: Group A: $SID < 40$ mmol/L (low),

and Group B: SID > 40 mmol/L (normal). Deaths, admission to ITU and daily Organ Failure scores (OFS; Marshall) during the first week were recorded.

Results: Median (range) APACHE-II score within 24h of admission was 7(0-16) in Group A (n=40) and 7(2-8) in group B (n=3). There was one death (2.5%) in group A and none in group B. Eight (20 %) patients of Group A scored 2 or more in one or more OFS: in this group the SID in the first 24h was median 36.1 (31-39). Six patients were admitted to the ITU for a median of 11(1-66) days. The SID in these patients was median 35 (28.9-39). None of 3 patients in Group B had any organ failure or required ITU admission.

Almost all patients with acute pancreatitis had SID <40 within 24h of admission. This renders low SID useless as an early predictor of severity in acute pancreatitis. Initial SID varied widely amongst patients who needed ITU treatment, with no obvious cut off of predictive value. Our series includes only primary admissions: the Glasgow report included a large proportion of tertiary transfers, and it may be that failure of the SID to rise after adequate resuscitation would be more informative. Persistent Organ Failure during the first week currently remains the most accurate method of predicting the need for ITU admission.

Reference

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14

Laparoscopic versus Open Distal Spleno-Pancreatectomy: A Retrospective Case-Matched Comparative Study

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Aim: To compare short term results of Laparoscopic versus Open distal pancreatectomy in a Tertiary Pancreatic Centre.

Methods: Since January 1999 a total of 48 distal pancreatectomies have been performed at our centre. Prior to April 2007 33 open procedures (79%) were performed. Subsequently, fifteen procedures (31%) were all performed laparoscopically.

The Laparoscopic Group (LG) was retrospectively compared with 15 matched cases from the Open Group (OG) which by today's criteria would have been considered feasible by a laparoscopic approach.

Results: Indication for surgery was a benign lesion in all but one case, in both groups. Median time for the LG and OG was 180 (120-300) and 240 (120-300) minutes respectively. Median blood loss was 100 (50-500) ml for the LG and 500 (75-2000) ml for OG. Hospital stay was 5 (4-7) days for LG and 11 (6-32) days for OG. In the LG there was no admission to ITU and the median HDU stay was 1 (0-1) day. mortality rate was 0% in the LG vs 6.6% for the OG group. Overall morbidity rate was 29% and 33% for LG and OG respectively.

Conclusions: In specialized centres laparoscopic distal spleno-pancreatectomy is feasible, safe and efficient and should be considered the gold standard approach for the treatment of benign lesions and borderline malignancies of the pancreatic tail.

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Post Operative Chyle Leak after Major Pancreatic Resections: Risk Factors and Impact on Outcome

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Aim: To determine the incidence of chyle leak, associated risk factors, its influence on outcome and hospital stay in a large current series of pancreatic resections.

Method: Data were collected retrospectively from all pancreatic resections performed in 2007. 81 pancreatic resections (62 Whipple's procedures, 7 total pancreatectomies 3 median pancreatectomies, 9 distal pancreatectomies were performed in our unit in 2007

Results: 10 patients (12.6 %) developed chyle leak (CL). Seven following Whipple's procedure, 3 following total pancreatectomy. Mesenteric vein resection was performed in 2 patients (20%) in the CL group vs 7 (9%) in the non-CL group. Of 12 patients who had extended lymphadenectomy, 6 developed a chyle leak. The median number of lymph nodes removed was 22 (13- 38) for CL compared to 15 (4-28) for non-CL {p=0.003, unpaired t-test}. Modified EN (MCT diet) was used for median 16 days (range: 11- 32) in CL patients as compared to median 10 days (4- 21) of EN in non CL patients. Median hospital stay in the CL group was 21 days vs 15 days in the NCL group, p=0.047 (t- test).

Conclusion: The incidence of chyle leak after major pancreatic resection is high. It is associated with more extensive resections and extended lymphadenectomy. Although chyle leak has no direct adverse effect on postoperative complications it substantially increases the duration of enteral feeding and subsequent hospitalization and costs. Fat restriction and MCT diet appears to be an efficient conservative management.

