

PANCREAS ALERTS

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A multi-institutional phase II trial of hepatic arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis.

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AIM. The objective of this study was to evaluate the response rate, survival, and adverse effects of hepatic arterial infusion chemotherapy (HAIC) using cisplatin in patients with advanced hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT). **METHODS.** Twenty-five patients of advanced HCC with PVTT in the main or first branch, having no prior history of chemotherapy, measurable lesions, adequate liver and renal function, and adequate bone marrow reserve, were enrolled. Cisplatin was administered at the dose of 65 mg/m² via the proper hepatic artery. Treatment was repeated every 4-6 weeks for a maximum of six courses until the appearance of evidence of tumor progression or unacceptable toxicity. **RESULTS.** The median number of treatments was 3 (range 1-6). Among the 25 enrolled patients, complete response was achieved in 1 (4%) patient and partial response in 6 (24%), corresponding to a response rate of 28% (95% CI 12-49%). The median progression-free and overall survival times and the 1-, 2-, and 3-year survival rates in the enrolled patients were 3.6 and 7.6 months and 40.3%, 36.0%, 20.0%, respectively. Four of the seven patients who showed complete or partial response survived for more than 3 years. The main grade 3/4 non-hematological adverse events of this treatment were elevation of the serum aspartate aminotransferase (44%) and alanine aminotransferase (24%). **CONCLUSION.** HAIC with cisplatin exerts moderate activity with mild toxicity in advanced HCC patients with PVTT. Especially, markedly prolonged survival can be expected in patients who respond to this treatment.

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Cancer risk in patients with cholelithiasis and after cholecystectomy: a nationwide cohort study.

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AIM. This study examined the association of cholelithiasis post-cholecystectomy with subsequent cancers and evaluated the risk of cancer in patients with both cholelithiasis and cholecystectomy. **METHODS.** The Taiwanese National Health Insurance Research Database was used to identify 15,545 newly diagnosed cholelithiasis patients from 2000 to 2010, and 62,180 frequency-matched non-cholelithiasis patients. A total of 5,850 (37.6%) with cholelithiasis patients received a cholecystectomy. The risk of developing cancer after cholecystectomy was measured using the Cox proportional-hazards model. **RESULTS.** The incidence of developing cancer in the cholelithiasis cohort was 1.52-fold higher than that in the comparison cohort (P<0.001). Compared with patients aged 20-34 years, patients in older age groups had a higher risk of developing cancer. The hazard ratio (HR) for developing gallbladder, extrahepatic bile duct, pancreatic, liver, stomach, and colorectal cancer was 59.3, 10.7, 3.12, 1.90, 1.71, and 1.36-fold higher for patients with cholelithiasis, respectively. After a cholecystectomy, the HR for developing stomach and colorectal cancer was 1.81-fold and 1.56-fold, respectively. The incidence rate ratio was higher for the first 5 years and over 5 years (5.05 and 4.46, respectively) (95% confidence interval 4.73-5.39 and 4.11-4.84, respectively) in proximal colon and stomach cancer patients with cholecystectomies. **CONCLUSIONS.** Cholelithiasis patients have a higher risk of gastrointestinal cancer, particularly of gallbladder and extrahepatic bile duct cancer. Post-cholecystectomy patients have a risk of colorectal and stomach cancer within the first 5 years and persisting after 5 years, respectively. This paper proposes strategies for preventing gastrointestinal cancer.

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Metformin inhibits pancreatic cancer cell and tumor growth and downregulates Sp transcription factors.

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Metformin is a widely used antidiabetic drug, and epidemiology studies for pancreatic and other cancers indicate that metformin exhibits both chemopreventive and chemotherapeutic activities. Several metformin-induced responses and genes are similar to those observed after knockdown of specificity protein (Sp) transcription factors Sp1, Sp3 and Sp4 by RNA interference, and we hypothesized that the mechanism of action of metformin in pancreatic cancer cells was due, in part, to downregulation of Sp transcription factors. Treatment of Panc1, L3.6pL and Panc28 pancreatic cancer cells with metformin downregulated Sp1, Sp3 and Sp4 proteins and several pro-oncogenic Sp-regulated genes including bcl-2, survivin, cyclin D1, vascular endothelial growth factor (VEGF) and its receptor (VEGFR1), and fatty acid synthase (FAS). Metformin induced proteasome-dependent degradation of Sp proteins in L3.6pL and Panc28 cells, whereas in Panc1 cells metformin decreased microRNA-27a and induced the Sp repressor, ZBTB10 and disruption of miR-27a:ZBTB10 by metformin was phosphatase-dependent. Metformin also inhibited pancreatic tumor growth and downregulated Sp1, Sp3 and Sp4 in tumors in an orthotopic model where L3.6pL cells were injected directly into the pancreas. The results demonstrate for the first time that the anticancer activities of metformin are also due, in part, to downregulation of Sp transcription factors and Sp-regulated genes.

