Pancreatology

Abstracts

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JPS Presidential Lecture

PL

Pancreatoduodenectomy for Pancreatic Cancer in Japan: My Experience

A. Nakao

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The first case of pancreatoduodenectomy (PD) in Japan was reported by Kuru in 1946, then Yoshioka in 1947, Mori in 1949, and then Honjyo performed a total pancreatectomy the same year. Portal vein resection combined with PD was reported by Kikuchi in 1956 and Asada in 1963. They used 70% alcohol-preserved homograft of the vein. Fortner's report of regional pancreatectomy in 1973 greatly impressed Japanese pancreatic surgeons. Then in 1981, I developed my own catheter-bypass method of the portal vein using antithrombogenic material. The isolated pancreatoduodenectomy combined with portal vein resection was completed. This bypass method made it possible to prevent portal congestion or hepatic ischemia during portal vein resection or simultaneous resection of the hepatic artery. Thus, vascular resection has become safer and easier during pancreatic surgery. Extended radical pancreatic resection was developed during the 1970s and 1980s. The high mortality rate of PD in the 1950s and 1960s decreased gradually to within 10% in the 1980s and 5% in the 1990s. Hanyu had performed and landmark 1000 PDs in 1997, and the mortality rate has been 1% since 1989.

We have performed 825 pancreatic resection, for various diseases since 1981 and mortality was observed in 14 cases (1.7%). Moreover 441 pancreatic resection for pancreatic cancer were along with combined resection of portal vein in 282 cases during 1981~2009. The mortality rate of PD for pancreatic cancer was 1.0% in my series, but no mortality has been experienced in the last 11 years. However, the prognosis for pancreatic cancer is still poor and adjuvant therapy has been combined with radical surgery such as intraoperative radiotherapy using linac, and intraportal continuous infusion of 5-FU. Adjuvant chemotherapy using gemcitabine or TS-1 and clinical trial of oncolytic virus therapy using herpes simplex virus (HF10) have been performed, yet numerous problems remained to be solved.

I have devised techniques such as isolated pancreatoduodenectomy combined with portal vein resection using catheter-bypass method for the portal vein and a mesenteric approach and pancreatic head resection with segmental duodenectomy (PHRSD) for IPMN. Every day I still feel great pleasure and a sense of fulfillment in performing surgery. Surgeons are able to care for patients all the way from diagnosis and surgery through postoperative management and follow-up after the patient leaves the hospital. This sense of accomplishment is truly great, and it is a specialty that I believe we should be sure to pass down to younger people. Let me say that I am filled with gratitude to my colleagues and the younger doctors I have worked with in medical practice and research.

State of the Art Lectures

SA-1

Biology of Pancreatic Cancers – Importance of the Differences

A.L. Warshaw

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A common perception of pancreatic cancer is that it is uniformly aggressive, rapidly lethal, and tantamount to a death sentence. In fact, although the histology and genetic characteristics of pancreatic adenocarcinomas in their final stages are essentially indistinguishable, one from another, the clinical and biological pathways to that point comprise a spectrum of difference neoplasms, behaviors, and time courses. These differences may be the product of differing cells of origin and different genetic mutations and drivers among pancreatic adenocarcinomas which lead to surprising variations in biological behavior. While death from progression commonly occurs around two years after curative resection of invasive adenocarcinoma, recurrences may be seen either later than 10 years or within 6 months after resection of small cancers with negative margins and lymph nodes. Conversely some patients with larger cancers, positive nodes, and positive resection margins remain long-term survivors. Even the route of potential spread may follow different preferential paths: hematogenous, lymphatic or peritoneal. These differences are illustrated by three histologically similar pancreatic adenocarcinomas with markedly different biological profiles: ductal adenocarcinoma, mucinous cystic adenocarcinoma and, intraductal papillary mucinous adenocarcinoma.

Pancreatic AdenoCa	Ductal AdenoCa	MCN	IPMN
Possible Precursor	PanIN	Ovarian rest	PDG's
Time to invasion	Rapid	Moderate	Long
Hereditary factor	10–20%	None	None
Environmental factor	Smoking	None	None
Sex predominance	None	Female	None
Lymph node (+)	70%	0	Uncommon
Peritoneal spread	Common	Rare	Rare
Resection curative	<20%	57%	60%

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New genetic and genomic profiles of pancreatic adenocarcinomas show both shared and disparate chromosomal abnormalities and gene mutations which accumulate during the stages of oncogenesis. Study of the underlying molecular biological differences among these cancers and their subtypes, rather than their ultimate similarities, may provide substantial insights which could lead to new targeted therapies.

SA-2

Pancreatic Carcinogenesis in Genetically-engineered Mice

D.S. Longnecker

Department of Pathology, Dartmouth Medical School, USA

Animal models have contributed to our understanding of cellular pathways and precursor lesions involved in pancreatic carcinogenesis. Chemically-induced acinar cell neoplasms in rats and ductal cell neoplasms in hamsters exhibited apparently distinct pathways for development of acinar and ductal carcinomas. However, the potential for acinar to ductal metaplasia (ADM) was demonstrated in vitro in both normal and malignant rat acinar cells—raising the question of whether ductal neoplasms might sometimes arise from acinar cells.

More recent studies of genetically-engineered mouse models have contributed additional insights into the cytogenesis of acinar, ductal, and islet cell neoplasms. Many of the models based on expression of an oncogene and/or loss of tumor suppressor function support the expected, i.e. that neoplasms are apparently derived from normal cells of the same phenotype. Examples include induction of acinar cell neoplasms when the abnormal gene is targeted by promoters such as elastase that are expressed in acinar cells, and islet cell tumors when the abnormal genes are under the control of the insulin or glucagon promoter. Induction of ductal adenocarcinomas has been more elusive, but has been achieved using conditional expression of mutated Kras. These new models were developed based on Cre-Lox strategy that resulted in the conditional/targeted activation of a mutated Kras allele in early pancreatic progenitors of all pancreatic cell types including ductal, acinar, and islet cells. These models yield a sequence of PanIN with progression to ductal adenocarcinoma with reasonable mimicry of corresponding human lesions. The yield of carcinomas is enhanced when mice with mutant Kras are crossbred with mice bearing a defective tumor suppressor such as p53 or Ink4 to yield offspring with both genetic abnormalities. The resulting "double mutant" carcinomas tend to be less differentiated and more aggressive than those arising in mice with a single genetic lesion.

These studies indicate that the phenotype of the neoplasm is also ultimately influenced by the oncogene or suppressor gene. Neoplasms induced using mutant Kras in mice are of ductal phenotype even when the oncogene is targeted to acinar or islet cells. ADM is often seen in such models. PanIN-type lesions develop in the ductules of ADM suggesting that neoplasms of ductal phenotype were derived from acinar cells. This hypothesis has been supported by cell lineage studies in mice, but the importance of this pathway in humans is unknown.

PanIN arising in small ducts are generally considered to be the origin of most pancreatic ductal adenocarcinomas (PDA) in humans. It has also been shown that PanIN commonly contain mutated Kras, and that the fraction with mutant Kras rises with the degree of dysplasia. Despite this mainstream view, it is recognized that ductal complexes apparently arising from ADM occur in human pancreas, especially in association with chronic pancreatitis, a known risk factor for PDA. Several experiments done in mouse models support the role of pancreatitis in promoting the development of carcinomas. Thus, there is a general correlation between findings in humans and genetically-engineered mouse models including the incompletely resolved issue of the importance of the ADM/PanIN/PDA pathway.

It is also documented that a minority of human PDA arise from malignant intraductal papillary-mucinous neoplasms (IPMN), and even fewer from malignant mucinous cystic neoplasms (MCN). While cystic lesions occur in the pancreas in some of the genetically-engineered mouse models, their mimicry of the human IPMN and MCN is less convincing than is true for mouse PanIN and PDA.

Finally, some progress has been made in applying transgenic technology to other species yielding a new model of ductal carcinoma in rat pancreas. Such studies may help to understand the impact of species differences.

SA-3

Recent Developments in Our Understanding of Pancreatic Cancer Etiology and Management

M. Goggins

Pathology, Medicine and Oncology, The Early Pancreatic Cancer Research Laboratory, Divisions of Gastrointestinal Pathology and Gastroenterology/Hepatology, Johns Hopkins Medical Institutions, USA

There is a great need to understand the causes and risk factors for pancreatic cancer to help prevent the development of this disease and whenever possible ensure its early detection and treatment. The deadly nature of pancreatic cancer has led to efforts to screen individuals with an inherited predisposition to pancreatic cancer. Screening studies demonstrate that patients with a strong family history of pancreatic cancer as well as those with mutations in pancreatic cancer susceptibility genes frequently have precursor lesions detectable by pancreatic imaging. The pancreatic cancer genome project highlighted the main genetic pathways targeted in pancreatic cancers. Personal genome analysis was recently employed to identify the Fanconi anemia pathway gene, *PALB2* as a pancreatic cancer susceptibility gene[9]. Currently exomes are being sequenced to identify rare variants that contribute to pancreatic cancer susceptibility. Genome wide association association data has linked ABO blood group variants and other variants with pancreatic cancer risk. The identification of new genetic contributions to pancreatic cancer development may provide vital clues to pancreatic cancer therapies. For example, pancreatic cancers with defective BRCA2/Fanconi pathways may be sensitive to Parp inhibitor therapy. The pancreatic cancer stroma is also important in pancreatic cancer progression. Recent studies indicate that the stromal fibroblasts mediate hedgehog pathway signals and are likely to be important target for therapeutic intervention. Other drugs such as abraxane may be be active against pancreatic cancers in part because of the expression of the stromal protein, Sparc which is known to bind abraxane.

IAP Symposium 1 International Consensus on Autoimmune Pancreatitis

IPSY1

Moderator's Remark

T. Shimosegawa[1], *S.T. Chari*[2]

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Since the epoch-making report on autoimmune pancreatitis (AIP) by Yoshida et al., 17 years have passed and AIP is now becoming well known worldwide. Although it has been well recognized that this peculiar type of pancreatitis is seen not only in Asia but also in Western countries, information on AIP is still coming from a limited number of countries. Typical AIP patients show diffuse inflammatory changes of the pancreas, but many others demonstrate segmental or focal involvement of the pancreas, which makes this benign disease quite difficult to differentiate from pancreatic cancer. Indeed, it is known that even in the most advanced institutes in the U.S. and Western countries, many patients with AIP had undergone pancreatic resections for suspected pancreatic cancer. Considering the prevalence of AIP in the elderly population and its responsiveness to steroids, precise diagnosis of AIP is required to prevent unnecessary surgeries. To accomplish this, the establishment of diagnostic criteria for AIP with an international consensus is essential to discuss and thoroughly understand this disease. However, there are several issues that need to be overcome.

The first issue is the fundamental difference in the concept of AIP between Japan and Western countries. In the Japanese literature the term "AIP" stands for the disease described by Yoshida et al in their original report. This form of AIP has a peculiar histopathologic pattern called lymphoplasmacytic sclerosing pancreatitis (LPSP). It is associated with elevation of serum IgG4 and the involvement of various extra-pancreatic organs. On the other hand, the term "AIP" in the West includes not only the AIP features mentioned above, but also a histologically different type of pancreatitis. This type of AIP has similar imaging findings to the Japanese description of AIP, but is not associated with serologic abnormalities, is frequently associated with inflammatory bowel disease and its histo-pathologic pattern is called idiopathic duct-centric chronic pancreatitis (IDCP) or granulocytic epithelial lesion (GEL). Recently, some researchers named AIP with LPSP and that with IDCP/GEL as Type 1 and Type 2 AIP, respectively. Confusion may come from possible differences in their prevalence. In Japan (and possibly in Korea) Type 1 AIP is the most prevalent form and Type 2 is quite rare. In retrospective studies of resected pancreata in Western countries, Type 1 and Type 2 reportedly account for 60% and 40% of AIP, respectively. International consensus criteria should recognize these entities as separate and develop separate diagnostic criteria for them.

The second issue is a controversy on the diagnostic reliability of EUS-FNAB (or TCB). Since Type 1 and Type 2 AIP are defined by their histological findings, it is important to evaluate whether currently available diagnostic procedures for histology are trustworthy.

The third issue is the difference in the diagnostic approach to AIP between Japan (and Korea) and Western countries. Japanese experts consider that ERP findings are essential for the diagnosis of AIP, while Western experts do not favor the use of ERP for the diagnosis of benign diseases, probably due to the fear of complications.

Finally, there are still differences concerning the diagnostic use of steroids, especially its necessity and its position in the diagnostic flow of AIP. These issues had not been discussed face-to-face between the experts in the East and West until the Autoimmune Pancreatitis International Cooperative Study Group (APICS) Consensus Meeting held in Hawaii on November 4th, 2009. Now is the time to conclude the discussion based on the mutual understanding of agreement and disagreement noted in the Hawaii Meeting.

At present, there are multiple diagnostic criteria for AIP proposed by Asian and Western countries from their respective viewpoints. The international consensus diagnostic criteria for AIP should define AIP clearly, cover all forms of AIP, and provide a clear diagnostic strategy for clinicians worldwide regardless of regional differences in practice. We hope that this symposium in Fukuoka will be fruitful and bring about a successful result.

Outline of the Session

AIP: Buildup of Consensus

1 **How Should be the International Consensus Criteria?**
Tooru Shimosegawa *(Division of Gastroenterology, Tohoku University Graduate School of Medicine, Japan)*
Suresh T. Chari *(Division of Gastroenterology and Hepatology, Mayo Clinic, USA)*

2 **Overview of AIP:Agreement and Disagreement in Hawaii**
Kazuichi Okazaki *(Department of Gastroenterology and Hepatology, Kansai Medical University, Japan)*
Guenter Klöppel *(Institut fur Pathologie des Technischen Universität München, Germany)*

3 **Should Diffuse and Focal Types be Distinguished in the Diagnostic Procedure?**
Kazuichi Okazaki *(Department of Gastroenterology and Hepatology, Kansai Medical University, Japan)*
Luca Frulloni *(Department of Biomedical and Surgical Sciences, University of Verona, Italy)*

4 **Imaging—Is ERCP Essential? Can it be Replaced with MRCP?**
Terumi Kamisawa *(Department of Gastroenterology, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Japan)*
Myung-Hwan Kim *(Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center, Korea)*
Luca Frulloni *(Department of Biomedical and Surgical Sciences, University of Verona, Italy)*

5 **Serology—Are IgG and Autoantibodies Necessary?**
Shigeyuki Kawa *(Shinshu University, Center for Health Safety and Environmental Management, Japan)*
Suresh T. Chari *(Division of Gastroenterology and Hepatology, Mayo Clinic, USA)*

6 **OOIs—Should They be Included in the Criteria?**
Shigeyuki Kawa *(Shinshu University, Center for Health Safety and Environmental Management, Japan)*
Suresh T. Chari *(Division of Gastroenterology and Hepatology, Mayo Clinic, USA)*

7 **Histology—Can LPSP be Differentiated from IDCP?**

Lizhi Zhang *(Division of Anatomic Pathology, Mayo Clinic, USA)*
Kenji Notohara *(Department of Pathology, Kurashiki Central Hospital, Japan)*
Mari Mino-Kenudson *(Gastrointestinal Pathology Service, Masachusetts General Hosital, USA)*
Guenter Klöppel *(Institut fur Pathologie des Technischen Universitat Munchen, Germany)*

8 **Diagnostic Use of Steroid—What is the Indication?**
Tooru Shimosegawa *(Division of Gastroenterology, Tohoku University Graduate School of Medicine, Japan)*
Myung-Hwan Kim *(Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center, Korea)*
Proposal of Consensus Criteria
Proposal of International Consensus Criteria for AIP (Draft)
Terumi Kamisawa *(Department of Gastroenterology, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Japan)*
Comment to the Consensus Criteria
Myung-Hwan Kim *(Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center, Korea)*
Suresh T. Chari *(Division of Gastroenterology and Hepatology, Mayo Clinic, USA)*
Markus M. Lerch *(Department of Medicine A, Greifswald University, Germany)*
Overall Discussion

***Presenters' abstracts are not available for this session.**

IAP Symposium 2 The Current Status of Pancreatic Neuroendocrine Tumors

IPSY2-1

Changing Clinical Practice for Pancreatic Neuroendocrine Tumors

M. Imamura
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Localization of gastro-entero-pancreatic neuroendocrine tumors (GEPNET) has been almost established by the development of both SASI test (Selective arterial secretagogue injection test) and SRS (Somatostatin receptor scintigraphy). These two techniques are specific methods for GEPNET and have been useful for preoperative localization of curative resection surgery.

Characteristic pathological findings have been accumulated as the number of resection surgery has increased, and have been used for deciding the modus of resection surgery of GEPNET. For example, Zollinger-Ellison syndrome is caused more often by the duodenal gastrinoma rather than by the pancreatic gastrinoma. The rate of hepatic metastases is more than 60% in pancreatic gastrinoma, but is less than 10% in case of duodenal gastrinoma. Thus pancreatic gastrinoma should be resected as soon as possible for preventing hepatic metastases. Sporadic duodenal gastrinoma is often single, although duodenal gastrinoma in patients with multiple endocrine neoplasia type 1 (MEN 1) are often multiple and sometimes numerous. In patients with MEN 1, there are usually multiple and microscopically numerous GEPNET in the pancreas, which are mostly GEPNET other than gastrinoma. In about 13% of patients with MEN 1 pancreaticd gastrinoma has been coexisted with duodenal gastrinomas.

We now perform pancreas preserving total duodenectomy (PPTD) for prevention of unresected minute microgastrinomas and de novo gastrinomas that may develop from duodenal precursor lesions due to menin gene mutations in MEN 1 and ZES.

Thus, curative resection surgery for GEPNET is principally a complete resection of the main tumors with dissection of regional lymph nodes guided by localization with SASI test and/or SRS. For resection of a benign pancreatic NET like insulinoma, intraoperative ultrasonography (US) is useful for both tumor localization and estimation of the distance between a tumor and the main pancreatic duct. As far as the tumor was apart more than 5mm from the main pancreatic duct, enucleation can be safely performed. For other pancreatic NET like gastrinoma or glucagonoma or VIPoma which are potentially malignant, modus of curative resection surgery includes the resection of the pancreas, such as distal pacreatectomy, pancreaticoduodenectomy, pylorus preserving pancreaticodudenectomy and central resection of the pancreas.

Treatment strategy for hepatic metastases of GEPNET has not been standardized, although many surgeons have recommended mass reduction surgery for multiple hepatic metastases. Chemotherapy for hepatic metastases of pancreatic NET has been performed with a variety of regimens. We have experienced and read many reports of a few cases in whom hepatic metastases were completely cured with streptozotocine alone or with 5FU. Cisplatin with etoposide for poorly differentiated rapidly growing GEPNET, and STZ with 5-FU for rapidly growing well differentiated GEPNET have been recommended by a few groups including Europian Neuroendocrine Tumor Study Group (ENETS).

Recent topic in medical therapy for pancreatic NET is the introduction of somatostatin analogs for inhibition of growth of GEPNET. Octreotide LAR is recommended for slow growing metastatic GEPNET by ENETS.

IPSY2-2

Epidemiology and Clinicopathological Features of PNET

B. Wiedenmann
Charite Medical School, Berlin

Based on its incidence (2–6 per 100 000), neuroendocrine tumors (NETs) are considered rare tumors. However, based on their known overall survival, combined with their high prevalence, NETs may be considered even as common rather than rare tumors.

Based on the primary location, tumor development and metastatic spread vary considerably. Whereas tumors originating from the foregut - (pancreas, bronchus, oesophagus, stomach, duodenum) and hindgut tumors (left colon and rectum) develop early metastases,

midgut, (jejunum, ileum, caecum and ascending colon) tumors fare better and grow slower locally and metastasize rather late.

In recent years, it has become evident that the incidence of NETs varies considerably geographically, whereby primaries in the hindgut are clearly more often observed in the Far East as compared to in the Western part of the world. Furthermore, studies in several centers worldwide have shown that hormone activity/functionality in these tumors is far less common than previously thought, i.e. only approximately 40% of all NETs are functional.

In the last 10 years, the pathological classification of tumors has been repeatedly revised The new clinical pathological classification of the European Neuroendocrine Tumor Society (ENETS) has especially advanced the field of clinical-pathological classifications. Very recently a newly revised WHO-classification has been published.

Current developments concerning newest epidemiological as well as clinicopathological data on PNET will be presented.