Recanalised Umbilical Vein: An Overlooked Method of Accessing the Portal Venous System

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The Edmonton Protocol produced a dramatic increase in the number of islet allografts. Islets are infused into the portal vein following percutaneous access associated with frequent minor and occasionally major complications (1). Following total pancreatectomy if islet autotransplantation is performed the digest is similarly infused into the portal vein. Originally we used the middle colic vein and infused via the left portal vein into the left lobe of the liver. This elevates the portal pressure and to ensure that this returned to normal we used the recanalised umbilical vein, which is exteriorised for five days postoperatively.

After removal of the pancreas and restoration of biliary and GI continuity the ligamentum teres is transected and the obliterated umbilical vein identified. This is easily recannalised with Bakes dilators giving access to the left portal vein. A Vygon nutricath "S" 11FG is then inserted into the umbilical vein and used for the islet infusion following digestion (and purification if necessary) is complete. If the ligamentum teres is to be exteriorised it is simply pulled through a 10mm laparoscopic port in the epigastrium, sutured to the skin and covered with a sterile dressing. To date we have performed 54 islet autotransplants and this technique has been used in the last 15 patients. We have exteriorised the falciform ligament for portal pressure measurements in 4 patients. There have been no complications and post-operatively we have also been able to confirm that this route ensures that the vast majority of islets are transplanted into the left lobe of the liver (2).

This method of portal venous access is very safe and has been used for many years for TPN in neonates (where the vein is patent) and occasionally in adults with difficult vascular access problems (3). In addition the umbilical vein can be simply approached above the umbilicus under local anaesthetic and would appear to be an ideal method for allograft patients, when it could be exteriorised if repeated transplants were required.

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Positive Correlation Between Butterfat Test and Faecal Elastase in Patients with End Stage Chronic Pancreatitis

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The butterfat test (BFT) has traditionally been used to assess pancreatic exocrine function. This test involves ingestion of a relatively large amount of butter coupling with 2 blood samplings within 2 hours. Faecal elastase (FE) measurement is a non-invasive stool enzyme assays that is becoming more widely available and has been shown to be highly sensitive and specific for pancreatic exocrine insufficiency. This study aim to identify any correlation between the more traditional BFT and FE level in patients with end stage chronic pancreatitis.

Methods: All patients who were assessed for total pancreatectomy and islet auto-transplantation since 1999 underwent BFT (one mg butter per kg body weight given orally without exogenous pancreatic enzymes). Differences in serum butterfat level between 0th and 2nd hour were studied. From 2003 onwards, FE measurements have also been routinely performed in addition to BFT. The results of BFT and FE levels were evaluated using statistical software SPSS 13.0 for Windows.

Results: Forty-seven patients with the diagnosis of chronic pancreatitis underwent assessment process for total pancreatectomy and islet auto-transplantation. Nine patients (19%) could not tolerate the BFT. FE concentration were measured in 21 patients. Statistical analysis demonstrated a significant correlation between the BFT and the FE level ($p=0.04$).

FE measurement can reliably assess pancreatic exocrine function in patients with chronic pancreatitis and should therefore replace the less well tolerated BFT to assess pancreatic exocrine insufficiency in patients with end stage chronic pancreatitis.

The Influence of Acinar Tissue on Cell Function Structure and Survival

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The practice of purifying islets prior to transplantation presupposes that they do not require bio-trophic support from other cellular and connective components of the pancreas. Previous studies contradict this assumption, as both extra-cellular matrix and ductal cells have been shown to promote islet survival. This study explores the influence of acinar tissue on islet structure and function.

Rodent pancreatic digest was harvested from Wistar rats using intra-ductal collagenase distension and mechanical dissociation. Islet, acinar and ductal tissues were separated on a discontinuous BSA gradient. Tissues were cultured in modified CRML, in suspension, over 8 days. Islets were co-cultured with acinar tissue over 8 days. This

