PANCREAS ALERTS

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Hereditary pancreatitis: endoscopic and surgical management.

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AIM: Hereditary pancreatitis is a rare cause of chronic pancreatitis. In recent years, genetic mutations have been characterized. The rarity of this disorder has resulted in a gap in clinical knowledge. The aims were to characterize patients with hereditary pancreatitis and establish clinical guidelines. METHODS: Pediatric and adult endoscopic, surgical, radiologic, and genetic databases from 1998 to 2012 were searched. Patients with recurrent acute or chronic pancreatitis and genetic mutation for either *PRSS-1*, *SPINK-1*, or *CFTR* or those who met the family history criteria were included. Patients with pancreatitis due to other causes, without a positive family history, familial pancreatic cancer, or cystic fibrosis, were excluded. RESULTS: Eighty-seven patients were identified. Genetic testing confirmed the diagnosis in 54 patients (62%). Eighty-five patients (98%) underwent 263 endoscopic procedures including sphincterotomy (72%), stone removal (49%), and pancreatic duct stenting (82%). Twenty-eight patients (32%) have undergone 37 operations which included 19 resections and 18 drainage procedures. The interval between procedures for recurrent pain was longer for surgery than for endoscopic therapy (9.1 *vs*. 3.4 years, P<0.05). CONCLUSIONS: Most children and young adults with hereditary pancreatitis can be managed initially with endoscopic therapy. When surgery is undertaken, the procedure should be tailored to the pancreatic anatomy and cancer risk.

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Comparison of prognosis between patients of pancreatic head cancer with and without obstructive jaundice at diagnosis.

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The aim of this study was to elicit possible differences in prognoses and clinicopathological factors in pancreatic head cancer with and without obstructive jaundice at diagnosis. The data from 169 patients with pancreatic head cancer were retrospectively analyzed. Patients were divided into two groups according to serum total bilirubin at diagnosis: ≥3 mg/dL for icteric group and <3 mg/dL for non-icteric group. In all cases, icteric group (n=104) had a significantly worse prognosis than non-icteric group (n=65) (median survival time: 7.5 vs. 13.5 months, respectively; P=0.049). In 84 resectable cases, icteric group had a significantly worse prognosis than non-icteric group (median survival time: 14.2 vs. 20.9 months, respectively; P=0.049) after almost equivalent treatment intensities. Icteric group had significantly larger T- and N-factors according to the UICC classification compared to non-icteric group. The total number of lymph node metastases in icteric group was significantly larger than in non-icteric group (P=0.008). The intrapancreatic nerve invasion in icteric group was significantly stronger than in non-icteric group (P=0.016). There were no significant differences in the mortality and morbidity between icteric and non-icteric groups. In 85 unresectable cases, there was no significant difference between the survival periods of icteric and non-icteric groups (median survival time: 5.2 vs. 5.3 months, respectively). In conclusion, the presence of obstructive jaundice at diagnosis in patients with pancreatic head cancer may predict an unfavorable survival compared to such patients without obstructive jaundice.

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Safety and effectiveness of vessel sealing for dissection during pancreaticoduodenectomy.

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Traditional pancreaticoduodenectomy dissection techniques are tedious and time-consuming. The LigaSure Vessel Sealing System is an alternative to standard dissection methods. LigaSure can be used in replace of ligatures, clips, and sutures in most of the pancreaticoduodenectomy procedure. The objective of this study was to examine our experience with LigaSure in pancreaticoduodenectomies and to show the safety and time-effectiveness. Forty-three pancreaticoduodenectomies were performed by a single surgeon using the LigaSure device in place of traditional dissection techniques. A retrospective chart review was conducted to evaluate patient management and outcome. Demographics, preoperative, intra-operative, and postoperative data were analyzed. The

average patient age was 61 years. Primary pathologic diagnoses were: periampullary carcinoma (56%), chronic pancreatitis (5%), cystic lesion (26%), neuroendocrine tumor (7%), and other (5%). The patient population demonstrated American Society of Anesthesiologists Class I (2%), Class II (14%), III (75%), and IV (9%). Average operative time was 4:11 hours. The study group required an average of 0.49±1.35 units of blood. Eight patients (19%) received blood transfusion, receiving an average of 2.63±2.13 units. Patients had a median hospital stay of 10 days (range: 5 to 41 days). An oral diet was ordered for most patients by day 4. Fourteen patients (32.5%) had a complication, including two patients requiring additional surgery for drainage of abscess. There were no postoperative deaths. The use of LigaSure is a practical and safe alternative to standard dissection techniques. Operative time, blood loss, and complication rate are favorable compared with published series.

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Variation in the gamma-glutamyltransferase 1 gene and risk of chronic pancreatitis.

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AIM: Individuals with chronic pancreatitis are at increased risk for pancreatic cancer. We hypothesized that genetic variation in the gamma-glutamyl-transferase 1 (*GGT1*) gene, which was recently reported associated with pancreatic cancer risk in a genome-wide association study, is also associated with risk of chronic pancreatitis. METHODS: Associations between common polymorphisms in *GGT1* and chronic pancreatitis were evaluated using data and samples from the North American Pancreatitis Study 2. Patients (n=496) and control subjects (n=465) were genotyped for 4 single-nucleotide polymorphisms: rs4820599, rs2017869, rs8135987, and rs5751901. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) for chronic pancreatitis risk were calculated using multiple logistic regression models. Interactions with cigarette smoking and alcohol use were explored. RESULTS: Single-nucleotide polymorphisms rs8135987 and rs4820599 were both statistically significantly associated with risk of chronic pancreatitis; compared with common allele homozygotes, individuals with at least one minor allele were at increased risk (rs8135987: OR 1.36, 95% CI 1.03-1.80, P_{trend}=0.01; rs4820599: OR 1.39; 95% CI 1.04-1.84, P_{trend}=0.0; adjusted for age, sex, race, smoking status, and alcohol use). No significant interactions with cigarette smoking and alcohol use were observed. CONCLUSION: The results suggest that common variation in the GGT1 gene may also affect risk of chronic pancreatitis.