IPSY2-3

Role of Angiogenesis in Pancreatic Neuroendocrine Tumors (PNET)

E. Raymond

Department of Medical Oncology, Beaujon University Hospital

PNET have a well developed vasculature and are vascular endothelial growth factor (VEGF)-driven, suggesting a role for angiogenesis inhibitors in treatment. Analysis of tissue from PNET also shows widespread expression of platelet-derived endothelial growth factor receptors PDGFR, stem cell factor receptor (c-KIT), and VEGF receptors (VEGFR)-2 and -3. Sunitinib inhibits the above mentioned kinases. Furthermore, sunitinib delayed tumor growth in the RIP1-Tag2 transgenic mouse model of PNET primarily by inhibiting VEGFR and PDGFR consequently leading to the reduction of endothelial cell density and pericyte coverage of tumor vessels. A phase 2 trial in 66 patients with PNET using sunitinib for 4/2 weeks on/off, yielded objective responses (ORR), sustained tumor stabilizations, and a median time to tumor progression of 7.7 months. We further conducted a multinational, randomized, double-blind, placebo-controlled phase 3 trial, enrolling patients with advanced, well-differentiated PNET and documented disease progression in the past 12 months. A total of 171 patients were randomized 1:1 to receive sunitinib 37.5 mg/day continuous daily dosing or placebo, each with best supportive care. The primary endpoint was progression-free survival (PFS); secondary endpoints included ORR, overall survival (OS) and safety. Median PFS was longer in patients receiving sunitinib (11.4 months) than in the placebo arm (5.5 months; hazard ratio: 0.418–95%CI: 0.263–0.662; $P<0.001$). Cox proportional hazards analysis of PFS according to baseline characteristics favored sunitinib in all subgroups studied. ORR was 9.3% in patients receiving sunitinib, versus 0% in the placebo arm. Median OS was not reached, but the observed hazard ratio of 0.409 favored sunitinib (95%CI:0.187–0.894; $p=0.02$). Adverse events were diarrhea, nausea, asthenia and vomiting, mostly of grade 1/2 severity. Angiogenesis appears to play a major role in PNET. Treatment with sunitinib continuous daily dosing improved PFS, OS, and ORR compared with placebo, independent of baseline characteristics.

IPSY2-4

Diagnostic Procedure for PNET

H. Igarashi

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Pancreatic neuroendocrine tumors (PNET) are relatively rare tumors that constitute approximately 2–3% of all pancreatic tumors. The growth of PNET is usually slow however malignant disease is frequent other than insulinoma. At the initial diagnosis of PNET, diagnosis of the presence of the disease is performed with the value of the basal hormone and biomarker. The functioning tumor can be diagnosed with a small tumor by symptoms with hormone secretion, while more than half patients with non functioning PNET harbor the distant metastasis at the initial diagnosis. For managing PNET, the preoperative evaluation of the tumor characterization (functioning or non functioning) and tumor localization is important. Although ultrasonography, abdominal CT, and MRI is conventionally used to detect the tumor, detecting a small tumor or liver metastases is sometimes difficult. The measurement of serum chromogranin A and the use of somatostatin receptor scintigraphy (Octreo Scan) are useful diagnostic tools however they are not covered by the public health insurance system in Japan. Therefore strategy for diagnosis of PNET in Japan has some difference from the western world. For the evaluation of localization of the PNET of functioning tumor, such as insulinoma or gastrinoma, selective arterial secretagogue injection test (SASI test) is used and sensitivity is more than 90%. We also use endoscopic ultrasonography (EUS) for detecting a small tumor and multiple tumors in the pancreas as well as obtaining the histology by EUS guided fine needle aspiration (EUS/FNA). To manage the unresectable tumor with distant metastasis or local invasion, WHO histological classification and the study for the expression of SSTR2 of the tumor is important to determine the strategy of the treatment including systemic chemotherapy and somatostatin analog. In this symposium, we are presenting our strategy and algorism as well as the difficulties for the diagnosis of PNET.

IPSY2-5

Determinants of Resection for Pancreatic Neuroendocrine Tumors

R. Doi

Department of Surgery, Japanese Red Cross Otsu Hospital

Pancreatic neuroendocrine tumors (PNETs) are believed to be relatively benign, and the long term outcome to be better than other pancreatic and gastrointestinal tumors; however, the management of this disease is often difficult because standardized treatment strategy is not established. The majority of the functioning tumors may demonstrate benign behavior, but tumors with metastases are difficult to handle.

Recent classification defines PNET into several categories; benign, benign or low-grade malignant, low-grade malignant and high-grade malignant. The definition is mainly based on the histo-

pathological findings of the tumors. The clinical information that can predict the tumor behavior is the hormone status and the size of the tumor. Extracorporeal ultrasonic or endoscopic biopsy would help the determination of resection a lot, but currently the method is not popular. Consequently, the determinants of resection depend on the hormone status, symptoms and the tumor size.

There is no question for resection if the symptom bothers patients even the tumor is small. The tumors larger than 2 cm may be considered for resection regardless of hormone status.

The treatment strategy for the synchronous metastatic PNET is not clear. Resection of the primary tumor maybe considered to eliminate the sauce of the metastasis. Reduction surgery of the metastatic tumors would be beneficial to hormone control as well as to survival outcome. In addition to the interventional treatments, resection of primary and metastatic tumors could always be considered.

IPSY2-6

Surgical Treatment of Hepatic Metastasis of Pancreatic Neuroendocrine Tumor

T. Ohtsuka[1], K. Tsutsumi[1], S. Takahata[1], M. Nakamura[1], K. Miyazaki[2], M. Tanaka[1]

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Hepatic metastasis of pancreatic neuroendocrine tumor (PNET), observed in 10–50% of cases at the initial diagnosis, is a major cause of death, and control of the metastatic lesions is important to improve the prognosis. Hepatic resection is the first aid of choices for curability or palliative cytoreduction to ameliorate the hormonal symptoms in patients with functional PNET. Overall 5-year survival rate after hepatic resection of metastatic PNET has been reported to range from 40 to 70%. Resectablity depends on the degree of metastatic spread in the liver, and somatostatin receptor scintigraphy is useful to evaluate the hepatic spread, although this modality is not available in Japan. Adjuvant radiofrequncy ablation is also relatively effective during palliative hepatectomy. Even in patients having unresectable hepatic metastasis, resection of the primary pancreatic tumor with regional lymph node dissection is recommended to focus on later treatment of hepatic tumors using transarterial chemoembolization (TACE). During pancreatectomy, additional cholecystectomy and ligation of right gastric artery are options to prevent the complications of TACE such as cholecystitis and gastroduodenal ulceration. Liver transplantation is also an option for unresectable hepatic metastasis from PNET; however, the Milan criteria do not recommend liver transplantation for metastatic PNET because of the insufficient postoperative outcomes. There have been several controversial issues regarding indications for hepatic resection of metastatic PNET, such as the number and size of the hepatic tumors, and timing of hepatectomy (synchronous or metachronou with pancreatectomy). Several recent reports have shown that the large number and large size of the hepatic tumors, and simultaneous hepatectomy with pancreatectomy cause poor prognosis after the resection of the hepatic metastasis of PNET.

IPSY2-7

Medical Treatment of Advanced Pancreatic Neuroendocrine Tumors

T. Okusaka[1], H. Ueno[1], C. Morizane[1], S. Kondo[1], S. Mitsunaga[2], K. Nakachi[2], M. Ikeda[2]

[1]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, [2]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital East

For patients with pancreatic neuroendocrine tumors (PNET) who are not fit for surgery, the choice of treatment depends on the symptoms, stage of disease, degree of uptake of radionuclide, and histological features of the tumor. Treatment choices for non-resectable disease include somatostatin analogues, biotherapy, radionuclides (not available in Japan), ablation therapies, and chemotherapy. Systemic chemotherapy may be used for metastatic well differentiated or poorly differentiated endocrine carcinoma. External beam radiotherapy may relieve bone pain resulting from metastases. For patients with unresectable well-differentiated endocrine carcinoma and liver-dominant metastases, hepatic regional therapies, including hepatic arterial embolization or chemoembolization and local ablation therapy, may be options.

For patients with well-differentiated endocrine carcinoma, chemotherapy with several agents, including streptozotocin, dacarbazine, 5-fluorouracil, and adriamycin, has been recommended, although the agents commonly used elsewhere in the world, namely, streptozotocin and dacarbazine, are not yet available in Japan. A number of studies have noted elevated expression levels of several growth factors and receptors in pancreatic neuroendocrine carcinomas. In preclinical models, disruption of these signaling pathways has been shown to inhibit neuroendocrine cell growth. Several multicenter clinical trials have been conducted in patients with advanced pancreatic well differentiated endocrine carcinoma to evaluate the effects of molecular agents targeting growth factor signaling pathways, which holds promise for improved prognosis for these patients in the future.

Patients with poorly differentiated endocrine carcinoma are thought to be more responsive to cytotoxic chemotherapy, such as cisplatin + etoposide, and cisplatin + irinotecan, which are regimens commonly used for small cell lung cancer. However, these responses are generally short lasting, and their survival benefit is very poor. Therefore, the development of more effective non-surgical treatments for this disease is essential.

IPSY2-8

Sandostatin Treatment for PNET

T. Ito

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Pancreatic neuroendocrine tumors (PNETs) may be treated with a combination of surgery, somatostatin analog therapy, chemotherapy, radiation therapy, and interferon therapy. Surgical removal of the tumor may lead to symptom relief or cure. Synthetic forms of somatostatin, such as octreotide (Sandostatin), work at the site of the tumor. Octreotide binds to sst-2/sst-3/sst-5 receptors, especially sst-2 recep-

tor, to regulate gastrointestinal hormone secretion and thereby affect tumor growth. The prognosis of patients with neuroendocrine tumors (NETs) was greatly improved as evidenced from the increase in overall survival after the advent of octreotide and octreotide LAR. Octreotide is highly effective in improving symptoms in patients with NETs, and is considered more effective than lanreotide. Octreotide acts on somatostatin receptors 2, 3, and 5. However, the efficacy expectations would depend on whether the tumor expresses sst-2 receptor. Thus to predict efficacy, it is important to investigate the expression of sst-2 receptor. There are three strategies for detection of sst-2 receptor, immunohistochemical staining, mRNA expression by RT-PCR and octreotide scan. In this speech, I am presenting PNETs patients with dramatically tumor suppressing by octreotide LAR. In conclusion, Sandostatin, a somatostatin analog, is a standard treatment in NETs patients to control symptoms. Additionally, Sandostatin LAR may have a stabilizing effect in NETs. Recently, the PROMID study revealed that octreotide LAR significantly prolongs time to progression in all patients with well-differentiated midgut NETs and patients with low tumor load (≤10%) show an even more impressive response. Thus, initiating octreotide LAR early may improve patient outcomes, attributing to its tumor-suppressing effect, ant that octreotide LAR should be considered the standard of care in patients with PNETs.

IPSY2-9

Overview and Future in PNET

R.T. Jensen

Digestive Diseases Branch, National Institutes of Health

During this presentation Dr Jensen will give both a brief overview as well as an in depth discussion of the problems confronting us in that management of these patients and the future directions that may address these problems. The overview will briefly summarize the important recent developments in the pathogenesis, diagnosis and management of PNETs, extending what was covered either partially or in depth in the previous presentations on specific subjects during the symposium. The key problems and unknowns confronting us in the management of patients with PNETs will be discussed including pathogenesis, medical treatments, surgical therapies and possible preventive strategies, in patients with inherited disorders with PNETs. Both important future studies that will be needed to address some of these unknowns will be discussed as well as future diagnostic, localization and treatment regimens that may be helpful.

IAP Symposium 3 International Consensus on Cystic Neoplasms of the Pancreas

IPSY3

Moderator's Remark

M. Tanaka[1], *C. Fernandez-del Castillo*[2]

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The IAP consensus guidelines for the management of IPMN and MCN of the pancreas published in 2006 (*Pancreatology* 2006;6:17–32) greatly contributed to better understanding and management of these entities. However, there remain many questions to be further clarified. At this consensus symposium the working group of IAP consisting of initial 14 members of the 2006 guidelines and additional 6 new members will present and discuss principal controversies to be solved for anticipated revision of the guidelines. The planned topics include:

1) Classification of IPMNs by duct type: Is the mixed category a separate entity?
2) Can branch duct IPMN be distinguished preoperatively from MCN and other pancreatic cysts? What is the role of cyst fluid analysis?
3) Criteria for resection of branch duct IPMNs: are the Sendai recommendations safe?
4) Definition of malignant IPMN: what do CIS and minimally invasive carcinoma imply, and are morphologic subtypes of prognostic significance?
5) Carcinoma derived from IPMN and carcinoma concomitant with IPMN: different or related entities?
6) Surveillance of IPMN. How, how often, and why?
7) What to do with IPMNs with a positive family history of pancreatic cancer?

Carlos Fernandez-del Castillo (#1), Max Schmidt (#2, new member), Martha Pitman (#2, new member), Jin-Young Jang (#3, new member), Volkan Adsay (#4), Michio Shimizu (#4), Koji Yamaguchi (#5), Philippe Levy (#6, new member), and Christopher Wolfgang (#7, new member) will give their 5-minute presentations on each topic in the presence of two to three discussants assigned beforehand. All of these presenting members will serve as discussants for the other topics. In addition, Suresh Chari, Kenji Yamao and Massimo Falconi as initial members of the working group and Wataru Kimura as a new member will be in the panel of discussants.

Outline of the Session

1 Classification of IPMNs by Duct Type: Is the Mixed Category a Separate Entity?
Presenter:
Carlos Fernandez-del Castillo *(Massachusetts General Hospital, USA)*
Discussants:
Kenji Yamao *(Department of Gastroenterology, Aichi Cancer Center Hospital, Japan)*

Jin-Young Jang *(Division of Hepatobiliary-Pancreatic Surgery, Department of Surgery, Seoul National University College of Medicine, Korea)*

2 Can Branch Duct IPMN be Distinguished Preoperatively from MCN and Other Pancreatic Cysts? What is the Role of Cyst Fluid Analysis?
Presenter #1:
C. Max Schmidt *(Department of Surgery, Indiana University School of Medicine, USA)*
Presenter #2:
Martha Bishop Pitman *(Pathology, Massachusetts General Hospital, Harvard Medical School, USA)*
Discussants:
Wataru Kimura *(Department of Gastroenterological and General Surgery, Yamagata University Faculty of Medicine, Japan)*
Kenji Yamao *(Department of Gastroenterology, Aichi Cancer Center Hospital, Japan)*

3 Criteria for Resection of Branch Duct IPMNs: Is the Sendai Recommendation Safe?
Presenter:
Jin-Young Jang *(Division of Hepatobiliary-Pancreatic Surgery, Department of Surgery, Seoul National University College of Medicine, Korea)*
Discussants:
Christopher L. Wolfgang *(Department of Surgery, Johns Hopkins University, USA)*
Philippe Levy *(Pole des Maladies de l'Appareil Digestif, Service de Gastroenterologie-Pancreatologie, Hospital Beaujon, France)*
Suresh T. Chari *(Division of Gastroenterology and Hepatology, Mayo Clinic, USA)*

4 Surveillance of IPMN. How, How Often, and Why?
Presenter:
Philippe Levy *(Pole des Maladies de l'Appareil Digestif, Service de Gastroenterologie-Pancreatologie, Hospital Beaujon, France)*
Discussants:
Kenji Yamao *(Department of Gastroenterology, Aichi Cancer Center Hospital, Japan)*
C. Max Schmidt *(Department of Surgery, Indiana University School of Medicine, USA)*

5 Definition of Malignant IPMN: What do CIS and Minimally Invasive Carcinoma Imply, and are Morphologic Subtypes of Prognostic Significance?
Presenter #1: "How to deal with CIS"
Volkan Adsay *(Pathology & Laboratory Medicine, Emory University School of Medicine, USA)*
Presenter #2: "Does distinction of gastric, intestinal, pancreatobiliary or oncocytic forms have a role"
Michio Shimizu *(Department of Pathology, Saitama Medical University, Saitama International Medical Center, Japan)*
Discussants:
Philippe Levy *(Pole des Maladies de l'Appareil Digestif, Service de Gastroenterologie-Pancreatologie, Hospital Beaujon, France)*
Koji Yamaguchi *(Department of Surgery 1, University of Occupational and Environmental Health, Japan)*

6 Carcinoma Derived from IPMN and Carcinoma Concomitant with IPMN: Different or Related Entities?
Presenter: Koji Yamaguchi *(Department of Surgery 1, University of Occupational and Environmental Health, Japan)*
Discussants: Volkan Adsay *(Pathology & Laboratory Medicine, Emory University School of Medicine, USA)*
Martha Bishop Pitman *(Pathology, Massachusetts General Hospital, Harvard Medical School, USA)*
Wataru Kimura *(Department of Gastroenterological and General Surgery, Yamagata University Faculty of Medicine, Japan)*

7 What to Do with IPMNs with a Positive Family History of Pancreatic Cancer?
Presenter:
Christopher L. Wolfgang *(Department of Surgery, Johns Hopkins University, USA)*
Discussants:
Massimo Falconi *(Department of Surgery, Universita Degli Studi di Verona, Policlinilo GB Rossi, Italy)*
Carlos Fernandez-del Castillo *(Massachusetts General Hospital, USA)*

***Presenters' abstracts are not available for this session.**

IAP Symposium 4 Acute Pancreatitis: Pathogenesis to Treatment

International Pancreatic Research Forum 2010 sponsored by Pancreatic Research Foundation of Japan

IPSY4-KN

Recent Advance in Pathogenesis of Acute Pancreatitis

A.K. Saluja

Department of Surgery, University of Minnesota

Pancreatitis is an inflammatory disease of the pancreas. Every year over 250,000 patients are diagnosed with pancreatitis and over two billion dollars are spent on their care. However, there is currently no treatment for these patients besides conservative management. Thus an urgent need exists to understand the pathogenesis of this disease so that specific treatment strategies can be developed. Current understanding of the pathogenesis of pancreatitis suggests that events culminating in inflammation of the pancreas are initiated in the acinar cells which synthesize, store and secrete digestive enzyme in an inactive form. There is evidence that early in pancreatitis intracellular activation of digestive enzymes occurs and these activated digestive enzyme zymogens are believed to be the injury-inciting stimuli.

Several publications from our and other laboratories have shown that early on in pancreatitis the inactive digestive enzymes co-localize with lysosomal enzymes, following which lysosomal cathepsin B in the co-localized organelles activates trypsinogen. This is corroborated by the fact that inhibition of cathepsin B protects against trypsinogen activation as well as injury in pancreatitis. Until now the role of cathepsin B in pancreatitis was believed to be in the activation of digestive enzyme zymogen. Now, however, the exciting finding emerges from recent studies in our laboratory that **cathepsin B can play a role in**

the activation of the apoptotic cascade and acinar cell injury during pancreatitis independently of activation of digestive enzyme zymogens. This is a new paradigm in the pathophysiology of pancreatitis. Also we have demonstrated for the first time that co-localized organelles become permeabilized in pancreatitis leading to release of cathepsin B into the cytosol, where it activates the apoptotic cascade.

We have shown previously that HSP70 (heat shock protein 70) expression protects against pancreatitis. Our preliminary data suggest that HSP70 does so by preventing co-localization and eventually inhibiting release of cathepsin B into the cytosol. Our studies have also shown for the first time in pancreatic acinar cells that HSP70 attenuates cytosolic calcium elevation in response to caerulein stimulation. Based on these facts as well as our data that cytosolic calcium is important for co-localization, we have proposed a novel hypothesis that HSP70 inhibits co-localization in pancreatic acinar cells by attenuating cytosolic calcium and thus protects against injury in pancreatitis. Since intracellular calcium is known to be involved in numerous and diverse cellular processes, this finding is of significance beyond its applicability to pancreatitis. These studies will eventually help in planning strategies to inhibit cathepsin B or to pharmacologically manipulate the levels of HSP70, so that these can be used as a tool to decrease the severity of clinical pancreatitis.

IPSY4-1

Pancreatic Acinar Cell Death Pathways in Acute Pancreatitis

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[1]Institute of Resource Development and Analysis, Kumamoto University, [2]Priority Organization for Innovation and Excellence, Kumamoto University, [3]Department of Surgery, Kumamoto Regional Medical Center

Introduction: Acute pancreatitis (AP) is an inflammatory disorder of exocrine pancreas, and the pathogenic mechanisms underlying acute pancreatitis are not clear. We previously generated serine protease inhibitor Kazal type 3 (Spink3), which is a mouse homologue of human SPINK1, deficient mice. In Spink3 deficient acinar cells, excessive autophagy was induced, suggesting that Spink3 is a negative regulator of autophagy. Autophagy is a vacuolar, self-digesting mechanism responsible for the removal of long-lived proteins and damaged organelles by the lysosome. Autophagy is negatively regulated by the mammalian target of rapamycin (mTOR), which regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription.

Objectives: The aim of present study was to explain the regulation mechanism of mTOR activity by SPINK1 (Spink3) in acute pancreatitis.

Materials and Methods: We analyzed whether recombinant SPINK1 protein can activate mTOR activity of the 3T3 fibroblast and 4 pancreatic cancer cell lines.