resulted in an 89% $\pm$ 3.2 loss of cell mass. Intracellular insulin and insulin positive cells increased 7.8 and 8.5 fold respectively, demonstrating selective survival of islets. By day 8 the remaining acinar tissue had formed large clusters (typically between 100-250 μ m) and was significantly enzyme depleted in that it had ceased secreting amylase (contained on average 163 $\pm$ 16.8 fold less amylase) and showed weak amylase staining with immuno-histochemistry (compared with fresh tissue). Interestingly, from day 4 onwards islets showed the propensity to attach to enzyme depleted acinar tissue and form stable structures. By day 8 of culture, 61% ($\pm$ 10.8) of islets had formed a firm attachment to the acinar tissue with the islets typically becoming more flattened and "cupping" the acinar clusters. These "flattened" islets showed comparable proportions of alpha, beta and delta cells to fresh islets (27% $\pm$ 9.3, 67% $\pm$ 13.4 and 6% $\pm$ 4.1 respectively) and an enhanced response to a glucose challenge (2.02 $\pm$ 0.76 vs. a glucose response of 1.65 $\pm$ 0.26 in purified islets), although this did not reach significance. Islet recovery at 8 days was 52% ($\pm$ 8.4) in islets co-cultured with acinar tissue whilst purified islets only showed 40 % ($\pm$ 11.2) recovery. However at higher seeding densities (10ul/ml and 20ul/ml), islet viability and function were adversely affected.

This data provides preliminary evidence that at low seeding densities, co-culture of islets with acinar tissue is not detrimental to islet function and may indeed confer some advantage with regards to islet survival.

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Pre-Treatment Neutrophil Count Independently Predict Outcome in Patients Receiving Gemcitabine Chemotherapy in Pancreatic Cancer

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For the majority of patients with locally advanced or metastatic pancreatic cancer the outcome remains poor, despite the modest advantages achieved with palliative chemotherapy and there remains a need to identify those patients who will benefit from such treatment. Recently, it has become clear that a number of biochemical and haematological markers may reliably predict survival in patients with a variety of inoperable common solid tumours. The aim of the present study was to examine the relationship between haematological markers and survival in patients with advanced pancreatic cancer receiving Gemcitabine chemotherapy.

Methods: Patient and clinicopathological characteristics (n=74) were extracted from a prospective database. A pre-treatment baseline full blood count was obtained. Standard thresholds for white blood cell (WCC, $>11 \times 10^9$), neutrophil (NC, $>7.5 \times 10^9$), lymphocyte (LC, $<1.0 \times 10^9$) and platelet count (PC, $>400 \times 10^3$) were used. Weekly Gemcitabine was given at standard dose-rate for 7 weeks, with further treatment delivered weekly for 3 weeks Q28 days in patients with stable or responding disease. Statistical analysis was performed using SPSS (Chicago, IL, USA).

Results: 39 patients were locally advanced and 35 had metastatic disease. Median survival of all patients was 6.2 months. The

minimum follow up was 2 months and the median follow up of survivors was 9 months. During follow up 44 (59%) patients died of their disease. On univariate analysis, an elevated WCC ($p<0.001$), NC ($p<0.001$), MC ($p=0.003$) and PC ($p=0.001$) were associated with cancer specific survival; but stage was not ($p=0.192$). On multivariate analysis only NC (HR 3.61, 95% CI 1.83- 7.11, $p<0.001$) and PC (HR 2.22, 95% CI 1.10- 4.47, $p=0.026$) were independently associated with cancer specific survival. Median survival in low (n=50) and high NC (n=24) group was 10.1 and 1.6 months respectively.

The systemic inflammatory response, in particular an elevated neutrophil count, predicts survival. Further work will examine the prognostic value of other measures of the systemic inflammatory response. It remains to be determined whether modulation of the systemic inflammatory response may improve outcome of patients with advanced pancreatic cancer receiving Gemcitabine.

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Long Term Outcome in Minimally Invasive Thoracoscopic Splanchnicectomy for Chronic Pancreatitis

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Minimally invasive thoracoscopic splanchnicectomy (MITS) in the treatment of chronic pancreatitis has been shown to be of short term benefit and previous studies have demonstrated a loss of benefit over time. As with other types of nerve block there is concern over efficacy in the longer term. This procedure has not been subject to 5 year follow up.

Methods: Patients with troublesome pain from chronic pancreatitis undergoing MITS have been regularly reviewed pre and post-operatively at a specialist pancreatic disease out patient clinic. In addition, a specific questionnaire regarding the perspective of the patient on this procedure has been performed.