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Dormant cancer cells contribute to residual disease in a model of reversible pancreatic cancer.

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The initiation and progression of pancreatic ductal adenocarcinoma (PDAC) is governed by a series of genetic and epigenetic changes, but it is still unknown whether these alterations are required for the maintenance of primary and metastatic PDAC. The authors show here that the c-Myc oncogene is upregulated throughout the entire process of neoplastic progression in human PDAC and in genetically engineered mice that express mutant K-*ras*. To experimentally address whether c-Myc is essential for the growth and survival of cancer cells, the authors developed a novel mouse model that allows a temporally and spatially controlled expression of this oncogene in pancreatic progenitors and derived lineages of the exocrine pancreas. Unlike previous reports, upregulation of c-Myc was sufficient to induce the formation of adenocarcinomas after a short latency without additional genetic manipulation of cell survival pathways. Deficiency in Cdkn2a increased the rate of metastasis but had no effect on tumor latency or c-Myc-mediated cancer maintenance. Despite a macroscopically complete regression of primary, metastatic, and transplantable tumors following the ablation of c-Myc, some cancer cells remained dormant. A significant number of these residual neoplastic cells expressed cancer stem cell markers, and re-expression of exogenous c-Myc in these cells led to rapid cancer recurrence. Collectively, the results of this study suggest that c-Myc plays a significant role in the progression and maintenance of PDAC, but besides targeting this oncogene or its downstream effectors, additional therapeutic strategies are necessary to eradicate residual cancer cells to prevent disease recurrence.

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Combining hedgehog signaling inhibition with focal irradiation on reduction of pancreatic cancer metastasis.

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Pancreatic cancer often presents in advanced stages and is unresponsive to conventional treatments. Thus, the need to develop novel treatment strategies for

pancreatic cancer has never been greater. The authors report that combination of focal irradiation with hedgehog (Hh) signaling inhibition exerts better than additive effects on reducing metastases. In an orthotopic model, the authors found that focal irradiation alone effectively reduced primary tumor growth but did not significantly affect metastasis. The authors hypothesized that cancer stem cells (CSC) of pancreatic cancer are responsible for the residual tumors following irradiation, which may be regulated by Hh signaling. To test this hypothesis, the authors showed that tumor metastasis in this model was accompanied by increased expression of CSC cell surface markers as well as Hh target genes. The generated tumor spheres from orthotopic pancreatic and metastatic tumors, which have elevated levels of CSC markers relative to the parental cells and elevated expression of Hh target genes. Irradiation of tumor spheres further elevated CSC cell surface markers and increased Hh target gene expression. Combination of Hh signaling inhibition with radiation had more than additive effects on tumor sphere regeneration *in vitro*. This phenotype was observed in two independent cell lines. In this orthotopic animal model, focal radiation plus Hh inhibition had more than additive effects on reducing lymph node metastasis. The authors identified several potential molecules in mediating Hh signaling effects. Taken together, these data provide a rationale for combined use of Hh inhibition with irradiation for clinical treatment of pancreatic cancer patients.

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Differential ezrin and phosphorylated ezrin expression profiles between pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm, and invasive ductal carcinoma of the pancreas.

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Intraductal papillary mucinous neoplasms (IPMNs) and pancreatic intraepithelial neoplasia (PanINs) are important premalignant lesions of pancreatic cancer. Ezrin is a member of the ezrin, radixin, and moesin protein family and acts as a cross-linker between the plasma membrane and the actin cytoskeleton. The authors investigated the roles of ezrin during carcinogenesis in IPMN and invasive ductal carcinoma and examined whether ezrin was a prognostic factor. We examined ezrin and phosphorylated ezrin (p-ezrin) expression in 131 IPMNs, 47 PanINs, and 59 invasive ductal carcinomas by immunohistochemical staining. Ezrin and p-ezrin (tyr354) expressions were significantly higher in IPMN with an associated invasive carcinoma, compared with those in IPMN with high-grade dysplasia (P=0.03 and P=0.0007, respectively). In all grades of PanINs, ezrin and p-ezrin (tyr353) were highly expressed. In patients with invasive ductal carcinoma, the presence of PanIN-2 or PanIN-3 was significantly correlated with positive ezrin and p-ezrin (tyr353) expression of the invasive ductal carcinoma component (P=0.01 and P=0.0004). The negative p-ezrin (tyr353) expression group of invasive ductal carcinoma showed a significantly worse prognosis than did the positive p-ezrin (tyr353) expression group by survival analysis (P=0.04) and there was a statistically significant adverse prognostic factor by both univariate and multivariate analyses (P=0.048 and P=0.015). Ezrin phosphorylation sites differ between the developments of IPMN and PanIN. Although p-ezrin (tyr354) expression in IPMNs is associated with tumor invasion, p-ezrin (tyr353) expression in invasive ductal carcinoma plays an important role not in tumor invasion and metastasis but in the early development of PanINs