Results: In cerulein-induced mice pancreatitis model, mTOR activity decreased in the pancreas. In Spink3 deficient pancreas, both mTOR and its specific substrates were deficient, suggesting that Spink3 is a regulator of mTOR activity in acinar cells. mTOR activity is regulated by some growth factors. Interestingly, there are structural similarities between SPINK1 and epidermal growth factor (EGF), so we hypothesized that SPINK1 binds to EGF receptor (EGFR) to activate its downstream signalings. We showed that SPINK1 induces proliferation of variety cancer cell lines, and can bind to EGFR. As expected, EGFR and its downstream molecules, signal transducer and activator of transcription 3 (STAT3), extracellular signal-regulated kinase 1/2 (ERK1/2), v-akt murine thymoma viral oncogene homolog-1(AKT), and mTOR were phosphorylated by SPINK1 as well as EGF.

Conclusion: These data suggest that mTOR activity decreases by imbalance between trypsin and SPINK1 (Spink3) and suppression of mTOR activity induces pancreatic acinar cell death in acute pancreatitis.

IPSY4-2

Cell Biology of Pancreatic Proteases

M.M. Lerch

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Background and Aims: Acute pancreatitis is characterized by a cascade-like activation of digestive proteases in the pancreas and the first of them, trypsinogen, can be activated intracellularly. Whether this activation occurs only in rodents, rather than man, whether autoactivation represents the initiating event, and whether lysosomal cathepsins are the required trigger for the proteolytic cascade, remains a matter of ongoing research.

Methods and Results: Using different animals models of pancreatitis and mouse strains in which various proteases were genetically deleted we made a number of observations that elucidate the process of protease activation in the earliest disease phase. The first observation was that, following supramaximal stimulation of rodent pancreatic acini, autoactivation of trypsinogen does not seem to play a physiological role. Rather the contrary, autodegradation of activated trypsin, appears to be the predominating mechanism in the proteolytic intracellular cascade. As far as the role lysosomal cathepsins is concerned we found that cathepsin-B is a potent activator of trypsinogen in vitro and in vivo, whereas the highly homologous cathepsin-L is an inactivator of trpysinogen and trypsin. Cathepsin-L-induced cleavage of trypsinogen occured three aminoacids towards the C-terminus from the cathpsin-B activation site.

Conclusions: At least in rodent models of pancreatitis autoactivation is not a disease causing mechanism whereas cathepsin-B-induced trypsinogen activation appears to play a critical role. Other cathepsins, such as cathepsin-L, and other serine proteases, such as elastase, appear to have different, and sometimes opposing functions in acinar cell biology

IPSY4-3

Investigating Pathobiology of Alcoholic Pancreatitis

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Pancreatic Research Group and Southern California Research Center for Alcoholic Liver and Pancreatic Diseases, Yale University and University of California, New Haven and Los Angeles

Alcohol abuse is one of the most common causes of pancreatitis. The risk of developing alcohol-induced pancreatitis is related to the amount and duration of drinking. Further, both smoking and dietary factors contribute to disease risk. Although the risk of developing disease increases as a function of these factors, only a small portion of patients with these risks develop disease indicating that unknown factors contribute to disease initiation. Studies from animal models are revealing that alcohol sensitizes the pancreas to key pathobiologic processes that are involved in pancreatitis. Current studies are focused on investigating the mechanisms responsible for the sensitization effect of alcohol and are revealing disorders in organelles including endoplasmic reticulum and mitochondria. As our understanding of alcohol's effects continue to advance, insights into potential therapeutic strategies will emerge providing opportunities for clinic trials to show clinical benefit.

IPSY4-4

Pathogenesis of Severe Acute Pancreatitis -Insights from Genetic Studies-

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Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas. The clinical course of AP varies between individuals. Factors that determine severity are not well understood, but likely include environmental, metabolic disorders, and genetic factors. Elucidation of the factors underlying genetic predisposition for development and progression of AP provides important insights to understand the pathogenesis of severe AP. CD14 is a pattern-recognition receptor that plays a critical role in innate immunity and directs the adaptive immune responses. We here evaluated the association of the promoter variants in the CD14 gene with AP in Japan. Three hundred forty six unrelated patients with acute pancreatitis (AP) (107 with severe and 239 with mild) and 319 healthy controls were genotyped for the single nucleotide polymorphisms at positions -260 and -651 from the AUG start codon in the CD14 gene. The allele and genotype frequencies of the -260C/T and -651C/T polymorphisms did not differ between controls and patients with AP. In subgroup analyses, patients with severe AP had more –651C allele than controls (P=0.005; odds ratio (OR) 1.71; 95% confidence interval (CI)=1.18–2.49) or patients with mild AP (P=0.001; OR 1.95; 95% CI=1.33–2.85). Genotype -651CC was more common (P=0.001 vs. controls and P=0.001 vs. mild AP) and -651CT was less (P=0.009 vs. controls and P=0.007 vs. mild AP) in patients with severe AP than healthy controls or patients with mild AP. The frequencies of pseudocyst development and requirement of surgery were higher in AP patients with -651CC than in those without this genotype. The -260C/T polymorphism was not associated with the severity of AP. In conclusion, -651C/T promoter polymorphism in the CD14 gene was associated with severity of AP in Japan, supporting a role of Toll-like receptors/CD14 system in the progression of severe AP.

IPSY4-5

Usefulness of Perfusion CT for Detection of Pancreatic Ischemia in Acute Pancreatitis

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Despite recent improvements in the treatment of severe acute pancreatitis (SAP), mortality rates remain high. SAP often leads to necrotizing pancreatitis, the most severe form of pancreatitis, which can result from pancreatic ischemia caused by vasospasms of the intra-pancreatic arteries. In addition, previous report indicated that the prognosis of SAP with pancreatic ischemia was extremely severe. In this regards, it is considered that the diagnosis of pancreatic ischemia is one of the most important factor to treat SAP patient. At present, vasospasms of the intra-pancreatic arteries can only be diagnosed accurately by angiography. However, neither unstable nor emergent cases lend themselves to examination by angiography: thus, an alternative non-invasive method for diagnosing pancreatic ischemia is required.

We recently reported that perfusion CT is capable of detecting pancreatic perfusion defects non-invasively, and accurately predict the development of pancreatic necrosis at the early stages of SAP. Also, in our recent study, vasospasms of the intra-pancreatic arteries by angiography cause perfusion defects by perfusion CT in the pancreas, and perfusion CT predicted the development of pancreatic necrosis with significantly higher accuracy than angiography. Thus, perfusion CT can be alternative method of angiography in diagnosing pancreatic ischemia in patients with severe acute pancreatitis.

We would like to report that usefulness of perfusion CT for detection of pancreatic ischemia in acute pancreatitis.

IPSY4-6

The Role of Antibiotics in The Prevention of Infection in Acute Pancreatitis

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In severe acute pancreatitis, infectious complication is the major contributor to poor prognosis. Particularly, infectious pancreatic necrosis (IPN) is the most serious form of complication. IPN usually

requires surgical intervention and the mortality rate is still extremely high. Thus, during these four decades, the prophylactic administration of antibiotics has been involved into routine procedure in the early phase treatment for the patients with sever acute pancreatitis. In fact, several randomized controlled trials (RCTs) of the prophylactic effect of antibiotics demonstrated that the broad-spectrum antibiotics such as imipenem decreased the incidence of infectious complications and the mortality rate. Currently, however, multiple meta-analyses for the validation of the evidence for the preventive use of the antibiotics have been made, and the usefulness was not validated. Moreover, excessive use of antibiotics induces microbial substitution, and brings down the refractory infection with drug-resistant strain such as MRSA or fungal infection. Although the prophylactic administration of the antibiotics is recommended in several clinical guidelines including JPN Guidelines 2010, uncritical indication of prophylactic use the antibiotics is doubtful and should be reconsidered. In Japan, on the other hand, continuous regional arterial infusion of protease inhibitor and antibiotics (CRAI) was invented in the early of 1990s, and now becomes widely used for the prevention of IPN in the patients with acute necrotizing pancreatitis. A nationwide survey of the CRAI therapy in acute necrotizing pancreatitis revealed that the frequency of IPN was significantly lower in the patients treated with both antibiotics and protease inhibitor than in the patients treated with protease inhibitor alone. It is possible that prophylactic administration of antibiotics via regional arteries is effective for the prevention of IPN, and multicenter RCT for its validation is now ongoing in Japan.

IPSY4-7

Surgical Strategies for Acute Pancreatitis

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Therapeutic intervention and surgery of acute pancreatitis are indicated in the cases with pancreatic necrosis or with the fluid and/or necrotic collections such as walled-off necrosis and pancreatic pseudocyst.

Although surgery is considered the gold standard treatment for infected pancreatic necrosis, recent studies demonstrated the benefit of postponing surgical intervention in reducing the mortality rate. The aim of interventional and surgical managements is to remove pancreatic and peripancreatic necrotic tissues in order to reduce the release of inflammatory mediators. Surgical strategies for necrotizing pancreatitis according to JPN guidelines 2010 include the following: (1) early surgery for necrotizing pancreatitis is not recommended, and it should be delayed as long as possible; (2) bacteriological examination by fine needle aspiration is useful for making a definitive diagnosis of infected pancreatic necrosis; (3) conservative treatment should be performed in sterile pancreatic necrosis; (4) infected pancreatic necrosis is an indication for interventional therapy such as CT-guided percutaneous drainage as a bridge to elective surgery. However, conservative treatment by antibiotic administration is available in the selected patients who are in stable general condition; (5) necrosectomy is recommended as a surgical procedure for infected necrosis, and less-invasive procedures by various approaches are currently being employed and better outcomes are reported than those achieved by conventional open surgery.

Interventional and surgical managements for pancreatic pseudocyst are the following: (1) interventional treatment should be performed for pancreatic pseudocysts that give rise to symptoms, accompany complications or increase the diameter of cysts and (2) percutaneous drainage, endoscopic drainage or surgical procedures are selected in accordance with the conditions of individual case.

In the last two decades, the emergence of new minimal invasive approaches in performing surgical debridement has been observed. However, no randomized controlled studies have been published in comparing different techniques, and thus we should await future studies.

IAP Symposium 5 Chronic Pancreatitis: Pathogenesis to Treatment

International Pancreatic Research Forum 2010 sponsored by Pancreatic Research Foundation of Japan

IPSY5-1

Chronic Pancreatitis: Advances in Understanding the Pathogenesis, Clinical Manifestations, and Diagnosis

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Background: Chronic pancreatitis (CP) is a syndrome of chronic pancreatic inflammation leading to variable destruction of acinar and islet cells, fibrosis, pain, and increased risk of pancreatic cancer. The heterogeneity of etiologies, and the variability in individual responses to pancreatic injury and inflammation results in major challenges for clinicians to predict disease development and progression, and for researchers to model the mechanisms of human disease.

Aim: To use reverse engineering approaches to determine the primary variables of susceptibility and progression, and to develop predictive models for personalized medicine.

Methods: We focused on specific components of complex human chronic pancreatitis to understand specific variables and mechanisms. We used genetics, epidemiology, pathology, molecular biology, and animal model for neurophysiology and toxicology, plus literature reviews to understand each component. We then developed working models to organize, test and integrate new knowledge.

Results: The SAPE hypothesis model is a "two hit" developed to understand the overall process leading to CP. The TIGAR-O classification system was developed to study gene-environment interactions.

The NAPS2 study gathered data on 1000 patients and 600 controls to determine common phenotypes and important variables (including alcohol and smoking), genetic factors, and features of pain, fibrosis, diabetes, cancer and maldigestion in RAP and CP. The SAPS and PROOF studies link AP with RAP and CP. Machine Learning and information theory is now being applied to understand complex interactions and to develop highly predictive models.

Conclusions: The basic framework for understanding chronic pancreatitis has been established and modeled in animal studies. Additional work is required to link risk factors, quantitative biomarkers of disease activity and quantitative outcomes within and between pathologic pathways. New predictive disease models must be tested to determine if patient-specific treatments are effective in preventing complications that cannot be reversed.

IPSY5-2

Molecular and Cellular Regulation of Pancreatic Duct Function

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Pancreatic duct epithelium secretes a HCO_3^--rich fluid, which is dependent on cystic fibrosis transmembrane conductance regulator (CFTR). Severe loss of CFTR function due to mutation causes impaired HCO_3^- secretion in cystic fibrosis. Mild dysfunction due to less severe mutations and/or polymorphisms is a risk factor for chronic pancreatitis. CFTR not only functions as a cAMP-activated anion channel but also regulates SLC26 Cl^--HCO_3^- exchanger and Na^+-H^+ exchanger (NHE3) in the apical membrane. In proximal part of the ductal tree close to acini where luminal Cl^- concentration is high, Cl^--HCO_3^- exchange mediates most of HCO_3^- secretion. In ducts isolated from Slc26a6 null mice, the exchange activity of luminal Cl^- with intracellular HCO_3^- was reduced. Luminal application of CFTRinh-172, a specific inhibitor of CFTR accelerated Cl^--HCO_3^- in wild-type (+/+) ducts but not in Slc26a6 -/- ducts. The data suggest that SLC26A6 is a major Cl^--HCO_3^- exchanger in the apical membrane and compensates low HCO_3^- permeability of CFTR. As a result of HCO_3^- secretion, luminal HCO_3^-concentration rises (luminal Cl^- falls) with distance along the duct. In distal ducts where luminal HCO_3^- reaches 120–130 mM, Cl^--HCO_3^- exchange runs slowly and HCO_3^- conductance of CFTR provides a major pathway of HCO_3^- secretion. Pancreatic juice in some of the patients with cystic fibrosis and advanced stage of chronic pancreatitis is acidic. This cannot be explained by decreased activity of HCO_3^- conductance and/or Cl^--HCO_3^- exchange. The activity of apical Na^+-H^+ exchange (probably NHE3) in ducts isolated from deltaF cystic fibrosis mice was greater than that in +/+ ducts and was activated by cAMP. This suggests that apical NHE is responsible for luminal acidification in cystic fibrosis pancreatic ducts and that the activity of NHE3 is inhibited in the presence of functional CFTR.

IPSY5-3

Genetic Aspects of Chronic Pancreatitis

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In 1896, Hans Chiari postulated that pancreatitis results from pancreatic autodigestion. An inappropriate conversion of pancreatic zymogens to active enzymes within the pancreatic parenchyma was proposed to initiate the inflammatory process.

Gain-of-function mutations in the cationic trypsinogen gene (PRSS1) and a triplication of an ~605-kb segment containing PRSS1 and PRSS2 has been reported in families with hereditary pancreatitis. In contrast, a p.G191R variant in the anionic trypsinogen (PRSS2) gene has been described that mitigates intrapancreatic trypsin activity and thereby plays a protective role against chronic pancreatitis.

Since gain-of-function mutations in PRSS1 leading to a super trypsin cause pancreatitis it was hypothesised that pancreatitis may also raised by loss-of-function mutations in pancreatic trypsin inhibitors such as SPINK1. In 2000, a p.N34S variant in SPINK1 was associated with chronic pancreatitis (CP), mostly found in patients without a family history – 15–40% of patients with so-called idiopathic CP carry N34S on one allele or on both alleles making SPINK1 to the strongest genetic risk factor in idiopathic CP so far.

Albeit the association between CFTR and idiopathic CP is now well established, the pathogenic mechanisms are poorly understood. Studies analysing the complete CFTR sequence as well as PRSS1 and SPINK1 found that 25% to 30% carried at least one CFTR mutation, but few patients were compound-heterozygous. Several CP patients, however, were trans-heterozygous for a CFTR and a SPINK1 or PRSS1 variant.

Because trypsin degradation serves as a protective mechanism against pancreatitis, we hypothesised that loss of function in trypsin degrading enzymes increases the risk for pancreatitis. Chymotrypsin C (CTRC) degrades all human trypsin and trypsinogen isoforms with high specificity. Analysing CTRC in German patients and controls, 2 alterations, p.R254W and p.K247_R254del, were significantly overrepresented in the pancreatitis group. Functional analysis of the CTRC variants revealed impaired activity and/or reduced secretion.

IPSY5-4

Genetic Background of Chronic Pancreatitis in Japan

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Background/Aim: Chronic pancreatitis is an inflammatory disease with multifactorial pathogenic mechanisms. Genetic mutations and polymorphisms have been suggested for the mechanism of pancreatitis. The aim of this study was to investigate the association of cationic trypsinogen (PRSS1), serine protease inhibitor Kazal type 1 (SPINK1), chymotrypsin C (CTRC) mutations, and anionic trypsinogen (PRSS2) variant with chronic pancreatitis in Japan.

Methods: Two hundred fifty-nine patients with chronic pancreatitis and 527 healthy controls were enrolled. The p.R122H and p.N29I mutations in the PRSS1 gene, the p.N34S and [-215G>A; IVS3+2T>C] mutations in the SPINK1 gene, and the p.G191R variant in the PRSS2 gene were determined by PCR-restriction-fragment length polymorphism. Sequence analysis was performed when necessary. All patients were tested for CTRC mutations by sequence analysis.

Results: In 11 families with hereditary pancreatitis, we found 8 families carrying the PRSS1 p.R122H mutation and one family carrying the p.N29I muation. The flequencies of SPINK1 p.N34S and [-215G>A; IVS3+2T>C] mutations were significantly higher in patients with familial pancreatitis (40% and 13%, respectively) and idiopathic chronic pancreatitis (11% and 12%) than healthy controls (0.4% and 0%). The PRSS2 p.G191R frequency (1.2%) in patients with chronic pancreatitis was lower than that in healthy controls (6.6%)(P=0.001; Odds ratio 0.178). We found only one missense variant in the CTRC gene.

Conclusions: PRSS1 and SPINK1 mutations were strongly associated with chronic pancreatitis, but CTRC mutations were rare. The [215G>A; IVS3+2T>C] mutation in the SPINK1 gene formed a unique genetic background in Japan. The PRSS2 p.G191R variant was suggested for a protective role against chronic pancreatitis. Here, we highlighted the genomic factors that affect susceptibility or resistance to chronic pancreatitis in Japan.

IPSY5-5

Role of Stellate Cells in Chronic Pancreatitis

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Prominent fibrosis is a characteristic histological feature of chronic pancreatitis. Over the past decade, evidence has accumulated to support a central role for activated pancreatic stellate cells (PSCs) in pancreatic fibrogenesis via their ability to regulate both the synthesis and degradation of the extracellular matrix proteins that comprise fibrous tissue. In vivo and in vitro studies have demonstrated that PSCs are activated early in the course of pancreatic injury and are the predominant source of collagen in the fibrotic pancreas. The factors responsible for inducing PSC activation include alcohol (a major cause of chronic pancreatitis) and its metabolites, oxidant stress and several cytokines (known to be upregulated during pancreatic injury). Interestingly, PSCs are themselves capable of synthesizing cytokines; this cytokine production is stimulated by factors such as ethanol, acetaldehyde and other cytokines indicating that in addition to paracrine pathways of activation, PSCs may also be activated in an autocrine manner, which might cause perpetuation of cell activation, even when the initial trigger factors are no longer present. Such persistent PSC activation may potentiate ECM production and pancreatic fibrosis.A number of intracellular signalling pathways have now been identified as important mediators of PSC activation including the mitogen activated protein kinase (MAPK) pathway, phosphatidylinositol-3-kinase (PI3K) and protein kinase C (PKC), and nuclear transcription factors NF kappaB and AP1. Researchers are now turning their attention to interventions aimed at inhibiting or reversing PSC activation so as to retard the fibrotic process. In this regard, our recent studies with a rat model of alcoholic chronic pancreatitis have demonstrated that withdrawal of alcohol facilitates loss of activated PSCs by enabling apoptosis of the cells, thereby leading to reversal of fibrosis in the pancreas.

IPSY5-6

Regulation of Pancreatic Fibrosis by the Immune System

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Exposure to various pathogens is known to affect the development of chronic pancreatitis through infiltration by inflammatory cells and the release of cytokines. We investigated whether pancreatic stellate cells (PSCs), which have been characterized as the major source of extracellular matrix and cytokine production in the pancreas, act as immune cells, such as macrophages and antigen-presenting cells. (1) Phagocytosis: Phagocytosis is essential as a means of protecting against inflammation and tissue remodeling. When apoptotic neutrophils, necrotic acinar cells, or bacteria were added to cultured PSCs, they were internalized into the cytoplasm of the PSCs. Engulfment of dead cells significantly decreased PSC cell growth and α-SMA expression, suggesting that PSCs act as local professional phagocytes and remove harmful cells as quickly as possible. (2) Toll-like receptor (TLR): Pathogens are recognized by both immune cells and non-immune cells through TLRs. PSCs express various TLRs, and a cell wall component of gram-positive bacteria, lipoteichoic acid (LTA), and lipopolysaccharide (LPS) significantly increased collagen secretion by PSCs, while blockade of TLR2 and TLR4 significantly inhibited the increase in collagen secretion in response to LTA and LPS, respectively. These results indicate that the fibrogenic action of PSCs is associated with activation of the TLR-dependent pathway. (3) Antigen-presenting cells (APCs): MHC class II molecules are found only on APCs, and hepatic stellate cells (HSCs) are known to be liver-resident APCs. Flow cytometry analysis revealed that stimulation by IFN-γ or ovalbumin failed to induce expression of MHC class II or HLA-DR on PSCs. Furthermore, cells simulated with IFN-γ expressed neither MHC class II nor HLA-DR at the transcriptional level. In contrast to HSCs, PSCs do not appear to be responsible for the MHC class II-dependent pathway of antigen presentation.