Results: In a 7 year period 37 patients with chronic pancreatitis had this procedure performed. Assessment of 22 patients with a minimum 5 year follow-up has been achieved. Visual analogue score was 8.5 pre-operatively and varied from a median of 1 on a good day to 3.5 on a bad day, for patients at review. All patients were on opiate analgesia pre-operatively, one required regular opiates at 5 years. Including patients who refused follow up or who had died as failure of treatment indicates 57% of the 37 patients had improvement of symptoms at 5 years.

This simple procedure has commendable results in a difficult condition in which aetiological factors such as continued alcohol use and cigarette intake are difficult to eliminate.

The Number of Failed Organs and the Response to Therapy Determines Outcome in Patients with Acute Pancreatitis Requiring Level 1 Organ Support

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Patients with severe acute pancreatitis have a mortality in excess of 30% despite modern management protocols. Those with established organ failure requiring support have the worst prognosis, however, there is little data in relation to outcome for this cohort of patients. The aim of this study was to establish if the number of organs failing at admission to the intensive care unit (ICU) and the response to support had a bearing on outcome of patients with severe acute pancreatitis. The influence of the failing system ? respiratory, cardiovascular, renal was also assessed.

Methods: Only those patients with organ failure requiring support were included and those admitted and observed because of a clinical scoring of severe pancreatitis were excluded from the analysis. The proportion of patients with 1, 2 or 3 system failure at baseline, 24, 48 and 72 hours that subsequently died were calculated. The maximum numbers eventually developing 1, 2 or 3 organ failure outside of this initial time frame and their mortality was also noted.

Results: 82 patients (53 men and 29 women) with a mean age of 59.4 years met the criteria for the study. No. BL 24 hr 48 hr 72 hr Max
1 20 3 (15%) 16 1 (6%) 13 0 (0%) 12 0 (0%) 11 0 (0%) 2 46 21 (46%)
39 16 (41%) 38 14 (37%) 35 14 (37%) 34 10 (29%) 3 16 11 (69%) 27
17 (67%) 31 21 (68%) 35 21 (68%) 37 25 (68%) For patients presenting with 1 organ failure, although 45% will deteriorate to 2 or 3 organ failure, most have done so within 48 hours, and after this time none of the patients with only 1 organ failure died. Although the numbers of patients with 3 organ failure increases as a result of deterioration of patients in other groups, the mortality rate is static. The course of patients presenting with 2 organ failure is less predictable as a quarter will deteriorate and the relative mortality of those remaining in the category improves. The type of system failing or the order of failure did not impact significantly on results.

This data allows prognostication of patients with acute pancreatitis requiring organ support. After 48 hrs, the prognosis of patients with 1 organ failure is excellent and that of patients with 3 organ failure remains poor throughout. For those with 2 organ failure, a guarded prognosis may be offered that improves with increased duration of stability.

The Stage of Periapillary Carcinomas Is Not Influenced by the Presence of an Inflammatory Cell Infiltrates or a Systemic Inflammatory Response

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Background: In the case of colorectal carcinoma, the presence of a systemic inflammatory response, as indicated by an elevated neutrophil-lymphocyte (NLR), is associated with a poor prognosis whereas a lymphocytic infiltrate within tumours carries an improved outcome. The aim of this study was to determine the relevance of NLR and tumour leukocyte infiltration in the prognosis of patients with periampullary carcinomas.

Methods: Patients undergoing resection or bypass of periampullary neoplasms during the period of January 2006 to October 2007 were included. NLRs were calculated from pre-operative full blood counts with a value of >5 been considered significant. Pre-operative Ca 19-9 and bilirubin levels were also noted as was the use of preoperative stenting.

Histopathological assessment of resection and biopsy specimens was performed with careful attention to the identification of tumour-related inflammatory cell infiltrates and the specific origin of the neoplasm in addition to standard TNM-based staging.

Results: 47 patients underwent resection and 17 had a bypass operation for periampullary neoplasms during the period of the study. A raised NLR was identified in only 10/64 (15.6%), being seen in 8/47 (17%) resection and 2/17 (11.8%) bypass patients respectively. There was no relationship to Ca 19-9 or bilirubin levels nor the stage of the disease. For patients undergoing resection, no difference was identified when pancreatic, ampullary and bile duct tumours were assessed separately. An inflammatory cell infiltrate within the tumour as seen in only 2 cases, both undergoing resection, in 1 case being lymphocytic and in the second a mixed cellularity. Both the patients had a normal NLR.