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Focal autoimmune pancreatitis: radiological characteristics help to distinguish from pancreatic cancer.

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AIM. To identify the radiological characteristics of focal autoimmune pancreatitis (f-AIP) useful for differentiation from pancreatic cancer (PC). METHODS. Magnetic resonance imaging (MRI) and triple-phase computed tomography (CT) scans of 79 patients (19 with f-AIP, 30 with PC, and 30 with a normal pancreas) were evaluated retrospectively. A radiologist measured the CT attenuation of the pancreatic parenchyma, the f-AIP and PC lesions in

triple phases. The mean CT attenuation values of the f-AIP lesions were compared with those of PC, and the mean CT attenuation values of pancreatic parenchyma in the three groups were compared. The diagnostic performance of CT attenuation changes from arterial phase to hepatic phase in the differentiation between f-AIP and PC was evaluated using receiver operating characteristic (ROC) curve analysis. We also investigated the incidence of previously reported radiological findings for differentiation between f-AIP and PC. RESULTS. The mean CT attenuation values of f-AIP lesions in enhanced phases were significantly higher than those of PC (arterial phase: 60 ± 7 vs. 48 ± 10 , $P<0.05$; pancreatic phase: 85 ± 6 vs. 63 ± 15 , $P<0.05$; hepatic phase: 95 ± 7 vs. 63 ± 13 , $P<0.05$). The mean CT attenuation values of f-AIP lesions were significantly lower than those of uninvolved pancreas and normal pancreas in the arterial and pancreatic phase of CT ($P<0.001$, $P<0.001$), with no significant difference at the hepatic phase or unenhanced scanning ($P=0.4$, $P=0.1$). When the attenuation value increase was equal or more than 28 HU this was considered diagnostic for f-AIP, and a sensitivity of 87.5%, specificity of 100% and an area under the ROC curve of 0.974 (95%CI: 0.928-1.021) were achieved. Five findings were more frequently observed in f-AIP patients: 1) sausage-shaped enlargement; 2) delayed homogeneous enhancement; 3) hypoattenuating capsule-like rim; 4) irregular narrowing of the main pancreatic duct (MPD) and/or stricture of the common bile duct (CBD); and 5) MPD upstream dilation ≤ 5 mm. CONCLUSION. Analysis of a combination of CT and MRI findings could improve the diagnostic accuracy of differentiating f-AIP from PC.

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Multifocal branch-duct intraductal papillary mucinous neoplasms (IPMNs) of the pancreas: magnetic resonance (MR) imaging pattern and evolution over time.

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AIM. The aim of study was to follow the evolution over time of multifocal intraductal papillary mucinous neoplasms (IPMN) of the pancreatic duct side branches by means of magnetic resonance imaging (MRI). METHODS. A total of 155 patients with multifocal IPMN of the side branches were examined with MRI and MR cholangiopancreato-