IPSY5-7

Proposal of a New Classification System of Chronic Pancreatitis

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[1]Department of Medicine II, University Medical Centre Mannheim, [2]European Institute of Oncology, Milan, Italy, [3]Karolinska Institute, Stockholm, Sweden

Introduction: The M-ANNHEIM classification represents a new classification of chronic pancreatitis (cP). It stratifies multiple (M) etiological risk factors: Alcohol (A), Nicotine (N), Nutrition (N), Heredity (H), Efferent duct factors (E), Immunity (I), and Miscellaneous factors (M), differentiates various disease stages and defines different degrees of disease severity with a clinical scoring system. A validation of this system has not yet been performed.

Aims: To determine whether the M-ANNHEIM classification provides a meaningful clinical disease description, is useful in monitoring disease course, and allows prognostic evaluation of disease activity.

Methods: Retrospective and partial prospective categorization of patients according to the M-ANNHEIM classification (1997 until 2007, Dept. Medicine II. Mannheim, exclusion of biliary pancreatits).

Results: We identified n=523 patients (n=137 with M-ANNHEIM possible cP, n=386 with probable or definite cP). The M-ANNHEIM stages of disease significantly correlated with disease duration ($p<0.0001$) and the M-ANNHEIM severity index ($p<0.0001$, Spearman correlation coefficient=0,72). The M-ANNHEIM classification was applied to patients with autoimmune pancreatitis (n=6) at comparable points in time and was useful in monitoring disease activity. Necessity of pancreatic surgery was not significantly associated with M-ANNHEIM stages of disease ($p=0.06$), but significantly correlated with the M-ANNHEIM severity index (n=22 patients with indications for pancreatic surgery; M-ANNHEIM severity index A and B (<11 points) in n=8/416 (2%); severity index D and E (>15 Punkte) in n=5/28 (19%); $p<0.0001$).

Conclusion: The M-ANNHEIM classification unifies clinical disease description, represents a useful tool for monitoring disease activity, and allows prognostic evaluation of necessity of pancreatic surgery.

IPSY5-8

Development of Diagnostic US and EUS of Chronic Pancreatitis

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Traditional imaging modalities, including B-mode ultrasonography (US), endoscopic untrasonography (EUS), MDCT, and MRI (MRCP) can be helpful to diagnose chronic pancreatitis. Of these diagnoses of chronic diagnosis, differentiation between focal masses in patients with chronic pancreatitis and pancreatic cancer is very important in the clinical setting. Recent developed contrast-enhanced US (CE-US) is useful to distinguish the mass forming chronic pancreatitis with pancreatic ductal cancer. In particular, newly developed contrast agent, Sonazoid can depict the fine vessel pattern compared to conventional Levovist. Interestingly, we can see the bubbles in the pancreatic ductal cancer irregularly move in the vessel compared to those in mass forming pancreatitis. With regard to development of EUS, recently, several endoscopists have conducted CE-EUS in patients with pancreatic masses. Furthermore, EUS-tissue elastography, which can obtain an information of tissue hardness, may be possible to detect which cannot be detected by conventional EUS. Until now, we assessed EUS elastography as a diagnostic tool in patients with pancreatic masses by tissue elastic distribution and elasticity semiquantitatification using a strain ratio of tissue elasticity. Elastography for all pancreatic ductal cancer showed intense blue coloration. While mass forming type pancreatitis presented the coloration pattern of mixed green, yellow and low intensity of blue. Concerning strain ratio, the mean strain ratio of mass forming chronic pancreatitis and pancreatic ductal cancer were each 25.2 +/- 11.1 and 46.5 +/- 19.5, respectively ($p=0.0026$). EUS makes it possible to obtain tissue samples to differentiate malignant from benign by cytology and histology by H-E staining if necessary. Several investigators have reported p53 and K-ras analysis is useful for differentiation mass forming chronic pancreatitis and pancreatic ductal cancer.

IPSY5-9

Endoscopic Strategies for Chronic Pancreatitis: Interventional Management

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The advent of endoscopy has provided unique opportunities for minimally invasive strategies for the management of chronic pancreatitis and its complications. Endoscopic ultrasonography (EUS) represents an ideal method to exclude neoplastic disease including cysts and mass lesions. More recently, interventional EUS has been shown to provide a minimally invasive route to safely and effectively drain pancreatic pseudocysts and even provide opportunities for treatment of pancreatic necrosis. Randomized trials have documented better outcomes for pseudocyst drainage with direct drainage by EUS rather than forward viewing endoscopy. Over the last decade, therapeutic ERCP has been shown to alleviate pain for patients with pancreatic ductal strictures. Placing multiple stents has improved short term success rates. Pancreatic ductal leaks are effectively treated endoscopically and may substitute for or work in conjunction with endoscopic trangastric/transduodenal drainage. Bile duct stricture can be temporized with biliary stenting but long term success is limited. Despite the efficacy of endoscopic solutions, recent studies show that in selected patients surgical management may be superior. Such comparative studies underscore the importance of a multidisciplinary approach to patients with chronic pancreatitis and its complications.

IAP & JPS Joint Symposium Multidisciplinary Approaches to Treatment of Pancreatic Adenocarcinoma

JS-1

A Multicenter Phase II Trial of S-1 and Concurrent Radiotherapy for Locally Advanced Pancreatic Cancer

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Background: The aim of this trial was to evaluate the efficacy and toxicity of S-1 and concurrent radiotherapy for locally advanced pancreatic cancer (PC).

Methods: Locally advanced PC patients with histologically or cytologically confirmed adenocarcinoma who had no history of prior chemotherapy were enrolled in this study. S-1 was administered orally at doses of 80 mg/m^2 bid on the day of irradiation during radiotherapy. Radiation therapy was delivered through three or more fields at a total dose of 50.4 Gy in 28 fractions over 5.5 weeks, and no prophylactic nodal irradiation was given. A maintenance dose of S-1 (80 mg/m2/day for 28 consecutive days, followed by a 14-day rest period) was then administered until the appearance of evidence of disease progression or of unacceptable toxicity.

Results: The study completed accrual of 61 patients enrolled at 20 institutions between Jul/06 and Nov/07. Among the 59 evaluable patients, 16 achieved a partial response (27.1%; 95% confidence interval (CI), 17.4 to 39.6%). The median progression-free survival, overall survival and 1-year survival in the 60 evaluable patients were 9.7 months (95% CI, 6.9–11.6 months), 16.0 months (95% CI, 13.5–21.3 months) and 71.7% (95%CI, 59.2–81.5%), respectively. The serum CA19-9 level was reduced by more than 50% as compared to the pretreatment level in 34 (81%) of the 42 patients who had shown a pretreatment level of 100 U/ml or greater. The major grade 3–4 toxicities were leukopenia in 6 patients (10%) and anorexia in 4 patients (7%), and the other toxicities were also generally transient, with the exception of one treatment-related death due to perforation of the duodenum and biliary tract.

Conclusion: S-1 with concurrent radiotherapy exerted extremely favorable activity with mild toxicity in patients with locally advanced PC.

JS-2

Gemcitabine and S-1 Combination Therapy as a Second-line Therapy in Patients with Advanced Stage of Pancreatic Cancer

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Aim: Gemcitabine monotherapy or S-1 chemotherapy is the standard first-line therapy for advanced pancreatic cancer. After disease progression, there is no standard regimen available. This study was conducted to assess the efficacy and toxicity of gemcitabine and S-1 combination therapy (GS therapy) as a second-line therapy after failure of either G or S monotherapy in advanced stage of pancreatic cancer in clinical practice.

Methods: Patients (Pts) with histologically and/or clinically proven pancreatic adenocarcinoma were eligible for the study. Other eligibility criteria included: with confirmation of progressive disease while receiving standard G (n = 10) or S (n = 3) first-line chemotherapy, age ≥20 and ≤80 years, PS of 0 1 or 2, and adequate organ function, and written informed consent. G was given intravenously at a dose of 1,000 mg/m^2 over 30 min on days 1 and 8, and S was given orally at a dose of 40 mg/m^2 twice daily from day 1 to day 14, in 21-day cycles. Administration was repeated until the appearance of disease progression or unacceptable toxicity. Overall survival included toxicity was evaluated.

Results: There were 9 males and 4 females. The mean age of pts was 59.4 (45–76) years. Although no CR and PR was seen, a SD was achieved 56%, whereas 44% had PD. The median survival was 20 (range 2–112) weeks. The major grade 3–4 toxicities were leucopenia (38%), thrombocytopenia (8%), anorexia (0%), rash (0%), and fatigue (0%). Most hematological toxicity was transient. Median overall survival of the group who used GS second line therapy was 56 (range 17–141) weeks (36% events).

Conclusion: GS therapy produced a good survival associated with an acceptable toxicity profile in patients with G or S refractory advanced pancreatic cancer.

JS-3

Long-term Results of Curative Resection Following Pre-operative Chemoradiation in Patients with Pancreatic Cancer

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Aim: We investigated long-term results of surgical resection following pre-operative chemoradiation (pre-CRT) for patients with pancreatic cancer that extended beyond the pancreas.

Methods: This study is consisted of 68 pancreatic cancer patients who underwent surgical resection between 2000–2005. Of 35 patients who underwent pre-CRT between 2001–2004, 27 patients underwent surgical resection (pre-CRT group). The other 41 patients were classified as surgery-alone group. All patients were followed up for at least 54 months, and underwent no adjuvant therapy.

Results: A lower frequency of lymph node metastasis was observed in pre-CRT group, relative to surgery-alone group ($p < 0.05$). The frequency of residual tumor grading in pre-CRT group was significantly different from that in surgery-alone group (R0/1/2%:52/15/33 vs 22/51/27, $p = 0.004$). The overall 1/2/3/4 actual survival rates (82/52/37/30%) in pre-CRT group had a higher tendency, relative to 66/42/27/10% in surgery-alone ($p = 0.0541$). In R0/1 cases, actual overall and disease-free survival rates in pre-CRT group were significantly longer than in surgery-alone (overall 1/2/3/4 survival rate: 89/67/56/44% vs 80/50/33/13%, disease-free: 59/53/47/47 vs 53/32/12/12, $p < 0.05$). The rate of local recurrence in pre-CRT group was significantly less than in surgery-alone (11% vs 47%, $p = 0.0024$).

Conclusion: Surgical resection following pre-CRT might be associated with the higher rate of R0/1, and with the lower rate of metastastic lymph nodes, resulting in improved prognosis of patients with pancreatic cancer that extended beyond the pancreas. Actual 5 year survival rate in this study will be presented in Fukuoka.

JS-4

Preoperative Full-Dose Gemcitabine Combined with Concurrent 3-D Conformal Radiation and Subsequent Surgery for T3-Pancreatic Cancer

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Introduction: Surgical resection alone as a treatment for pancreatic cancer (PC) seems to afford the minimum survival benefit because of a high risk of distant and/or local failure even after curative resection. The aim of this study is to characterize the locoregional effect and surgical outcome of preoperative full-dose Gemcitabine combined with concurrent 3-D conformal radiation and subsequent surgery for T3-PC.

Method: 131 consecutive patients with T3-PC (UICC 6th edition), proven based on either histological or cytological examination, were included in this study. 3-dimensional radiation was targeted to the following fields and administered at a total radiation dose of 50 Gy with a daily fraction of 2 Gy five times/week: the primary pancreatic tumor, celiac and superior mesenteric arteries, retroperitoneal soft tissue, and para-aortic region. Intravenous administration of gemcitabine (1000 mg/m2) was initiated concurrently on days 1, 8, and 15 during each 4-week cycle; this was performed repeatedly for 3 cycles. Patients underwent restaging after completion of preoperative CRT and, in the eligible for resection, received the subsequent surgery.

Results: A total of 110 patients received the preoperative chemoradiation therapy (CRT) and subsequent surgery and the remaining 21 patients avoided resection due to the occurrence of unresectable factors (resection rate: 84.0%). Margin negative resection (R0) was achieved in 108 patients (98.2%). Positive for lymph nodal involvement was observed in 19 patients (17.3%). Although 73 out of 110 patients (66.3%) had primary tumors with vascular involvement at pretreatment staging, pathological vascular involvements were observed only in 18 (16.4%). The 5-year survival rate and 5-year local failure-free survival after resection were 56.9% and 88.9%, respectively.

Conclusion: This study demonstrated that preoperative full-dose Gemcitabine based CRT and subsequent surgery provided the low incidence of local failure and seemed promising for improved overall survival for patients with T3-PC.

JS-5

The Impact of Histological Tumor Destruction After Neoadjuvant Chemoradiotherapy for Locally Advanced Pancreatic Cancer Patients on Disease-free Survival

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Background: We performed neoadjuvant chemoradiotherapy (NCRT) for locally advanced pancreatic cancer patients. The objective was to evaluate whether histological tumor destruction after NCRT affects survival following pancreatectomy.

Patients and Methods: We reviewed our pancreatic surgery database (April 2005 - October 2009) and identify the 36 patients who underwent resection after NCRT for UICC-T3 pancreatic cancer. The median follow-up period was 16 months (3–50 months). Histological examination of the tumor destruction was evaluated according to Evans's histopathological criteria. We divided the 36 patients into the two groups; Group A (n=10): more than 50% of tumor destruction and Group B (n=26): less than 50% of tumor destruction.

Results: The 1-, 2- and 3- year overall survival rates (OS) were 75.8%, 48.3% and 42.3%, and median OS was 14 months. The 1-, 2- and 3- year disease-free survival rates (DFS) were 58.4%, 46.1% and 38.4%, and median DFS was 10.5 months. Serum CA19-9 levels decreased to less than half of the pretreatment levels in 7 (70%) cases of group A and in 15 (58%) of group B. The 1-, 2- and 3- year OS were better in group A than those in group B, despite no significant differences (90.0%, 66.7%, 66.7% v.s. 69.6%, 38.0%, 28.5%, p=0.1072). The 1-, 2- and 3- year DFS were significantly higher in group A than in group B (80.0%, 66.7%, 66.7% v.s. 55.5%, 37.0%, 18.5%, p=0.0445). Three out of 10 patients in group A developed cancer recurrence and all of them had distant metastasis. Fifteen out of 26 recurred in group B and almost of them had distant metastasis and only one had locoregional recurrence.

Conclusions: Our challenge for UICC-T3 pancreatic cancer patients by means of NCRT is feasible and effective, especially as to disease-free survival. Histological tumor destruction after NCRT is one of the important prognostic factors.

JS-6

Perioperative Chemotherapy for Pancreatic Cancer

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Introduction: Systemic recurrence occurs with a high probability even after curative resection of a pancreatic lesion in patients with pancreatic cancer (PC). This indicates that subclinical metastases might be already present in most patients at the time of operation.

Patients and Methods: We have introduced a novel multimodality therapy composed of pancreatic resection and intraoperative radiation therapy (IORT) combined with neoadjuvant (NAC) and adjuvant (AC) combination chemotherapy for patients with PC. For NAC, 5-FU was administered at a dose of 125 mg/m2 on days 1–5 every week as a continuous pancreatic and hepatic arterial infusion, and gemcitabine (GEM) was infused intravenously at a dose of 800 mg/m2 once weekly for 2 weeks. Pancreatic resection combined with IORT (30 Gy, 12 Mev) was performed after a one-week rest following the completion of NAC. AC was performed in the same regimen as NAC after the recovery from surgery. We performed intension to treat analyses.

Results: This study enrolled 44 patients. The most common toxicities were hematological and gastrointestinal events. Toxicities in postoperative chemotherapy were more critical and frequent than preoperative ones. There was no perioperative chemotherapy associated death. Median follow up time was 30.0 months. Median survival time (MST) was 33.0 months with a 30.5% of the overall 5-year survival. Average relative dose intensity of perioperative 5-FU and GEM was 54.8% and 72.0%, respectively. Based on Spearman correlation analysis relative dose intensity (RDI) of GEM was statistically correlated with survival (p=0.0065), although there was no statistical correlation between RDI of 5-FU and survival. MST was 36.5 months in those who received more than 50% of the RDI of GEM, significantly longer than in those who received less than 50% of the RDI (p=0.0001).

Conclusions: This treatment contributes to survival of pancreatic cancer patients . RDI of GEM was statistically correlated with survival.

JS-7

Postoperative Adjuvant Treatment for Resected Pancreas Ductal Adenocarcinoma

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Surgical resection still remains the only potentially curative therapeutic modality for pancreas ductal adenocarcinoma, but local recurrences or systemic metastases are very common even after extended L/N and nerve plexus resection in addition to standard pancreaticodu-

odenectomy. Therefore, local or systemic adjuvant treatment was required and expected to have an impact to reduce both local and systemic recurrences.

So, several controlled randomized studies were conducted to evaluate the efficacy of postoperative adjuvant treatment for resectable pancreas cancer. First RCT from GITSG in 1984 demonstrated the over-all survival benefit with chemoradiation with bolus 5-FU. (median survival 20 months vs 11 months, 5 YSR 18% vs 8%) Second RCT was published by the EORTC in 1999. They compared 5-FU and concurrent radiotherapy group with observation group following resection for PDCA. However, they did not recommend routine use of adjuvant chemoradiotherapy because of small survival benefit. Third RCT published in 2001 was the adjuvant ESPAC-1 study. They showed definite survival benefit in chemotherapy group especially following pathologically curative resection, but not in chemoradiation group. The CONKO-001 (Charitie Onkologie) trial published in 2007 evaluate gemcitabine vs surgery alone following complete resection of pancreatic cancer and demonstrated a statistically significant improvement in disease-free survival without an improvement in over-all survival. ROTG 97-04 trial published in 2008 showed better survival tendency in gemcitabine and chemoradiation group compared with 5-FU and chemoradiation group. (median survival 20.5 months vs 16.9 months, 3 YSR 31% vs 22%, P=.09) As described above, indications and method as well as the role of adjuvant treatment for resectable pancreas cancer is still controversial in spite of several RCT.

Recently published three retrospective studies suggested that adjuvant treatment is effective only for advanced stage pancreas cancer or R1 resection group. Further randomized controlled studies seem to be required.

JS-8

Efficacy of a Novel Postoperative Adjuvant Strategy for Resectable Pancreatic Cancer

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Introduction: It has been recently reported that adjuvant gemcitabine (GEM) prolonged postoperative disease-free survival in resectable pancreatic cancer. However, the efficacy was limited and further studies are clearly required to improve prognosis. In particular, postoperative hepatic recurrence still often occurs even after GEM treatment and needs to be overcome.

Methods: To establish novel postoperative adjuvant strategy, we are currently trying to evaluate the efficacy of combination therapy of high-dose 5-FU arterial infusion with systemic GEM under the IRB approval. Patients received weekly high-dose 5-FU (WHF: 1g/m^2 /5hours) through the hepatic artery using a port-catheter system plus concurrent systemic GEM (1g/m^2 /0.5hour). We hypothesized that this regimen might have a synergistic effect on hepatic recurrence, thereby resulting in prolongation of patient survival.

Results: Thirty-one patients were enrolled. To induce maximum efficacy of arterial infusion chemotherapy while avoiding adverse effect, blood supply alteration by interventional radiological techniques was performed in 9 cases (29%). The toxicity was acceptable and this regimen was well feasible as an outpatient treatment. In 107 patients as a historical control, the median disease-free survival time (DFS) was 180 days. In addition, hepatic recurrence was occurred in 49%, and the time to hepatic recurrence was 220 days. By sharp contrast, the DFS was 449 days in treated group and four patients (12.9%) developed hepatic recurrence on 432 days after surgery. Thus, this treatment significantly delayed the development of postoperative recurrence and inhibited hepatic recurrence (P=0.0004 and P=0.0006, respectively, vs. controls). Furthermore, 100% one-year survival could be achieved, while it was 56.7% in control group (P=0.0008).

Conclusion: Our novel postoperative adjuvant strategy had a significant therapeutic efficacy, especially on the inhibition of hepatic recurrence. The treatment may lead to a breakthrough for the patients with resectable pancreatic cancer.