Conclusions: Whilst a systemic inflammatory response is seen in a proportion of patients with periampullary neoplasms, and an inflammatory cell infiltrate in a small number, neither parameter appears to be related to tumour stage. This observation may be important in planning neoadjuvant therapy.

The Impact of Adjuvant Chemotherapy for Ductal Adenocarcinoma Head of Pancreas: Improved Survival Following Resection

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The result of ESPAC 1 affirmed a clear role for adjuvant chemotherapy for patients with resected pancreatic adenocarcinoma. From 2001 all patients having resection ductal adenocarcinoma head of pancreas were offered chemotherapy if considered to have adequate performance status. The aim of the present study was to assess the outcome of this change in practice by measuring survival.

Patient and tumour characteristics were extracted from a prospective database. Patients who died within 30 days were excluded from the analysis. Statistical analysis was performed using SPSS (Chicago, IL, USA). As shown in the table below, patients were similar in terms of age, sex, resection margin, lymph node status, perineural invasion and tumour differentiation over the two study periods. In contrast, patients in the latter period (2002-2006) had more advanced tumour stage and more vascular invasion. A larger proportion of patients received adjuvant chemotherapy with 5FU/FA in the second time period (26% vs 69%). The minimum follow up was 21 months and the median follow up of survivors was 28 months. During follow up 79 (86%) patients died of their disease. The median survival was significantly greater in the latter period ($p < 0.01$). 1997-2001 ($n = 47$) 2001-2006 ($n = 45$) Sig Age [Median(range)] 62 (39-78) 65 (41-77) 0.617 Sex (M/ F) 25/ 22 27/ 18 0.510 Stage (I/ II/ III) 12/ 2/ 33 1/ 7/ 37 0.057 R1/R0 33/ 14 31/ 14 0.890 Tumour size (< 25 / > 25 mm) 18/ 29 13/ 32 0.340 Lymph node invasion (-/ +) 15/ 32 8/ 37 0.117 Perineural invasion (-/ +) 2/ 45 2/ 43 0.965 Vascular invasion (-/ +) 30/ 17 18/ 27 0.022 Tumour differentiation (well/ moderate/ poor) 8/ 33/ 6 3/ 34/ 18 0.163 Adjuvant chemo (y/ n) 12/ 35 31/ 14 < 0.001 Survival [Median(range)] 13.5 (9.9-17.2) 24.3 (14.7-31.9) 0.006

This study demonstrates an increase in median survival of 11 months for patients undergoing resection ductal adenocarcinoma head of pancreas within a five year period. The major difference between cohorts appears to be reflect increased use of adjuvant chemotherapy in the later period, however other confounding variables such as patient selection, enhanced multidisciplinary team working etc cannot be excluded.

Pancreatic Acinar Cell Necrosis from Ca^{2+} Overload Depends on the Mitochondrial Permeability Transition Pore

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Mitochondrial inhibition from Ca^{2+} overload could be of paramount importance to acinar cell fate in pancreatitis. Toxins that cause

pancreatitis induce the mitochondrial permeability transition pore (MPTP), but the mechanism and effects of its induction have yet to be determined. We have investigated the role of the MPTP in pancreatic acinar cell injury from bile salts known to cause pancreatitis.

Confocal fluorescence microscopy of isolated murine pancreatic acinar cells was undertaken to measure cytosolic calcium ($[\text{Ca}^{2+}]_c$), NAD(P)H autofluorescence (to assess ATP production), mitochondrial membrane potential (μM), necrosis (propidium iodide) and apoptosis (caspase:R110-aspartic acid amide). Responses were examined in cells exposed to tauroolithocholic acid 3-sulphate (500 μM TLC-S) with or without MPTP inhibition using either 50 μM bongkrekic acid or 50 μM cyclosporine, or the cytosolic Ca^{2+} chelator BAPTA. TLC-S induced falls in μM , and cellular NAD(P)H levels, marked elevation in $[\text{Ca}^{2+}]_c$ and acinar cell necrosis. Pre-treatment with bongkrekic acid or cyclosporine significantly reduced falls in μM , NAD(P)H levels, rises in $[\text{Ca}^{2+}]_c$ and acinar cell necrosis, but not apoptosis. Pre-treatment with BAPTA prevented these changes.