graphy (MRI/MRCP). Inclusion criteria were patients with ≥ 2 dilated side branches involving any site of the parenchyma; presence of communication with the main pancreatic duct and previous investigations by MRI/MRCP within at least six months. Median follow-up was 25.8 months (range 12-217 months). Patients with a follow-up period shorter than 12 months (n=33) and those with a diagnosis of multifocal IPMN of the side branches without any follow-up (n=14) were excluded from the study. The final study population thus comprised 108 patients. A double, quantitative and qualitative, analysis was carried out. The quantitative image analysis included: number of dilated side branches in the head-uncinate process and body-tail; maximum diameter of lesions in the head-uncinate process; maximum diameter in the body-tail; maximum diameter of the main pancreatic duct in the head and body-tail. The qualitative image analysis included: presence of malformations or anatomical variants of the pancreatic ductal system; site of the lesions (head-uncinate process, body-tail, ubiquitous, bridge morphology); presence of gravity-dependent intraluminal filling defects; presence of enhancing mural nodules. RESULTS. At diagnosis, the mean number of cystic lesions of the side branches was 7.09. The mean diameter of the cystic lesions was 13.7 mm. The mean diameter of the main pancreatic duct was 3.6 mm. At follow-up, the mean number of cystic lesions was 7.76. The mean diameter of the cystic lesions was 13.9 mm. The mean diameter of the main pancreatic duct was 3.7 mm. Intraluminal filling defects in the side branches were seen in 18/108 patients (16.6%); enhancing mural nodules were seen in 3/108 patients (2.7%). CONCLUSIONS. Multifocal IPMN of the branch ducts shows a very slow growth and evolution over time. In our study, only 3/108 patients showed mural nodules which, however, did not require any surgical procedure, indicating that careful nonoperative management may be safe and effective in asymptomatic patients.

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miR-320c regulates gemcitabine-resistance in pancreatic cancer via SMARCC1.

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AIM. Gemcitabine-based chemotherapy is the standard treatment for pancreatic cancer. However,

the issue of resistance remains unresolved. The aim of this study was to identify microRNAs (miRNAs) that govern the resistance to gemcitabine in pancreatic cancer. METHODS. miRNA microarray analysis using gemcitabine-resistant clones of MiaPaCa2 (MiaPaCa2-RGs), PSN1 (PSN1-RGs), and their parental cells (MiaPaCa2-P, PSN1-P) was conducted. Changes in the anti-cancer effects of gemcitabine were studied after gain/loss-of-function analysis of the candidate miRNA. Further assessment of the putative target gene was performed *in vitro* and in 66 pancreatic cancer clinical samples. RESULTS. miR-320c expression was significantly higher in MiaPaCa2-RGs and PSN1-RGs than in their parental cells. miR-320c induced resistance to gemcitabine in MiaPaCa2. Further experiments showed that miR-320c-related resistance to gemcitabine was mediated through SMARCC1, a core subunit of the switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex. In addition, clinical examination revealed that only SMARCC1-positive patients benefited from gemcitabine therapy with regard to survival after recurrence (P=0.046). CONCLUSION. The results indicate that miR-320c regulates the resistance of pancreatic cancer cells to gemcitabine through SMARCC1, suggesting that miR-320c/SMARCC1 could be suitable for prediction of the clinical response and potential therapeutic target in pancreatic cancer patients on gemcitabine-based therapy.

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Prevalence and risk factors of extrapancreatic malignancies in a large cohort of patients with intraductal papillary mucinous neoplasm (IPMN) of the pancreas.

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AIM. The objectives of this study are to estimate prevalence and incidence of extrapancreatic malignancies (EPMs) among intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, and to identify risk factors for their occurrence. METHODS. The authors conducted multicentric cohort study in Italy from January 2010 to January 2011 including 390 IPMN cases. EPMs were grouped as previous, synchronous (both prevalent) and metachronous (incident). The authors calculated the observed/expected (O/E) ratio of

prevalent EPMS, and compared the distribution of demographic, medical history and lifestyle habits. RESULTS. Ninety-seven EPMS were diagnosed in 92 patients (23.6%), among them 78 (80.4%) were previous, 14 (14.4%) were synchronous and 5 (5.2%) were metachronous. O/E ratios for prevalent EPMS were significantly increased for colorectal carcinoma (2.26; 95% CI 1.17-3.96), renal cell carcinoma (6.00; 95% CI 2.74-11.39) and thyroid carcinoma (5.56; 95% CI 1.80-12.96). Increased age, heavy cigarette smoking, alcohol

consumption and first-degree family history of gastric cancer are significant risk factors for EPMS, while first-degree family history of colorectal carcinoma was borderline. CONCLUSION. Authors observed an increased prevalence of EPMS in Italian patients with IPMN, especially for colorectal carcinoma, renal cell and thyroid cancers. A systematic surveillance of IPMN cases for such cancer types would be advised.

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