JS-9

Multidisciplinary Therapy for Pancreatic Cancer: From Surgery to Immuno-chemotherapy

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Surgical resection has only a chance to lead the cure for the patients with pancreatic cancer. However, pancreatic cancer demonstrates the high incidence of recurrence, and survival rate still remains low. Since 1987, we performed intra-arterial infusion chemotherapy using 5-FU for postoperative chemotherapy to prevent hepatic metastasis. Moreover, we performed systemic chemotherapy by gemcitabine against recurrence including local recurrence. The 5-year survival rate and median survival time (MST) were 13.2% and 410 days, respectively, for resectable pancreatic cancer patients. Multivariate analysis demonstrated that postoperative chemotherapy by gemcitabine was predicted the factor to improve the survival for resectable pancreatic cancer patients (P<0.01), and we perform a postoperative chemotherapy using gemcitabine (1,000mg/m^2, 6 cycle). Both the MST of JPS-stage III patients and MST of JPS-stage IV patients were prolonged by postoperative chemotherapy by gemcitabine (JPS-stage III, 1,077 days vs. 449 days, P=0.013; JPS-stage IVa, 505 days vs. 264 days P=0.033; JPS-stage IVb, 377 days vs. 172 days, P=0.018), resulting that postoperative chemotherapy was essential for pancreatic cancer patients. For marginal resectable pancreatic cancer patients, preoperative therapy is possible to improve the survival after operation. The standard regimen is thought to be established for the marginal resectable pancreatic cancer. On the other hand, we conduct approaches to the problem for unresectable pancreatic cancer. One is a new immuno-chemotherapy using combination of gemcitabine and peptide targeting the anti-angiogenesis of vascular endothelial growth factor. Optimal dose was indicated by a phase I trial, suggesting the improvement of the survival for unresectable pancreatic cancer. Now, the phase II/III trial is ongoing. The other is S-1 of alternate-day regimen. Only 25% (2/8) patients show a hema-

tological adverse effect, however, 2 patients can continue S-1 of alternate-day regimen.

Conclusion: Pre-operative therapy and postoperative therapy are keys to improve the prognosis of the patients with pancreatic cancer.

JS-10

Multidisciplinary Approach for Pancreatic Cancer in Korea

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Most of the pancreas cancer patients present with advanced disease at diagnosis, with 10~20% of patients diagnosed at resectable stage. Perioperative complication and mortality rate has declined significantly with the improvement in operative techniques, however, despite "potentially curative" resection for pancreatic carcinoma the 5-year survival in these patients is less than 20%.

The GITSG trial showed a survival advantage with postoperative chemoradiotherapy. However, ESPAC-1 study, failed to show a survival benefit with chemoradiotherapy. Instead, postoperative chemotherapy with 5-fluorouracil (5-FU) and leucovorin (LV) demonstrated a survival benefit. In CONKO-001 study, adjuvant chemotherapy with gemcitabine rendered a trend toward overall survival benefit. In ESPAC-3 trial, 5-FU/LV was compared with gemcitabine. In this study, gemcitabine was not superior to 5-FU/LV, however, safety profile was better with gemcitabine. Despite these efforts, the outcome of resected pancreatic cancer remains poor.

To improve the outcome further, a multimodality adjuvant treatment protocol incorporating adjuvant chemotherapy and chemoradiotherapy was developed and tested at the Seoul National University Hospital. A similar approach has been tested for locally-advanced pancreatic cancers. The results of these trials will be discussed at the meeting.

JPS Symposium 1 Recent Advances in the Imaging Studies of Pancreatic Diseases

JPSY1-1

Usefulness of New Ultrasonography Techniques Using Sonazoid in Pancreatic Diseases

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Introduction: Recently, several investigators have reported the usefulness of contrast-enhanced ultrasonography (CEUS) in the detection, diagnosis, and characterization of pancreatic tumors. Moreover, the appearance of CEUS with the second generation contrast agent of low MI, Sonazoid, has led to an extension of its use from screening to qualitative diagnosis.

Aim: The aim of our study is to evaluate whether the new techniques with Sonazoid of ultrasound imaging lead to improvements in the diagnostic performance of pancreatic mass lesions compared to standard method with Levovist.

Methods: The subjects were 50 cases confirmed histologically. 30 pancreatic carcinomas, 7 mass forming pancreatitis, 3 solid-pseudopapillary neoplasms, 3 metastatic pancreatic tumor, 3 endocrine tumors, 4 pancreatic cystic tumors. The ultrasound used was Aplio (Toshiba) and the contrast agents were Sonazoid and Levovist. DI and MFI with Sonazoid and standard methods with Levovist were used to observe the hemodynamics and microvasculature in the lesions and their peripheries.

Results: While most lesions were classified into the same enhancement pattern with both contrast agents (the rate of concordance; 85%), the microvasculature and hemodynamics in the tumor could be clearly visualized in real time in DI and MFI with Sonazoid. The imaging with Levovist has been based mainly on assessing the extent of the enhancement pattern of tumors and therefore it has been difficult to clearly visualize the microvasculature in the tumors. The grade of visualization of eanhancement patterns and microvasculature with Sonazoid compared to Levovist was excellent. The diagnostic precision in using Sonazoid was better than that of Levovist in contrast to pathological diagnosis (the rate of improvement; 8%).

Conclusion: The use of DI and MFI with Sonazoid results in better visualization of the microvasculature in mass lesion than Levovist. This study indicated that the new techniques led to improvements in diagnostic performance of pancreatic disease.

JPSY1-2

Sonazoid-enhanced US and EUS for Pancreatic Diseases

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Purpose: In this study, the usefulness of Sonazoid-enhancement in pancreatic diseases was evaluated by external US and/or EUS.

Subjects & Methods: Twenty-two cases in which contrast-enhanced (CE)-US was performed from June, 2007 to November, 2009 and 9 cases in which CE-EUS was performed from October to November, 2009. Differences in the effect of Sonazoid-enhancement in different diseases were studied. For liver metastasis detection, comparisons were studied with CT and MRI.

Results: CE-US and/or CE-EUS was performed in 10 cases of pancreatic carcinoma, 7 cases of IPMN, 1 case of pancreatic carcinoma & IPMN, 1 case of neuroendocrine tumor, 1 case of acinar cell carcinoma, and 2 cases of chronic pancreatitis. In all cases of pancreatic carcinoma, a mass with less blood flow compared to the surrounding pancreatic parenchyma was evident. In IPMN, there was no enhancement effect in cysts and debris. Nodular elevations were easily identifiable based on blood flow. Neuroendocrine tumors showed abundant blood flow. In the 1 case of acinar cell carcinoma, the lesion was diagnosed as splenic vein thrombosis before enhancement, but was found upon enhancement to be a tumor extending into the vein. Two cases of chronic pancreatitis showed enhancement equivalent to that of the surrounding pancreatic parenchyma. Liver metastases were observed in 3 out of 22 cases. More lesions of liver metastases were detected compared to CT in one case and MRI in another case.

Conclusions: CE-US and EUS can be used to reliably and objectively detect subtle lesions based on comparison of blood flow between a lesion and its surroundings.

JPSY1-3

Dynamic Quantification of Contrast-enhanced Endoscopic Ultrasonography for Diagnosis of Pancreatic Diseases

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Background: The usefulness of endoscopic ultrasonography (EUS) for diagnosing pancreatic diseases is widely recognized, on the other hand, the characteristic vascularity of each disease is well known. Further improvement of the diagnostic accuracy using second-generation ultrasound contrast agents has recently been expected. Objective: Investigation of the usefulness of contrast-enhanced EUS (CE-EUS) for the differential diagnosis of pancreatic diseases.

Patients and Methods: Patients who underwent CE-EUS at our institute between January 2007 and March 2008 were analyzed retrospectively. Twenty-nine patients with pancreatic ductal cancer (PC), 9 with autoimmune pancreatitis (AIP), 9 with mass-forming pancreatitis (MFP), and 10 with pancreatic endocrine tumor (PET). Contrast agent, Sonazoid(R) (Daiichi Sankyo, Tokyo, Japan), was injected intravenously. Time-intensity curve (TIC)-based quantitative evaluation of the pancreatic diseases, association between the TIC of PC and histopathological type, and performance of EUS in combination with TIC to diagnose benignancy or malignancy were assessed. This study was approved by the Institutional Review Board of our institute, and performed after obtaining written informed consent from the patients.

Results: The echo brightness (EB) reduction rates from the peak at 1 and 3 minutes after the injection of contrast agents were the greatest in PC, followed by MFP, AIP, and PET ($p < 0.05$). The EB reduction rate at 1 minute was significantly greater in PC than AIP and MFP. The EB reduction rate was greater in histologically well-differentiated PC. Sensitivity, specificity, and accuracy of the diagnoses of benignancy and malignancy by EUS were 82.3, 88.9, and 85.1%, respectively.

Conclusions: The CE-EUS with the dynamic quantitative analysis of TIC increased the diagnostic accuracy for pancreatic diseases, and may predict the differentiation grade of PC.

JPSY1-4

Contrast-enhanced Harmonic Endosonography in Diagnosing Pancreatic Diseases

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Background: EUS is superior to any other modality with respect to spatial resolution. Sonazoid, produce harmonic signals at lower acoustic powers, and are therefore suitable for EUS imaging at low acoustic powers. We have recently developed EUS system specifically for contrast-enhanced harmonic EUS (CH-EUS).

Materials: EUS was performed an echoendoscope (GF-UE260-AL5) and ALOKA ProSound α-10 (ALOKA Co. Ltd., Tokyo, Japan) using Extended Pure Harmonic Detection (ExPHD) mode was employed.

Patients and Methods: A total of 553 patients suspected of having pancreatic diseases underment fundamental B-mode EUS (FB-EUS), CH-EUS and contrast-enhanced computed tomography (MDCT). CH-EUS was imaged after infusion of Sonazoid (15μ/kg) in a real-time fashion, following the initial screening by FB-EUS. Among 214 lesions with histological diagnosis, diagnostic ability for depicting pancreatic tumors were compared between MDCT, FB-EUS and CH-EUS.

Results: FB-EUS depicted 197 hypoechoic solid tumors in the pancreas, which were classified into 4 patterns; Type I (Avascular), Type II (Hypovascular), Type III (Isovascular) and Type IV (Hypervascular) by CEH-EUS. Most lesions with Type II pattern (93%) and Type IV pattern (73) were ductal carcinomas and endo-

crine tumors, respectively. On the other hand, all lesions with Type I pattern and 70% of lesions with Type III pattern were fatty necrosis and tumor-forming focal pancreatitis, respectively. Among 27 cystic lesions in the pancreas, FB-EUS depicted intra-cystic structure in 17 lesions, 13 and 4 of which were confirmed as mural nodules with enhancement and mucous clots without enhancement by CH-EUS, respectively. The values of sensitivity in depicting pancreatic neoplasms by CH-EUS (97%) were significantly higher than that of MDCT (89%). Particularly, the sensitivity in depicting mural nodules was remarkably different between the 2 imaging modalities (CH-EUS 87%, MDCT 40%).

Conclusion: CH-EU is useful for differential diagnosis of small lesions that FB-EUS detected in the pancreatic region.

JPSY1-5

Usefulness of Endoscopic Ultrasound in the Diagnosis of Early Chronic Pancreatitis

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The clinical course of chronic pancreatitis (CP) leads to a high rate of morbidity and mortality over a 20- to 25-year period. Therefore, it's important to diagnose it at its early stage and for optimal management. Endoscopic ultrasound (EUS) provides excellent detail of parenchyma and duct which are not detectable by other imaging modalities, because of its ability to place the transducer in close proximity to the pancreas. Therefore, EUS can detect the minimal changes of duct and parenchyma, and will represent early CP. Traditional EUS criteria for CP include hyperechoic foci, hyperechoic strands, lobularity, duct irregularity, hyperechoic ductal margins, visible side branches, duct dilation, calcifications and cysts. EUS can indicate high sensitivity and specificity (> approximately 85%) in diagnosis depending on the number of criteria present. In general, presence of early CP is diagnosed when EUS revealed 2–4 of above features. Although EUS are inter-observer variability may affect interpretation, the authors demonstrated the diagnosis of CP on the basis of EUS criteria was objectively supported by quantitative analysis of EUS images using computer analysis. Thus, we believe EUS can objectively distinguish between normal pancreas and early CP. Recently, however, it is considered that individual EUS criterion has its own importance in CP grading. Thus, to discriminate against EUS features in every stage of CP, each EUS criterion was made reviews. Recent consensus meeting of EUS for CP proposed the new EUS diagnostic criteria in consideration of value of each EUS finding (Rosemont classification, GIE 2009). In the Japanese criteria for CP 2009, diagnostic criteria for early CP are indicated using 7 features as specific EUS findings on the basis of the Rosemont classification. Because EUS is useful modality for diagnosing CP without invasiveness, understanding the role of EUS for diagnosis of early CP is important in clinical practice.

JPSY1-6

Preoperative Diagnosis of Small Pancreatic Cancer by MDCT, DWI, and EUS

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Aim: To retrospectively evaluate the diagnosis of small pancreatic cancer (TS1 = tumor size 2 cm or less) using Multidetector-row CT (MDCT), diffusion-weighted imaging (DWI), and EUS.

Patients and Methods: Between April 1997 and June 2009, 629 cases of pancreatic cancer were diagnosed at our institution. Surgical resection was performed in 138 (21.9%) cases. Histopathological evaluation of the surgical specimens classified 31 (4.9%) cases (18 men, median age 68) as TS1. Evaluation targets included: (1) the number of TS1 cases identified before and after introduction of MDCT and after introduction of DWI, (2) mass detection rates by MDCT, DWI, and EUS, (3) other findings in cases where no mass was detectable by MDCT and DWI, and (4) comparison of preoperative and postoperative diagnosis.

Results: (1) 6 cases were diagnosed as TS1 before the availability of MDCT, and 25 cases were diagnosed subsequently. In 8 of the 31 cases, DWI was performed. (2) The rates of mass detection by MDCT, DWI, and EUS were 80% (20/25), 75% (6/8), and 100% (31/31). In DWI, apparent diffusion coefficient (ADC) average value was 1.59*10–3mm^2/sec, and lesion spine ratio (LSR) average value was 0.85. (3) In cases where MDCT failed to detect a mass, it detected indirect findings: bile duct dilatation, pancreas duct dilatation, and pancreatic cysts. In 2 cases where DWI failed to detect a mass, EUS provided the final diagnosis. Only 1 case was diagnosed as SPN by CT and EUS preoperatively. ADC value in this case was 1.618, but LSR was 1.20 suggesting malignancy.

Conclusions: In the diagnosis of small pancreatic cancer MDCT is valuable, as it can detect not only masses, but also indirect findings. DWI may also contribute to the diagnosis of pancreatic cancer. In some cases where confirmation of a diagnosis is difficult using MDCT and DWI, EUS is useful.

JPSY1-7

Intraductal Ultrasonography Is Useful for the Assessment of Lateral Spread Along the Main Pancreatic Duct in Branch-duct Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Background: Intraductal papillary mucinous neoplasms of the pancreas (IPMNs) tend to spread intraepithelially along the pancreatic duct wall.

Objective: To evaluate the usefulness of intraductal ultrasonography (IDUS) for preoperative diagnosis of intraductal lateral spread (LS) along the main pancreatic duct (MPD) in branch-duct IPMNs.

Patients and Methods: Twenty-four patients with branch-duct IPMNs who had undergone preoperative IDUS and surgery were included in this study. The efficacy of LS assessment by IDUS was evaluated by comparing preoperative IDUS findings and histological findings.

Results: LS along the MPD was observed in 54% of the subjects, the mean length being 25.2 +/-16.8 mm (5–50 mm). The mean maximum diameter of the MPD was 6 mm or greater in those patients. Of the patients with LS, those in whom the length of LS along the MPD was longer than the diameter of the cystic dilated branch accounted for 30%. The sensitivity, specificity, and overall accuracy of IDUS in the detection of LS were 92%, 91%, and 92%, respectively.

Conclusions: Preoperative transpapillary IDUS is useful for the detection of LS in patients with branch-duct IPMN, especially in those with a MPD 6 mm or greater in diameter, and is deemed to contribute to the determination of the resection line in surgical candidates.

JPSY1-8

CT Perfusion Imaging of the Pancreas

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Perfusion CT is an exciting CT technology that allows functional evaluation of tissue vascularity. Because of rapid technologic advancements in CT systems (multidetector and dual energy CT) and the availability of commercial software, perfusion CT offers a wide array of clinical and research applications. Currently, the major clinical applications of perfusion CT are in acute stroke and oncology. Interestingly, both of these applications have been stimulated by the development of new therapeutic options: thrombolysis in acute stroke and anti-angiogenesis therapy for tumors. In the field of oncology, perfusion CT has found applications in diagnosis, staging, prognostic evaluation, and monitoring of response to therapies.

The perfusion values of normal human pancreas show an age-dependent physiologic decline. It was reported that pancreatic perfusion values were higher in patients who had Wilson's disease and reduced in patients who had diabetes and in failing pancreatic transplants. In acute pancreatitis, perfusion CT has been found to have a sensitivity and specificity of 100% and 95.3%, respectively, in detection of pancreatic ischemia. Substantially high blood perfusion was observed in hypervascular tumors, such as insulinomas, compared with background pancreatic parenchyma.

CT perfusion has been used to evaluate tumor vascularity in pancreatic cancer and to determine whether CT perfusion can predict tumor response to chemoradiotherpy and antiangiogenic treatment. Park and colleagues found that tumor with high baseline perfusion values tended to have a good response to combined chemoradiotherapy. High perfusion values in association with a good response to combined chemoradiotherapy can be explained by increased cytotoxic effects and better delivery of the chemotherapeutic drug to the tumor, resulting in increased radiosensitization.

JPSY1-9

Pancreatic Perfusion Analysis of Autoimmune Pancreatitis

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Background: Steroid therapy for the patients with autoimmune pancreatitis (AIP) is effective. However, AIP patients sometimes relapse demonstrated during clinical course. It is currently unclear whether it is possible to predict early AIP relapse by serum and imaging tests. Histopathological findings of AIP are mainly characterized by lymphoplasmacytic pancreatitis (LPSP) in Japan. Because the obstructive phlebitis is one of the typical histological findings in LPSP, pancreatic perfusion may be attenuated in AIP.

Aim: The aim of this study is to clarify whether the pancreatic perfusion computerized tomography (CT) analysis can predict AIP relapse.

Methods: 1) Patients: Clinical records of 4 AIP patients were retrospectively investigated. All 4 patients were male. Mean age of these patients was 65.3 years old. The results of imaging tests showed typical AIP features in all patients. The results of serum IgG4 were high level (>135 mg/dL) in all patients and the average of IgG4 was 529.3 mg/dL. Serial perfusion CT analyses were performed before and after the initial steroid therapy. 2) Perfusion CT protocol: a 16-slice helical CT scanner (Somatome Definition; Siemens Co.) was used in this study. Perfusion CT was performed after a injection of 40ml iodixanol at a rate of 5mL/second via antecubital vein using a 20-G needle. A deconvolution method (Ziostation: Ziosoft Co.) was used in this analysis to estimate pancreatic blood flow (mL/100g/min).

Results: One patient relapsed after initial steroid therapy and no significant difference of pancreatic blood flow was observed before (132.5mL/100g/min) and after (130.7mL/100g/min) steroid therapy. In contrast the pancreatic blood flow of AIP patients (n=3) without relapse were increased from 110.7mL/100g/min to 191.3mL/100g/min after steroid therapy.

Conclusion: Pancreatic perfusion analysis may predict AIP relapse.

JPSY1-10

Ischemia Penumbra in Early Stage of Severe Acute Pancreatitis

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Introduction: In cerebral ischemia, there are two major zones of injury: the core ischemic zone and the "ischemic penumbra". The ischemic penumbra is generally used to define ischemic but still viable tissue. Similarly, ischemic pancreatitis can lead to necrotizing

pancreatitis. However, not all ischemic pancreases develop necrosis. In these regard, we investigated about ischemic penumbra in early stage of severe acute pancreatitis (SAP).

Methods: Seventy-six consecutive patients with SAP were enrolled. Of all enrolled patients, we divided the pancreas into three areas, the head, body and tail, and measured pancreatic blood flow (PBF) and volume (PBV) in each area by perfusion CT with one compartment method, within three days after symptoms onset. Three weeks later, all patients underwent contrast-enhanced CT to diagnose each area with or without development of pancreatic necrosis.

Results: Of the 228 pancreatic areas from 76 SAP patients, 30 areas were diagnosed as positive for pancreatic necrosis. PBF and PBV in areas developed pancreatic necrosis were significantly lower than those in areas without development of necrosis (37.5±51.6 vs 164.8±92.9 ml/min, $p<.01$ and 3.4±2.6 vs 8.4±8.8%, $p<.01$). Of 19 areas (PBF<37.5 ml/min and PBV<3.4%), all areas developed pancreatic necrosis. Of 60 areas (PBF≥37.5 ml/min and PBV<3.4%), 7 (11.7%) developed necrosis. Of 7 areas (the PBF<37.5 ml/min and PBV≥3.4%), 4 (57.1%) developed necrosis. In 142 areas (PBF≥37.5 ml/min and PBV≥3.4%), no area developed necrosis.