Ca^{2+} overload induces the MPTP in murine pancreatic acinar cells, which significantly impairs mitochondrial function and is a major cause of pancreatic acinar cell necrosis from toxins that induce acute pancreatitis.

CCK-58 and CCK-8 Have Indistinguishable Effects on Secretion and Cell Death in Murine Pancreatic Acinar Cells

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CCK-58 is the main circulating form of cholecystokinin (CCK) and may have different biological actions to CCK-8, used in the majority of experimental studies of CCK action. We have found no differences in Ca^{2+} signaling evoked by CCK-58 and CCK-8, so investigated whether CCK-58 and CCK-8 have different effects on secretion and cell death.

Comparison of CCK-58 and CCK-8 actions was made using: (1) confocal microscopy of isolated murine pancreatic acinar cells measuring changes in fluorescence from quinacrine (taken up by zymogen granules, lost from the cell after secretion); (2) on-line fluorometric assay with direct perfusion of murine pancreatic tissue to measure amylase activity; (3) confocal microscopy to measure apoptosis (R110-aspartic acid amide) and necrosis (propidium iodide). Physiologically representative concentrations (2 pM, 10 pM) of CCK-58 and CCK-8 evoked typical decreases of quinacrine fluorescence indicative of exocytosis, which did not occur when no stimulus was applied. CCK-58 and CCK-8 (both 10 pM) elicited sustained and reversible increases in amylase secretion of similar magnitude. Supramaximal (10 nM) CCK-58 or CCK-8 induced similar levels of cell death, with similar relative proportions of apoptosis and necrosis.

These data show no significant differences between the actions of CCK-58 and CCK-8 on secretion and cell death. The findings are consistent with our previous data that do not show any difference between the effects of CCK-58 and CCK-8 on isolated murine pancreatic acinar cells.

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Protective Role of Reactive Oxygen Species in Pancreatic Acinar Cell Death

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Oxidative stress is implicated in the pathogenesis of pancreatitis, but mechanisms and clinical consequences are unclear. We have investigated effects of reactive oxygen species (ROS) on acinar cell death induced by bile salts, precipitants of acute pancreatitis.

Isolated murine pancreatic acinar cells were exposed to tauro-lithocholic acid sulphate (TLC-S) or the oxidant menadione and examined by confocal microscopy to measure ROS (CM-H₂DCFDA),

cytosolic Ca²⁺ ([Ca²⁺]_C; Fluo-4), NAD(P)H (autofluorescence, a measure of mitochondrial metabolism), apoptosis (caspase:R110-aspartic acid amide) and necrosis (propidium iodide). ROS generation was potentiated with dimethoxy-2-methylnaphthalene (DMN), an inhibitor of the antioxidant enzyme NAD(P)H quinine oxidoreductase (NQO1), or inhibited with the antioxidant N-acetyl-L-cysteine (NAC). 500 μM TLC-S caused elevation of ROS, sustained rises of [Ca²⁺]_C and decreases of NAD(P)H. DMN (30 μM) potentiated 500 μM TLC-S-induced ROS, and unmasked ROS generation by 200 μM TLC-S. ROS production by TLC-S was blocked by NAC, whereas [Ca²⁺]_C and NAD(P)H signals were unaffected. TLC-S induced a concentration-dependent increase of both apoptotic and necrotic cell death. DMN caused no change in cell death from TLC-S, but increased apoptosis (500 μM TLC-S, 44% increase in apoptotic cells compared to controls), whilst reducing necrosis (36% reduction). Conversely, scavenging ROS with NAC (10 mM) reduced apoptosis to control values, but increased necrosis by 35%. Menadione (30 μM) induced apoptosis almost exclusively, reduced by NAC with an increase in necrosis.

ROS generation is protective in the pancreatic acinar cell, inducing apoptosis in preference to necrosis. These data suggest antioxidant therapy will be harmful in acute pancreatitis.

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