Discussion: If PBF and PBV were high, the area did not develop necrosis. If PBF and PBV were low, the area developed necrosis. If PBF or PBV was low, not all area developed pancreatic necrosis, thus, it was considered that the area could include ischemic penumbra.

JPSY1-11

Computed Tomography Reflected Endocrine Function of Pancreas

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In this study, we examined the correlation between CT parameters and endocrine parameters (blood glucose and HbA1c) of the pancreas. Sixty eight patients were underwent enhanced CT for pancreatic disease from January to December in 2008. CT parameters including volume, arterial phase density, portal phase density and its ratio of the pancreas were measured with OsiriX imaging software. We divided patients into two groups by median of each CT parameters and compared blood glucose and HbA1c. Stepwise multiple regression analysis was performed for detecting the most useful CT parameter for assessment of endocrine function. Blood glucose level tended to be lower in larger volume group than smaller volume group and HbA1c level was significantly lower in larger volume group compared to the smaller volume group ($p=0.04$). Grouping by arterial phase density, blood glucose level was significantly lower in higher arterial density group than that of lower group ($p=0.0007$). Grouping by A/P ratio, blood glucose was significantly lower in higher A/P ratio group than that of lower A/P ratio group ($p=0.0007$) and Stepwise multiple regression analysis showed A/P ratio was the most strongly correlated with blood glucose ($F=7.82$, $p=0.007$). CT is the useful modality for evaluation of pancreatic endocrine function.

JPSY1-12

Quantitative MR Imaging of the Pancreas: Parameteric Exploration

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Magnetic resonance (MR) imaging plays an increasingly important role in the evaluation of patients with pancreas disease because of its high contrast resolution, lack of ionizing radiation, and the possibility of performing functional imaging sequences. In fact, MR imaging, as a completely noninvasive technique, can provide quantitative assessment of perfusion, diffusion, viscoelasticity and metabolism, yielding diverse information about pancreatic function. With advances in hardware and coil systems, diffusion-weighted (DW) MR imaging and perfusion MR imaging can now be applied to pancreas imaging with improved image quality. Perfusion MRI can be used for the characterization of focal pancreatic diseases and the quantification of blood flow parameters. It also can be used for evaluating pancreatic functional changes related to type II diabetes. An extended new application is the evaluation of the therapeutic effect of antiangiogenic drugs on pancreatic tumours. In addition, measurement of apparent diffusion coefficient (ADC) of the water molecules through tissues has developed into another useful tool in the characterisation of pancreatic lesions and in the evaluation of diffuse pancreataic disease. Another novel method, MR elastography, has already been established as the only technique able to stage hepatic fibrosis and expected to be applicable for evaluating fibrotic changes of the pancreas. In addition, degree of malignancy of focal pancreatic lesions can be accurately determined with MR spectroscopy.

JPSY1-13

Recent Advances in Intraoperative Diagnostic Techniques for Pancreatic Cancer

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We have been aggressively performing extensive surgical resections for pancreatic cancer using a non-touch isolation technique. The presence of a cancer-free dissected peripancreatic tissue margin is the most important prognostic factor. Accurate diagnosis of peripancreatic tissue invasion and distant metastases are necessary for determining the treatment strategy and patient prognosis. Intraoperative findings represent the best diagnostic tool for pancreatic cancer.

To obtain an accurate intraoperative diagnosis of the extent of pancreatic cancer invasion, we use both intraoperative ultrasound (IOUS) and intraportal endovascular ultrasonography (IPEUS). For the intraoperative diagnosis of liver metastasis, we use real-time tis-

sue elastography (RTE). With regard to the IPEUS technique, we use an 8-French catheter with a rotating radial 20-MHz transducer. The axial resolution using this technique is 120microm and tissue penetration is 20 mm. IPEUS was the most reliable modality for the diagnosis of portal vein invasion.

Intraoperative differential diagnosis of liver metastases is also important for adequate surgical management. IOUS is indispensable to evaluate the existence and location of liver tumors. However, small and iso-echoic tumors are sometimes difficult to detect. Surgeons usually detect liver metastases by palpation. Until quite recently, it had been impossible to objectively determine the extent of tissue elasticity, which is obtained though palpation. However, the development of RTE has made it possible to visualize and share the information about tissue elasticity and to avoid any physician bias. RTE can be performed at the same time as routine IOUS examination using the high-end Hitachi EUB 8500 (Hitachi Medical, Tokyo, Japan) with a 6–13MHz liner electronic probe. Intraoperative RTE enabled us to accurately distinguish between benign tumors and liver metastases of pancreatic cancer.

In conclusion, intraoperative examinations are important for correctly diagnosing the extent of cancer invasion, and help to optimize surgical resection for the treatment of pancreatic cancer.

JPSY1-14

Mass-forming Autoimmune Pancreatitis and Pancreatic Carcinoma: Differential Diagnosis on the Basis of CT, MRCP, and Diffusion-weighted MR Images

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Purpose: To differentiate mass-forming autoimmune pancreatitis (AIP) from pancreatic carcinoma using CT and MR imaging findings.

Materials and Methods: We retrospectively reviewed CE-CT, MR MRCP, and DWI for 10 patients with 11 mass-forming AIP and for 70 patients with pancreatic carcinoma. We evaluated the following findings: contrast-enhancement pattern, capsule-like rim, calcification, cyst, bulging contour, distal pancreatic atrophy, and appearance of the common bile duct and main pancreatic duct (MPD). Lesion visibility on DWI was determined and the apparent diffusion coefficient (ADC) was calculated. The sensitivity, specificity, and odds ratio of significant radiological findings were calculated.

Results: Seven radiological findings (early homogeneous enhancement, delayed homogeneous enhancement, capsule-like rim, absence of distal pancreatic atrophy, smooth MPD stenosis, MPD upstream dilatation < 4 mm, and ADC < 0.88 x 10^{-3} mm^2/s) were found to be significant for differentiation of mass-forming AIP from pancreatic carcinoma ($P < .05$). When delayed homogeneous enhancement and ADC < 0.88 x 10^{-3} mm^2/s were used in combination, the sensitivity and specificity for diagnosing mass-forming AIP were 100% and 98%, respectively. When 4 of the 7 findings were used for the diagnosis of mass-forming AIP, a sensitivity of 91% and specificity of 100% were achieved.

Conclusion: Specific radiological findings can help differentiate mass-forming AIP from pancreatic carcinoma with high accuracy.

JPSY1-15

The Usefulness of PET/CT and Diffusion MRI in Pancreatic Cancer

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Objective: SUVs of FDG-PET are semi-quantitative and are affected by various factors (e.g., blood sugar, tumor diameter, examination time following FDG injection). Although SUVmax may be a prognostic factor, it is especially difficult to predict the survival of low-SUVmax patients from our previous study. On the other hand, in the diffusion MRI the apparent diffusion coefficient (ADC) is measured as an index. In this study, we examined the significance of SUV and ADC from the viewpoint of prognosis in pancreatic cancer.

Methods: The subjects were 23 pancreatic cancer patients who underwent PET/CT and diffusion MRI. The acquisition time of PET/CT was 60 min after FDG injection and SUVmax were measured. Diffusion MRI was performed with a b-factor of 1000sec/mm2 and ADCmin was measured. The survival times were compared among the patients who were divided into two groups at median SUVmax and ADCmin using the Kaplan - Meyers and log-rank test.

Results: The UICC stages were as follows: stage II; 4, stage III; 3, stage IV; 16. The therapeutic modalities were as follows: surgery; 4 patients, chemotherapy; 19 patients. SUVmax ranged from 3.33 to 11.33 with a median value of 8.33. ADCmin ranged from 0.50 to 1.46 with a median value of 0.81. The median survival time in all patients was 262 days. There was no correlation between SUVmax and ADCmin. Each patient in the high-SUVmax group and low-ADCmin group had a poor prognosis although it was not significant. Moreover when we divide the low-SUV max group into two groups by the value of ADCmin, low ADCmin patients in the low-SUVmax group had a poor prognosis (MST low 300, high 420 days, $p = 0.07$).

Conclusion: Using ADC and SUV, we may predict the prognosis more precisely in pancreatic cancer patients.

JPS Symposium 2 Translational Research for Future Therapy of Pancreatic Cancer

JPSY2-KN

Chromatin-Mediated Regulation of the Tumor Microenvironment Reveals Future Therapies for Pancreatic Cancer

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Studies on the role of the tumor microenvironment are emerging as one of the most promising areas in Pancreatic Cancer research. This field has recently been fueled by demonstrations that: 1. co-implantation with stellate cells favors the growth of pancreatic epithelial tumor cells and 2. significant decrease of desmoplastic reaction in mice in vivo reduces tumorigenesis. Therefore, we and others are trying to better understand the biology and remodeling of the tissue microenvironment, as well as to discover new signaling and transcriptional pathways which can be exploited therapeutically. We demonstrate that genes in the tissue microenvironment cannot only act as tumor promoters, but others behave as tumor suppressors. These pathways are being studied with the final goal of developing combinatorial therapies that by targeting the epithelial cell (conventional therapy), together with pathways from the tumor microenvironment (new therapy arm), may help to more efficiently treat pancreatic cancer. Thus, from the biology to its therapeutic promises, studies on the tumor microenvironment are a promising frontier in Pancreatic Cancer research.

JPSY2-1

Blockade of Tumor-stromal Interaction by Inhibiting CXC Chemokine/CXCR2 Axis as a Potent Therapeutics for Pancreatic Cancer

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Pancreatic ductal adenocarcinoma (PDAC) is characterized by abundant stroma with desmoplasia, which suggests that tumor-stromal interaction might be important in PDAC progression. We have established pancreas epithelium-specific transforming growth factor-ß receptor type II knockout mice in the context of Kras activation, which resulted in aggressive PDAC and recapitulated histology of human disease. By using this model, we analyzed tumor-stromal interaction and potential impact of its inhibition as a novel therapeutics for PDAC.

We isolated PDAC cells and fibroblasts from the mouse pancreas tissues and screened cytokines highly produced by the PDAC cells. The PDAC cells highly produced CXC chemokines 1, 2, 5 and 16, and the receptor CXCR2 was highly expressed in the pancreatic fibroblasts. The chemokines did not accelerate autocrine PDAC cell proliferation in vitro, but induced expression of connective tissue growth factor (CTGF), a well-known tumor-promoting factor, in the fibroblasts. When the fibroblasts were co-injected with the PDAC cells into nude mice, the subcutaneous tumors demonstrated a rapid growth compared to the PDAC cells alone-injected tumors. The CTGF induction and enhanced tumor growth of the mixed-cell xenografts were both CXCR2-dependent. Mice treated with the CXCR2 inhibitor demonstrated a significant decrease of tumor volume and longer survival compared to the control. Immunohistochemistry showed that CXCR2 inhibition decreased CTGF expression, tumor microvessel density and infiltration of macrophages and neutrophils in the tumor tissues, which suggested a broad modulation of tumor microenvironment.

In conclusion, blockade of CXC chemokine/CXCR2 axis, which can modulate a broad network of stromal components in the autochthonous PDAC model, might be a potent therapeutics for PDAC.

JPSY2-2

Heat Shock Protein 90 Inhibitors as a Possible New Candidate for the Treatment of Human Pancreatic Cancer

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Heat shock protein (HSP) 90 is known to be a molecular chaperone whose association is required for the stability and function of oncogenic protein including epidermal growth factor receptor (EGFR) that promote cancer cell growth. Therefore, HSP90 is a promising target for therapy against cancers including pancreas, some of which are highly dependent on EGFR. In the present study, we investigated the effects of HSP90 inhibitors on cytotoxicity and desensitization of EGFR in human pancreatic cancer cells (KP3, BxPc3 and AsPc1). 17-allylamino-17-demethoxy-geldanamycin (17-AAG), an inhibitor of HSP90, caused desensitization of EGFR in a time dependent manner with concurrently inducing phosphorylation of EGFR at Ser1046/1047 (Ser1046/7), a site which plays an important role in EGFR desensitization in these pancreatic cancer cells. We also found similar effects in KP3 cells treated with other HSP90 inhibitors, geldanamycin and 17-dimethylamino-ethylamino-17- demethoxy-geldanamycin (17-DMAG). In KP3 cells, 17-AAG induced activation of either p44/p42 mitogen-activated protein kinase (MAPK) or p38 MAPK. Interestingly, whereas the inhibition of p44/p42 MAPK

attenuated neither phosphorylation of EGFR at Ser1046/7 nor desensitization of EGFR, the phosphorylation at Ser1046/7 induced by 17-AAG was markedly attenuated by the inhibition of p38 MAPK, indicating that p38 MAPK induced this phosphorylation. Moreover, the inhibition of p38 MAPK significantly attenuated 17-AAG-induced EGFR desensitization. These results strongly suggest that EGFR phosphorylation at Ser1046/7 via activation of p38 MAPK induced by HSP90 inhibitors plays a pivotal role in EGFR desensitization in human pancreatic cancer cells. Whereas gemcitabine is currently considered to be the standard of care for the treatment of advanced pancreatic cancer, it is of interest to elucidate new combination of gemcitabine and HSP90 inhibitors for the clinical therapy of human pancreatic cancer.

JPSY2-3

Novel Therapeutic Method of HF10 Oncolytic Virus Therapy for Advanced Pancreatic Cancer

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HSV oncolytic virus is 150kbp DNA virus, and possesses great potential of new therapeutic agent. We have started clinical trial from early 2003 using HSV natural mutated virus, HF10. The replication capacity of HF10 is comparable or slightly higher than that of the wild type HSV-1 in most types of transformed cells. This strong oncolytic effect is one of differences from previous oncolytic HSV. Clinical trials of oncolytic virus therapy already have been performed over 1000 patients worldwide, however, in Japan clinical trials using oncolytic virus have been reached only 17 patients in Nagoya University School of Medicine, including 3 patients of recurrent head and neck cancer, 6 patients of recurrent breast cancer, 6 patients of advanced pancreatic cancer (3 injections group) and 2 patients of advanced pancreatic cancer (6 injections group). Regarding 6 patients of advanced pancreatic cancer (3 injections group), we observed clinical efficacy in 4 of the 6 patients. The tumors were classified as SD or PR in 4 patients and PD in 2 patients. A patient showed significant tumor reduction over 60% PR on PET and CT. There were no adverse side effects. We found CD4 and CD8 massive invasion inside of tumor caused by injected virus. Surprisingly even if after over 318 days, still HF10 antigen remained inside of tumor. It has become clear that a major effecter of oncolytic herpes simplex virus efficacy is the host immune response. We also report most recent new date of advanced pancreatic cancer (6 injections group) using EUS (endoscopic ultrasound) too.

JPSY2-4

Remodeling Abnormal Tumor Vasculatures by Transplantation of Vascular Progenitor Cells Reduces Tumor Hypoxia and Drug Resistance in Pancreatic Cancer

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Blood vessels deliver oxygen to tissues, and the vascular network is spatially organized to meet metabolic needs to maintain homeostasis. However, in tumors, the vasculature is immature, resulting in insufficient delivery of nutrients and oxygen. In view of the vasculogenic process that normally occurs in adult tissues to repair "injured" blood vessels, bone marrow-mononuclear cells (BMMNCs) may have the potential to restore appropriate vessel function in the tumor vasculature. Culturing BMMNC with EGM2 medium resulted in the early outgrowth of spindle-shaped attached cells expressing CD11b with pro-angiogenic as well as angiostatic function. We were curious to determine whether the $CD11b^{+}$ vascular progenitor cells (VPCs) can also 'repair' tumor vessels and tested this hypothesis using pancreatic ductal adenocarcinoma (PDAC) as a model for a hypoxic tumor. Intravenous administration of VPCs into nude mice bearing human PDAC xenografts and *Pdx1-Cre*;*LSL-Kras*^{G12D} $p53^{lox/+}$ mice that spontaneously develop PDAC did not enhance tumor growth but instead significantly reduced areas of tumor hypoxia. The resulting vasculature structurally mimicked normal vessels with intensive pericyte coverage. Increases in the vascularized area within VPC-injected xenografts were visualized with contrast-enhanced ultrasound, indicating a functional normalization of the tumor vasculature. In addition, gene expression profiles on the VPC-transplanted xenografts revealed a marked reduction in major factors involved in drug resistance and "stemness" of cancer cells. These results highlight the possibility of therapeutic manipulation to promote functional "normalization" of the tumor vasculature as well as the microenvironment. Collectively, we identified an alternative approach to regulate abnormal tumor vessels, which has the potential to improve delivery and efficacy of anti-cancer drugs to hypoxic tumors like PDAC.

JPSY2-5

FOXP3+ Regulatory T Cells and Tumoral Indoleamine 2,3-dioxygenase Expression Predicts the Carcinogenesis of the Pancreas

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Purpose: FOXP3+ regulatory T cells (Tregs) play a central role in self-tolerance and suppress effective antitumor immune response. Recent study revealed that indoleamine 2,3-dioxygenase (IDO)-mediated tryptophan depletion was able to affect the local tumor infil-

trating lymphocytes. The aim of this study was to investigate the clinical significance of the tumor infiltrating Tregs and tumoral IDO expression during the progression of the pancreas tumor.

Experimental Design: We investigated the localization of FOXP3+ Tregs, cytotoxic T lymphocytes (CTLs), and IDO expression in pancreas ductal carcinomas (PDCs) and intraductal papillary mucinous neoplasm of the pancreas (IPMNs) by immunohistochemistry. We recruited 135 cases of PDCs and 39 cases of IPMNs (adenoma n=11, borderline malignancy n=9, noninvasive IPMC n=7, invasive IPMC n=12).

Results: The prevalence of Tregs was increased step by step of carcinogenesis of the pancreas ($P<0.0001$). On the other hand, the prevalence of CTLs was gradually decrease step by step of carcinogenesis of the pancreas (Kruskal-Wallis test: $P=0.0014$). The prevalence of CTLs was inverse correlated with the prevalence of Tregs ($P=0.0012$). IDO expression in the tumor was observed 12.8% in IPMNs (IPMC n=1, I-IPMC n=4) and 87.5% in PDCs. IDO expression wasn't observed in IPMA and IPMB, and non-neoplastic lesions also didn't express IDO. IDO expression in the tumor was significantly correlated with the prevalence of Tregs ($P=0.0066$). IDO expression in the tumor and the prevalence of Tregs were significantly correlated with overall survival of the patients .

Conclusions: FOXP3+ Tregs play a role in controlling the immune surveillance against pancreas tumor to suppressing the number of CTLs from the premalignant stage to advanced stage. IDO expression in the tumor is one of the late stage phenomena of multistage carcinogenesis of the pancreas. FOXP3+ Tregs and IDO expression in the tumor have a predictive value for a poor prognosis of pancreas tumors.

JPSY2-6

Hypoxia Induces Tumor Aggressiveness by an Acquired Stem-like Phenotype in Pancreatic Cancer Through HIF-1α Signaling

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Background: Intratumoral hypoxia is a negative prognostic indicator, as it has been associated with increased aggressiveness and distant metastasis. Although hypoxia can drive the metastatic phenotype secondary to genetic instability and clonal selection of aggressive tumor cells, the interplay underlying them is to be unanswered. We hypothesized that mature cancer cells might acquire the stem-like phenotype under hypoxia, consequently leading to aggressive phenotype.

Methods: Under normoxia (20% O2) or hypoxia (1% O2) condition, the expression of CD133 (cancer stem cell marker), CXCR4 (chemokine receptor), HIF-1α, and pimonidazole (hypoxic probe) were examined by quantitative RT-PCR and imuunohistochemistry using human pancreatic cancer cell lines. Moreover, we evaluated the expression of CD133 and hypoxia markers (pimonidazole, HIF-1α, and CA) in xenograft and human pancreatic cancer specimen. Furthermore, we transfected dominant active HIF-1α (HIF-1α dODD) by the retroviral gene transfer and examined the effects both in vitro and in vivo.

Results: We demonstrated that hypoxia induces tumor aggressive phenotype in pancreatic cancer, including invasiveness and CXCR4 expression. Furthermore, this phenotype is followed distinctively by the subpopulation of CD133+ pancreatic cancer cells, which themselves show hypoxic and invasive properties, indicating that mature cancer cells might reacquire an undifferentiated stem-like phenotype. In addition, both acquired stem-like phenotype and invasiveness under hypoxia are predominantly in a HIF-1α/CXCR4-dependent manner, and dominant active HIF-1αdODD transfected cells promoted their tumorigenic ability. Surprisingly, orthotopic engraftment of these cells showed liver metastasis, while the engraftment of mock transfected cells did not occur any liver metastasis.

Conclusion: We demonstrated that mature cancer cells acquired the stem-like phenotype under hypoxia and showed aggressive phenotype including invasiveness and metastasis through HIF-1α signaling.

JPSY2-7

Effect of GSK3β Inhibition Against Gemcitabine-induced Epithelial-mesenchymal Transition and Invasive Ability of Pancreatic Cancer Cells: Its Therapuetic Implication

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Pancreatic cancer represents the malignant tumor that is most refractory to treatment and in which the identification of molecular targets is urgently required. We have found that glycogen synthase kinase (GSK) 3β is a potential therapeutic target and combination of gemcitabine (GEM) and GSK3β inhibitor (GSKI: a pharmacological inhibitor, AR-A014418) has a synergistic effect against pancreatic cancer cells (PANC-1, MIA-PaCa-2 and BxPC-3) and PANC-1 xenografts in mice. Our current study showed that treatment with GEM caused distinct morphological changes in PANC-1 cells, which were consistent with epithelial-mesenchymal transition (EMT) as demonstrated by Western blotting and immunofluorescence staining for EMT-related factors. The time-lapse microscopic observation of the 2D mono-layer and the 3D spheroid formations showed an increased migration of GEM-treated PANC-1 cells, which was suppressed by GSKI. The combination of GEM and GSKI decreased invasive ability of PANC-1 cells and prevented them from acquiring EMT phenotype. RNA interference for GSK3β reduced the survival and proliferation of these cancer cells and predisposed them to undergo apoptosis. These data suggest novel pathological roles for GSK3β and undesirable effect of GEM for pancreatic cancer cells. The pres-

ent observation that GSKI compromises the undesirable effect of GEM and enhances its anti-tumor effect led us to propose a potential combination therapy using GEM and GSKI for pancreatic cancer. We are planning a clinical trial using available drugs that exert inhibiting GSK3β in combination with GEM.

JPSY2-8

Peptide Vaccine Therapy for Patients with Advanced Pancreatic Cancer – A Clinical Trial Design from Phase I to Phase II/III for the Development of Therapeutic Cancer Vaccine

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Vascular endothelial growth factor receptor 2 (VEGFR2) is an essential factor in tumor angiogenesis and growth of pancreatic cancer. Immunotherapy using epitope peptide for VEGFR2 (VEGFR2–169) is expected to improve the clinical outcome. Therefore, a phase I clinical trial in a combination of VEGFR2-169 with gemcitabine was conducted for patients with advanced pancreatic cancer (ClinicalTrial.gov, number NCT 00622622). Patients with metastatic and unresectable pancreatic cancer were eligible for the trial. Gemcitabine was administered at a dose of 1,000 mg/m^2 on days 1, 8 and 15 in a 28-day cycle. VEGFR2-169 peptide was subcutaneously injected weekly in a dose-escalation manner (doses of 0.5, 1.0, 2.0 mg/body, 6 patients/1 cohort). Safety and immunological parameters were assessed. No severe adverse effect of grade 4 or higher was observed. Of 18 patients who completed at least one course of the treatment, 15 (83%) developed immunological reactions at the injection sites. Specific CTLs reacting to VEGFR2-169 peptide were induced in 11 (61%) of the 18 patients. The disease control rate was 67% and the median overall survival time was 8.7 months. This combination therapy for pancreatic cancer patients was tolerable at all doses. Peptide specific CTLs could be induced by VEGFR2-169 peptide vaccine at a high rate even in the combination with gemcitabine. From an immunological point of view, the optimal dose for further clinical trial might be 2.0 mg/body. Based on the results of this Phase I clinical trial, we developed randomized, placebo-controlled, double blind, multicenter Phase II/III clinical trial. The phase II/III trial enrolled the first patient in January 2009, and completed the enrollment of 150 patients in January 2010.

JPSY2-9

Stem Cell Research in Pancreatic Cancer

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Cancer stem cells (CSCs) are a rare population that are thought to be originated from tissue stem or progenitor cells through the dysregulation of self-renewal pathways including Notch, Wnt/b-canenin, Hedgehog, and BMI-1. The existence of CSCs was first studied in AML classified by surface marker CD34+CD38-. Recently, identification of CSCs and their markers in various cancers including melanoma, brain, breast, prostate, colon, liver, and pancreatic cancer are under investigation. CSCs are now defined as "cells within a tumor that possess the capacity for self-renewal and that can cause the heterogeneous lineages of cancer cells that constitute the tumor." CSCs are regarded as not only the source of tumor but also drives carcinogenesis including tumor progression, metastasis, resistance to chemotherapy and cancer recurrence.

It is evident that transformed oval cells which are considered as liver stem cells can be a cellular origin of liver tumors. The activation of oval cells is observed in HCC. Hepatic stem cells transduced with Bmi1 or mutant b-catenin acquired enhanced self-renewal capability and tumorigenicity.

Pancreatic stem cells are less well defined. However, pancreatic cancers probably arise from ductal metaplasia or centroacinar cells. CD133-CXCR4 and CD24-CD44-ESA are considered as the surface marker of pancreatic CSC. CD133 is expressed on the centroacinar position as well as apical membrane of ductal cells, and CD44 expression in centroacianr cells and ductal cells were observed. These results suggest that pancreas stem cell might be present among centoacinar cells and ductal cells. It is reported that centroacinar cells express Pten to control its population, and the misregulation of the PI3-K pathway in centroacinar cells many initiate carcinogenesis.

Understanding the importance of CSCs in pancreatic carcinogensis could lead to the identification of better markers for diagnosis and treatment and even cancer prevention for the most desperate cancer in human.

JPSY2-10

The mTOR Inhibitor RAD001 (Everolimus) Potentiates Cytotoxic Therapy Through Tumor Vessel Thrombosis in Xenograft Models of Human Pancreatic Cancer

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Introduction: Despite current chemotherapies, pancreatic cancer remains an uncontrollable progressive disease. The mammalian target of rapamycin (mTOR) is one of the effectors regulated via the PI3 kinase/Akt signaling pathway, and plays a role in cell survival. Recent studies have shown that the mTOR inhibitor rapamycin, used

as an immunosuppressant in organ transplantation, is a potent antiangiogenic substance. In addition, mTOR inhibitor rapamycin induces tumor-specific thrombosis via tissue factor in the presence of VEGF. Previous clinical studies have shown that pancreatic cancer is highly angiogenesis dependent. We hypothesized that pancreatic cancer progression may be sensitive to antiangiogenic therapy by mTOR inhibitors, particularly when combined with standard cytotoxic therapy.

Experimental Design and Results: RAD001 is one of the rapamycin derivatives, suitable for oral intake. We examined RAD001 against 6 pancreatic cancer cell lines in vitro. RAD001 showed significant antiproliferative effect in CFPAC-1, and moderately in Suit-2. In vivo study, RAD001 showed significant antiproliferative effect in the CFPAC-1 subcutaneous xenograft model and in the Suit-2 subcutaneous xenograft model. Histologic examination of the tumors by hematoxylin and eosin (HE) staining, phosphotungustic acid hematoxylin (PTAH) staining, Elastica van Gieson (EVG) staining and Masson Trichrome (MT) staining showed that the presence of thrombosis is predominant in tumors of mice treated with RAD001 alone or with RAD001 in combination with gemcitabine. No thrombi were found in tumors of either placebo-treated or gemcitabine-treated mice. Furthermore, treatment of pancreatic cancer cells with RAD001 led to the inhibition of hypoxic activation of hypoxia-inducible factor-1, one of the main regulators of VEGF gene expression.

Conclusion: RAD001, not only reduces tumor vascularization, but also forms thrombosis. We propose RAD001 in combination with gemcitabine as a new strategy against pancreatic cancer.

JPSY2-11

The Function of Rho-kinase in Human Pancreatic Cancer Growth

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It has been reported that Rho and Rho-kinase are involved in actin cytoskeleton organization and associated with carcinogenesis and progression of human cancers. However, the mechanism how the Rho/Rho-kinase pathway is involved in cell cycle progression has not been precisely characterized. We recently reported that Rho-kinase regulates negatively epidermal growth factor (EGF)-induced colon cancer cell proliferation (Nakashima M. et al, In J Oncol in press). In brief, we found that Y27632, a specific inhibitor of Rho-kinase, induced cell proliferation. Interestingly, while EGF induced Rho-kinase activation, EGF-induced activations of cell survival signals such as Akt or glycogen synthase kinase (GSK)-3β were enhanced when the cells were pretreated with Y27632. Moreover, whereas EGF increased the phosphorylation of retinoblastoma tumor suppressor protein as well as cyclin D1 protein level, Y27632 accelerated them. In the present study, we investigated the role of Rho-kinase in Panc1 and KP3 pancreatic cancer cells and found that the inhibition of Rho-kinase utilizing Y27632 or small interfering RNA augmented the phosphorylation of EGFR at tyrosine residues, subsequently activation of either p44/p42 mitogen-activated protein kinase or Akt-GSK-3β pathway in Panc1 cells. Our results could show a potential role of Rho-kinase as a new biomarker or treatment for human pancreatic cancers. Although further investigations are required, upregulation of Rho-kinase might be considered as a new therapeutic target for human cancers including pancreas.

JPSY2-12

Focused DNA Array (FDA) Using Pancreas Cancer Tissue Obtained by EUS-guided FNA -For Exploring Possible Predictors of Metastasis-

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Background: DNA microarray technique allows of examining hundreds of genes simultaneously. EUS-guided FNA brings us not only cytological diagnosis but also gene analysis. The purpose of this study is to determine the usefulness of Focused DNA Array (FDA) analysis using the pancreatic cancer tissue obtained by EUS-guided FNA in predicting metastasis.

Methods: Pancreatic cancer tissues were obtained from 26 patients. mRNA was harvested from each sample and cDNA was composed by reverse transcription polymerase chain reaction (RT-PCR). Expression of mRNA was analyzed using FDA which was restricted to 133 genes. FDA included genes such as growth factors and their receptors (EGFR, TGF beta 1, 2, 3), pro-angiogenic factors (VEGF), and invasiveness factors (MMP 1,2,3,7,9,14,16, Integrin alfa 2,3,4,5, Integrin beta 1,3,5), which are known as important substances for tumor development. The patients were divided into two groups depend on having liver metastasis or not at the time of biopsy. The Mann-Whitney U-test was used to compare the difference of the gene expression between these two groups.

Results: Twenty three of 26 (88.5%) samples were suitable for analysis. Fifteen (65.2%) patients had liver metastasis at the time of EUS-guided FNA. A significant difference between these two groups was observed in the expression of Integrin beta 5 ($p=0.037$), which was known to mediate attachment between a cell and tissues surrounding it.

Conclusion: FDA analysis using pancreatic cancer tissues obtained by EUS-guided FNA could be a useful method to predict the metastatic potential. Integrin beta 5 might have an important role in liver metastasis of pancreas cancer.

JPSY2-13

The Exploration of Novel Strategy for Treatment of Pancreactic Ductal Adenocarcinoma Targeting Angiogenesis with the Use of Genetically Engineered Mouse

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Background and Aim: Pancreatic ductal adenocarcinoma (PDAC) is an almost uniformly lethal disease in human. Previously, we have reported a genetically engineered mouse PDAC progression model which has pancreas-specific transforming growth factor-beta receptor type II knockout in the context of Kras activation. This model recapitulates the signature of human PDAC well. Using this model, we explored novel strategy for PDAC treatment targeting angiogenesis.

Materials and Methods: We used sunitinib and axitinib, which are multikinase inhibitors, and 5 kinds of anigiotensin II receptor blockers (ARBs), TCV-116 (candesartan), telmisartan, losartan, valsartan, and olmesartan, which were previously reported as inhibitors of vascular endotherial growth factor (VEGF). For single agent experiments, mice were treated with these reagents, respectively. For combined agent experiments, mice were treated with axitinib and gemcitabine. In vivo anti-tumor effect and survival time were assessed. Immunostaining of tumor tissue for caspase 3, Ki67, CD31, and VEGF was performed.

Results: Median survival time (MST) of single use of axitinib and sunitinib group was statistically longer than that of control group. MST of TCV-116 and telmisartan group also tended to be longer than control. Combined treatment with axitinib and gemcitabine showed further statistically longer MST than gemcitabine or axitinib alone. Axitinib, sunitinib, TCV-116, and telmisartan showed significant anti-tumor effect in vivo. Axitinib and sunitinib group showed significantly higher caspase 3 score and lower Ki67 score than that of control, however, TCV-116 and telmisartan group showed no change of these scores, compared to control. Microvessel density of axitinib, sunitinib, TCV-116, and telmisartan group was significantly lower than that of control and other ARBs. VEGF expression of TCV-116 and telmisartan group was significantly lower than that of control and other ARBs.

Conclusion: Targeting angiogenesis with multikinase inhibitor or ARB in addition to gemcitabine may be a promising therapeutics for PDAC.

JPSY2-14

Resolution of the Function of Cancer Cells and the Application for Tailor-made Therapy Using Bio-simulation Analysis

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Metabolome analysis technology has been dramatically improved in recent years and applied not only to the research in bacteria and plants but also to clinical and drug efficacy studies including cancer science. Among various analytical methods available for metabolome analysis, we particularly selected capillary electrophoresis mass spectrometry (CE-MS) and established a CE-MS-based method to comprehensively analyze charged, low-molecular-weight compounds. Metabolome analysis by CE-MS targets the compounds involved in glycolysis, the pentose phosphate pathway, the TCA and urea cycles, and the intermediates involved in amino acid, polyamine, purine, and pyrimidine metabolisms, and thus, is best-suited for the integrative quantification of metabolites that characterize the energy metabolism of cells. Meanwhile, research in drug sensitivity has been conducted mainly by applying genomics and transcriptomics approaches; however, few studies conducted metabolome-scale analysis of compounds and examined the property of drug sensitivity based on the time-change of cell metabolism. Accordingly, in order to elucidate the effect of gemcitabine on the metabolism of cancer cells and clarify the potential drug resistance mechanisms, we conducted time-course metabolome analysis of Panc-1 (a pancreatic cancer cell line) after the treatment with gemcitabine. As a result of quantifying the time-change of 239 metabolites in gemcitabine-treated Panc-1 by using CE-MS, we observed both predicted fluctuations primarily in the pyrimidine metabolites and unexpected changes such as the significant increase of TCA intermediates, amino acids, and purine metabolites. We will attempt to elucidate the resistance mechanism of cells against gemcitabine using the drug-resistant and sensitive strains by exploiting a comparative metabolomics approach in future. We will thus contribute to the establishment of an easy-to-use approach in individualized therapy based on metabolome analysis.

JPSY2-15

The Application of Homeobox Gene MSX2 Down-regulation as a Therapeutic Strategy for Pancreatic Cancer

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Background and Aim: Recent studies revealed a direct link between the epithelial to mesenchymal transition (EMT) and the gain of epithelial stem cell properties. We have shown that MSX2 induced EMT in pancreatic cancer. Therefore, we investigated the association

of MSX2 with stem cell like phenotype to assess whether this gene would be therapeutic target for pancreatic cancer.

Methods: The expression levels of MSX2 and ABCG2 were assessed by real-time RT-PCR. The role of MSX2 was evaluated by over-expression or knock-down of MSX2 in the pancreatic cancer cell line. The association of MSX2 and cancer cell metastasis was examined by the injection of pancreatic cancer cells into pancreas of nude mice. The gemcitabine sensitivity was measured by MTT assay.

Results: BxPC3 cells stably expressing MSX2 showed a flattened and scattered morphology accompanied by a change in localization of E-cadherin and beta-catenin from membrane to cytoplasm and enhanced cellular migration. Immunohistochemistry revealed that MSX2 was frequently expressed and increased expression of MSX2 was significantly correlated with higher tumor grade, vascular invasion. MSX2 expressing BxPC3 cells also show significantly more frequent liver metastases and disseminations in nude mice than did control cells when cells were injected into pancreas. This effect was reversed when MSX2 was down-regulated in Panc-1 cells that express very high levels of endogenous MSX2. In addition, induced expression of MSX2 resulted in the up-regulation of transporter gene ABCG2 and the gemcitabine resistance in BxPC3 cells. On the other hand, down-regulation of MSX2 in Panc-1 cells demonstrated the reduced expression of ABCG2 and sensitized cells to the gemcitabine treatment.

Conclusion: These data indicate that MSX2 plays a crucial role in pancreatic cancer cells to gain of cancer stem cell properties and that this molecule is a good candidate for therapeutic target of the pancreatic cancer.

JPS Symposium 3 Randomized Controlled Trials against Pancreatic Cancer

JPSY3-1

Randomized Controlled Trials of Adjuvant Chemotherapy for Resectable Pancreatic Cancer – Experience of The Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP)

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Effective adjuvant therapy for pancreatic cancer has been sought because of extremely low survival rate after potentially curative resection.

The Gastrointestinal Tumor Study Group performed the first multicenter randomized controlled trial (RCT) to evaluate the efficacy of adjuvant treatment, and they concluded that adjuvant chemoradiotherapy prolonged the postoperative survival of patients with pancreatic cancer. However, the results of a few subsequent RCTs were inconsistent. Consequently, standard adjuvant therapy for pancreatic cancer had not been established for a long time.

The Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP) conducted two phase III multicenter RCTs. JSAP-01 was aimed to evaluate the efficacy of adjuvant chemotherapy with cisplatin and 5-FU (FP) after margin-negative resection in patients with pancreatic cancer. JSAP-02 was designed to determine whether adjuvant chemotherapy with gemcitabine improves the outcomes of patients with resected pancreatic cancer. Patients in the control arms of both trials were observed without adjuvant treatment.

JSAP-01 failed to show any survival benefit of adjuvant FP. However, JSAP-02 demonstrated significant prolongation of disease-free survival with adjuvant gemcitabine although improvement of overall survival was not statistically significant. These results were similar to those of CONKO-001 trial. In consequence, JSAP-02 contributed to establish gemcitabine monotherapy as the current standard of adjuvant therapy for resectable pancreatic cancer. At present, we are conducting phase I/II trial of adjuvant gemcitabine and S-1 therapy (JSAP-03) in preparation for the next phase III RCT.

Before the year 2000, conducting RCTs of adjuvant therapy for resectable pancreatic cancer was extremely difficult, especially in patient recruitment, and most of the trials were underpowered. Recently large-scale RCTs have been carried out principally by the European study groups. We have to discuss strategies for maintaining continuous activity to create clinical evidences applicable to Asian patients.

JPSY3-2

Randomized Controlled Multicenter Trial to Establish the Adequate Extent of Resection for Pancreatic Head Cancer in Korea

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There have been controversies in the extent of resection for pancreatic cancer. Four RCTs comparing standard and extended pancreatoduodenectomy have been performed to evaluate the role of extended surgery. None of the studies showed a benefit of extended resection in long-term survival. However, each study was criticized due to the heterogeneity of disease, inadequate dissection of retroperitoneal tissue including nerve plexus, malnutrition induced by diarrhea and small number of patients. Despite of negative result of RCTs, many surgeons still perform extended or modified extended pancreatoduodenectomy for pancreatic head cancer.

We have performed RCT to explore the role of extended pancreatoduodenectomy to overcome the drawback of previous RCTs. Twelve hospitals participated in this study. Randomization was done centrally by an independent statistical institute using web based program. Operation methods (to be shown) were standardized after several working group meetings. All operative fields were recorded and reviewed by study committee.

From 2006 to 2009, a total of 221 patients were enrolled in this study. Seventy two were excluded due to the improper dissection as well as intra-operative detection of metastasis. Mean age was 62.9 years old and male to female ratio was 1.12:1. Seventy one patients

were allocated in standard group and 78 in extended group. There were no differences in demographic findings, portal vein resection rate, pathologic stage, cellular differentiation, lymph node metastasis between two groups. Although there was no statistical difference of morbidity and mortality between two group, morbidity of standard group was 29.5%, that of extended group was 38.5%. There were two mortality related with surgery in extended group. The primary endpoint of this study is two year survival, so we are waiting for the long-term survival of this study.

JPSY3-3

Randomized Trials of Adjuvant Chemotherapy for Patients with Resected Pancreatic Cancer Using Gemcitabine and/or 5-FU Prodrugs

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Aim: Although the adjuvant chemotherapy with gemcitabine (GEM) is widely performed for patients with resected pancreatic cancer, the efficacy is still limited. We examine the efficacy and toxicities of adjuvant chemotherapy using GEM and/or 5-FU prodrugs, uracil/tegafur (UFT) or S-1 through randomized clinical trials.

1) GEM + UFT vs. GEM: Patients with invasive ductal pancreatic cancer who underwent radical surgery were enrolled and assigned to receive UFT and GEM together (GU) or GEM alone (G). GEM was administrated at a dosage of 1g/m^2 weekly X3 out of 4 weeks and UFT at a dosage of 200mg/body/day continuously. The primary endpoint was disease free survival (DFS) and secondary endpoints included overall survival (OS) and toxicity.

Results: Between 2002 and 2005, 100 patients were randomized into the two arms of the trial (50 patients to GU and 50 to G). One- and 3-year DFS rates were 50.0% and 17.7% in the GU group and 49.0% and 21.6% in the G group, respectively. The median OS was 21.2 months in GU group and 29.8 months in G group. Toxicity was minor and acceptable, and no grade 4 or 5 adverse events were observed in both groups.

2) GEM vs. S-1 vs. GEM + S-1: Following this trial, we are now managing new trial using another 5-FU prodrug, S-1. Patients with same criteria are enrolled and assigned to receive GEM alone, S-1 alone or GEM and S-1 together. Patients' enrolment has begun at December 2007 and 75 patients were enrolled so far. At the presentation, we will introduce the detailed protocol of this trial.

Conclusion: Postoperative GEM-based adjuvant chemotherapy was safe and well tolerated. However, addition of UFT with GEM did not improve DFS as compared with GEM alone. We expect S-1 may improve the survival and are starting new clinical trial.

JPSY3-4

Randomized Phase III Trial of Adjuvant Chemotherapy with Gemcitabine Versus S-1 in Patients with Resected Pancreatic Cancer: A Clinical Study of Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC-01)

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A randomized controlled trial is in progress to compare S1 with gemcitabine (GEM) as adjuvant chemotherapy for patients with resected invasive ductal carcinoma of the pancreas. Patients with R0 or R1 residual disease are registered within 10 weeks after surgery and randomly assigned to either orally administered S-1 (80mg/m^2/day for four weeks, repeated every six weeks for a total of four courses) or intravenous GEM (1000mg/m^2 on days 1, 8 and 15, repeated every four weeks for a total of six courses). After treatment with S-1 or GEM, patients are followed-up with abdominal computed tomography and chest X-ray every three months during the first two years and then every six months for next three years. The primary endpoint is overall survival and secondary endpoints are relapse-free survival, adverse events and health-related quality of life. The hypothesis to be tested is that overall survival is not significantly worse after adjuvant chemotherapy with S-1 than GEM (non-inferiority study). Each treatment arm needs 180 patients. The study period includes three years for accrual and two years for follow-up. We started this study in April 2007 and 320 patients have been already enrolled during 34 months.

JPSY3-5

Randomized Controlled Trials for Pancreatic Surgery – Wakayama Experiences

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We introduce our experiences of three RCTs regarding pancreatic surgery. First, Pylorus-preserving pancreaticoduodenectomy (PpPD) is an aggressive surgery involving pancreatic head resection for periampullary lesions. The pathogenesis of delayed gastric emptying (DGE) after PpPD has been speculated to be related to several factor, and previous retrospective studies have shown a lower incidence of DGE after antecolic duodenojejunostomy. To determine this hypothesis, a RCT is accomplished (Ann Surg 2006). Antecolic reconstruction for duodenojejunostomy during PpPD decreases postoperative

morbidity and length of hospital stay by decreasing DGE. Our data suggest that PpPD with antecolic duodenojejunostomy is a safer operation.

Second, a stent is often placed across the pancreaticojejunostomy. However, no study has previously compared pancreatic stent types with regard to postoperative course. Therefore, we conducted a prospective randomized trial with 100 patients who underwent pancreaticoduodenectomy, and compared the effects on postoperative course (Am J Surg 2009). Both of internal drainage and external drainage were safety devices for pancreaticojejunostomy. However, it might be suggested that internal drainage affects and simplification of postoperative managements and shortening of postoperative stay for pancreaticoduodenectomy.

Third, we determine in a RCT whether pylorus-resecting pancreatoduodenectomy (PrPD) with preservation of nearly the entire stomach reduces the incidence of delayed gastric emptying (DGE) compared to pylorus-preserving pancreatoduodenectomy (PpPD). 130 patients were randomized to preservation of the pylorus ring (PpPD) or to resection of the pylorus ring with preservation of nearly the entire stomach (PrPD).The incidence of DGE was 4.5% in PrPD and 17.2% in PpPD, a significant difference. DGE was classified into three categories proposed by the International Study Group of Pancreatic Surgery. Thus, PrPD significantly reduces of the incidence of DGE compared to PpPD (manuscript submitted).

Randomized controlled trial could provide the hypothesis, thus the reasons for our studies regarding pancreatic surgery.

JPSY3-6

The Final Results of a Randomized Controlled Trial on Surgery Versus Radiochemotherapy for Pancreatic Cancer

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The outcome of surgery for locally advanced pancreatic cancer remains poor but the 5-year survival rate has been improving up to about 10% in Japan. The surgical resection is the only hope for patients to survive longer period; however, it is not clear the surgical resection is justified for the patients with advanced stage of tumors. We report the final results of the multi-institutional randomized controlled trial (RCT) comparing surgery and radiochemotherapy after 5 years of follow-up.

Patients with preoperative findings of pancreatic cancer invading the pancreatic capsule without involvement of the superior mesenteric or common hepatic arteries, or distant metastasis, were included in this RCT, with their consent. If the laparotomy findings were consistent with these criteria, the patient was randomized to a surgery group or a radiochemotherapy group (5-fluorouracil 200 mg/m2/day and 5040 Gy radiotherapy). We compared the mean survival time, 3-and 5-year survival rates, and hazard ratio. Patients were followed up for 5 years or longer, or until an event occurred to preclude this.

The surgery group had significantly better survival than the radiochemotherapy group ($P < 0.03$). Surgery increased the survival time and 3-year survival rate by an average of 11.8 months and 20%, respectively, and it halved the instantaneous mortality (hazard) rate.

Therefore, we would conclude that locally invasive pancreatic cancer without distant metastases or major arterial invasion is treated most effectively by surgical resection.

(Contributed JPCSG members are Imamura M, Hosotani R, Imaizumi T, Hatori T, Takasaki K, Funakoshi A, Wakasugi H, Asano T, Hishinuma S, Ogata Y, Sunamura M, Yamaguchi K, Tanaka M, Takao S, Aikou T, Hirata K, Maguchi H, Aiura K, Aoki T, Kakita A, Sasaki M, Ozaki M, Matsusue S, Higashide S, Noda H, Ikeda S, Maetani S, Yoshida S and Doi R.)

JPSY3-7

Effects of Adjuvant Intra-operative Radiation Therapy After Curative Resection in Pancreatic Cancer Patients: Results of a Randomized Study by 11 Institutions in Japan

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Background: To evaluate the benefits of adjuvant intra-operative radiation therapy after curative resection in advanced pancreatic cancer (APC) patients, a multi-center phase III trial was conducted by 11 participating institutions in Japan.

Method: Eligibility included pts with potentially resectable APC (duct cell origin) by image diagnosis. Patients were randomized in a 1:1 ratio to adjuvant IORT or surgery alone less than a week before surgery. Stratification factors were tumor size (TS1/TS2,3,4), location (head/body and tail), and institution. Patients who were assigned to adjuvant IORT arm received IORT after curative resection before reconstruction. IORT consisted of 25Gy with electron beam energies of more than 6MeV and was delivered by the round shaped acrylic cylinder of 6–8cm diameter. The radiation field included the tumor bed and in most cases included the celiac axis, superior mesenteric artery, and the portal vein. The primary endpoint was overall survival. The secondary endpoint was local control rate at 2 years after surgery.

Results: Between 05/2002 to 12/2006 198 pts were randomized and 153 pts underwent curative resection with assigned treatment. Among the 153 pts with curative resection, seven pts revealed ineligible by the histological examination. Full Analysis Sets were 70 pts in the surgery alone arm and 74 pts in the IORT arm. Adjuvant IORT could be safely delivered. There was no survival benefit of adjuvant IORT for over all and relapse free survival and was no statistical difference in the local control of disease at 2 years in the two groups.

Conclusion: A single high dose adjuvant IORT alone after curative resection for pancreatic cancer is not recommended.

JPS Symposium 4 Management of Complications after Pancreatic Surgery by Endoscopy and Interventional Radiology

JPSY4-1

Risk Factors for and Management of Intraperitoneal Hemorrhage Due to Pseudoaneurysm Rapture After Pancreatic and Biliary Surgery

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Background: Delayed intraperitoneal hemorrhage (DIH) due to pseudoaneurysm rapture is still an important cause of postoperative mortality in pancreatic and biliary surgery.

Methods: One hundred forty patients who underwent pancreatic and biliary surgery with skeletonization for lymphadenectomy of the hepatodoudenal ligament between 2002 and March 2009 were included in this study. Statistical analyses of the risk factors for DIH were performed using multivariate analysis. And we tried to present the guidelines for the prevention, diagnosis, and management of DIH from the results of treatment courses of patients with DIH.

Results: DIH occurred in 8 patients (5.7%) within a median time of 15 days after surgery. Stepwise logistic regression analysis identified "intra-abdominal abscess formation" as the independent predictor of DIH (Odd's ratio 5.9, p=0.03). All 8 patients had "sentinel bleed" before the onset of DIH, and all 8 patients had the pseudoaneurysms of hepatic or gastrodoudenal arteries. Six patients succeeded to be treated by transarterial embolization (TAE), but 2 patients were failed and were treated by emergent surgical intervention. Three patients had TAE or ligation of common hepatic arteries, but no patients had complicated with severe liver failure. Maybe due to the ischemia of the bile duct, three patients had liver abscess and two patients had delayed bile leakage from hepatico-jejunostomy site after hemostasis of DIH. All 8 patients recovered and were discharged from the hospital.

Conclusions: The independent predictor of DIH is "intra-abdominal abscess", and patients with intra-abdominal abscess after pancreatic biliary surgery should be considered with additional drainage or irrigation. If patients had "sentinel bleed" after pancreatic and biliary surgery, an angiography or CT-angiography should be performed to check if a pseudoaneurysm has formed. After hemostasis of DIH, patients should be strictly followed to be complicated with liver abscess or delayed bile leakage from hepatico-jejunostomy site.

JPSY4-2

Treatment Strategy and Outcomes of Fistula and Bleeding after Pancreatic Surgery

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Background: Pancreatic fistula (PF) is one of the most common complications after pancreatectomy and sometimes leads to intraabdominal-bleeding. Endoscopy and interventional radiology play important roles in management. The purpose of this study is to review our management strategy.

Methods: Between 1981 and 2009, there were 430 pancreatectomies performed for invasive ductal adenocarcinoma at our institution. Total pancreatectomies (73 cases) were excluded from this analysis. PF was diagnosed according to the classification of the International Study Group of Pancreatic Fistula (ISGPF). Amylase level in discharge was checked on postoperative day (POD) 1, 3, 5, and 7. When leakage was suspected or confirmed, radiological exchange of the drainage tube was performed weekly after the first intervention on POD 7. Closed suction or daily irrigation was performed as indicated. Antibiotics were not used, unless there was obvious evidence of systemic infection. In cases of intraabdominal-bleeding, radiological embolization was the first line treatment, and laparotomy was also considered. Multivariate analyses were performed to identify factors predictive of prolonged drainage (> 30 days).

Results: Of 357 patients, PF was diagnosed in 73 (20.4%). Regarding PF grade, 14, 48 and 11 were classified into A, B, and C, respectively. Eleven patients with Grade C fistulae had intraabdominal bleeding, of whom six underwent radiological embolization, and one underwent laparotomy. Four patients (1.1%) died from bleeding or other complications related to PF. Duration of drainage was 9.8+-2.5, 32.0+-14.8, and 74.7+-16.1 days in Grades A, B, and C, respectively. A predictor of prolonged drainage was a main pancreatic duct less than 4mm in diameter (odds ratio=2.47; p=0.049)

Conclusion: Mortality rate in the entire group was low, but the outcome in patients with PF related intraabdominal bleeding was unsatisfactory. Careful management of drainage tubes and prompt radiological embolization are preferrred treatment strategies for PF and intraabdominal-bleeding.

JPSY4-3

Endoscopic Transpapillary Pancreatic Duct Drainage for Treatment and Prevention of Pancreatic Fistula After Pancreatic Surgery

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This study investigated usefulness and complication of endoscopic transpapillary pancreatic duct drainage (EPD) for treatment and prevention of pancreatic fistula (PF) after pancreatic surgery.

Methods: Five patients with prolonged PF after pancreatic surgery (4 patients after distal pancreatectomy (DP), 1 patient after enucleation (EN)) and 4 patients performed EPD before EN to prevent postoperative PF were included. In our institute, endoscopic nasopancreatic drainage (ENPD, external drainage) was selected to prevent retrograde fistula infection for treatment of postoperative PF. On the other hand, ENPD and endoscopic pancreatic duct stent (EPS, internal drainage) were inserted into the distal main pancreatic duct (MPD) across the location of tumor before EN for prevention of postoperative PF. The tube stent used for EPS was 5Fr straight plastic tube with side hole and 5Fr tube with side hole was used for ENPD. The efficacy and complications of EPD were examined retrospectively.

Results: In the patients with postoperative PF, the median time from operation to ENPD was 32 days (range, 11–75 days) and the median time from ENPD to percutaneous drain removal was 22 days (range, 8–38 days). And the volume of percutaneous drain was decrease in all patients after ENPD, the average volume of percutaneous drain before and after ENPD were 212ml and 8.08ml a per day, respectively ($p=0.0003$). In one patient after DP, ENPD was dislocated because of short MPD. In the patients performed EPD for prevention PF, the median time from EN to percutaneous drain removal was 6 days (range, 4–22 days). In one patient with pancreatic body endocrine neoplasms, acute pancreatitis was occurred after EPS. It was thought that using long EPS was the reason of post procedure pancreatitis.

Conclusions: Though it was required care of complication, EPD was useful for treatment and prevention of pancreatic fistula after distal pancreatectomy and enucleation.

JPSY4-4

Endoscopic Pancreatic Stenting for Prevention and Treatment of Postoperative Pancreatic Fistula

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Background: Pancreatic fistula is a common complication after distal pancreatectomy or local pancreatic resection. A pancreatic stent seems to treat or prevent leakage from a main pancreatic duct stump as well as small pancreatic branch ducts not identified or ligated intraoperatively, via the pancreatic decompression effect. We investigated therapeutic and prophylactic effect of endoscopic pancreatic stenting against postoperative pancreatic fistula.

Method: Preoperatively, 15 patients underwent endoscopic placement of a pancreatic stent (7fr, 3cm) before distal pancreatectomy ($n=10$) or local pancreatic resection ($n=5$). Postoperatively, five patients underwent endoscopic pancreatic stenting for pancreatic fistula after distal pancreatectomy.

Results: Of the 15 patients with preoperative stenting, only one developed pancreatic fistula postoperatively. In four of the five patients with pancreatic fistula, the fistula resolved within 14 days after pancreatic stenting. Two of the 20 patients experienced complications related to stenting (mild pancreatitis).

Conclusion: Endoscopic pancreatic stenting is effective for prevention and treatment of pancreatic fistula after distal pancreatectomy or local pancreatic resection.

JPSY4-5

A Multidisciplinary Classification of Invasive Procedures for Treating the Local Complications of Acute Pancreatitis

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Purpose: Standardising terminology is a strategy to improve the communication between clinicians. The lack of a system to classify invasive procedures to treat the local complications of acute pancreatitis is an obstacle to comparing interventions. This study aimed to develop a comprehensive multidisciplinary classification and determine its acceptability and reliability.

Methodology: International Classification of Diseases terminology was used to develop a system to classify procedures based on three components: how the lesion is visualised (V), the route (R) used during the procedure, and the procedure's purpose (P).

Gastroenterologists, radiologists, and surgeons from three centres in New Zealand assessed the classification and independently classified fifteen published technique descriptions. The classification's clarity, ease of use and potential to achieve its objectives were rated on a Likert scale. Inter-rater reliability was calculated for each component of the classification.

Results: The technique descriptions were classified by 22 clinicians (6 gastroenterologists, 11 radiologists, 5 surgeons). The classification's clarity, ease of use, and potential to achieve its objectives had median scores of 4/5. Inter-rater reliability for visualisation, route and purpose components was substantial at 0.73 (95% CI 0.63 to 0.82), 0.79 (0.70 to 0.87), and 0.64 (0.53 to 0.74), respectively.

Conclusion: This paper describes the development and validation of a multidisciplinary classification for procedures used to treat the local complications of acute pancreatitis. This VRP Classification has substantial inter-rater reliability and high acceptability, which should enhance communication between clinicians and facilitate comparison of procedures.

JPSY4-6

EUS-guided Drainage of the Pancreatic Fistula or Pancreatic Duct Dilatation After Resection of the Pancreas: A New Alternative?

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Background: EUS-guided drainage is a widely used modality for pancreatic pseudocysts and has challenged more innovative drainage techniques. Here, we report successful six cases of EUS-guided drainage of pancreatic juice through the gastrointestinal tract.

Patients: Three patients (Cases 1–3) underwent subtotal stomach preserving pancreaticoduodenectomy (SSPPD) following a clinical diagnosis of pancreatic carcinoma (PC) or hepatopancreaticoduodenectomy following a clinical diagnosis of bile duct cancer. Several months later, all three patients had the pancreatic fistula near the anastomosis of pancreatojejunostomy. One patients (Case 4) underwent distal pancreatectomy following a clinical diagnosis of PC. One month later, this patient had a pancreatic fistula near the stump of the pancreatic body. One patient (Case 5) underwent SSPPD following a clinical diagnosis of ampullary carcinoma. Two months later, this patient had an anastomic stenosis of the pancreatojejunostomy and dilatation of the pancreatic duct. One patient (Case 6) underwent SSPPD following a clinical diagnosis of ampullary carcinoma. Two years later, the patient had a recurrence at an anastomosis of the hepatocholangiojejunostomy, and developed a cavity near the dilated jejunum and pancreatic duct as a result of pancreatic juice statis.

Interventions: The technique included transenteric EUS-guided puncture; placement of a guidewire into the cavity near the pancreatic fistula, dilated pancreatic duct, or dilated jejunum; and artificial fistula between the cavity and gastrointestinal tract.

Results: EUS-guided transenteric drainage of pancreatic juice was successfully performed in all six cases without severe complication. Only one case developed a growth of the cavity and leakage of pancreatic juice, and required re-drainage. In the remaining five cases there was no recurrence (mean follow-up of 7.5 months; range, 1–27 months).

Conclusions: EUS-guided drainage of the pancreatic fistula is technically feasible, appears safe, and provides an attractive alternative to percutaneous or surgical drainage.

JPSY4-7

Endoscopic Treatment for Anastomotic Pancreatic Duct Stenosis After Pancreaticoduodenectomy

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Background and Aims: Pancreaticoduodenectomy (PD) is a standard operation for pancreatic head lesions, which rarely cause an anastomotic pancreatic duct stenosis as a late complication. Endoscopic approach for the anastomotic pancreatic duct stenosis is difficult because a scope hard to reach to the anastomotic site. Recently endoscopic equipment and technique are well developed; therefore in some case endoscopic treatment becomes possible for the anastomotic pancreatic duct stenosis. The aim of this work is to assess the endoscopic management for anastomotic pancreatic duct stenosis after PD.

Patients and Methods: 3 patients with anastomotic pancreatic duct stenosis after PD were treated by endoscopic management in our center. Original diseases for PD were IPMN in 2 and pancreatic cancer in 1. The time interval from surgery to endoscopic treatment was 8–103 months. Pancreatic duct reconstruction was pancreaticogastrostomy in 2 and pancreaticojejunostomy in 1. All patients have dilated main pancreatic duct ranged from 6 to 28mm. Details of endoscopic management, technical success, complication, and clinical course were assessed.

Results: In 2 pancreaticogastrostomy patients, EUS-guided pancreatic duct puncture was performed, and then 7 French plastic stent was placed into the main pancreatic duct. In a pancreaticojejunostomy patient, pancreatography performed from the anastomotic site using single balloon endoscopy, and then plastic stent was placed.

In all patients, pancreatic duct drainage succeeded without any complications.

2 patients of pancreaticogastrostomy, the stents were dislocated spontaneously in 1–4 months. One of them, a stent placed again, and the stenosis was improved of all cases.

1 patient of pancreaticojejunostomy, the stent was removed 2 month after the placement.

There was no recurrence of pancreatic duct dilatation in the follow-up period ranged 5 to 14 months.

Conclusions: Endoscopic treatment for anastomotic pancreatic duct stenosis after PD is safe and effective procedure, however further study is required including long-term results after the procedure.

JPSY4-8

EUS-guided Treatment in the Cases of Dilated Pancreatic Duct/Retention Cyst Due to Obstruction of Gastro-pancreatic Anastomosis After Pancreaticoduodenectomy

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Aim: EUS-guided drainage was recently established for pancreatic pseudocyst, dilated pancreatic/biliary duct for cases in which the duct cannot be drained using conventional ERCP. We retrospectively evaluated EUS-guided transmural treatment for the complications due to obstruction of gastro-pancreatic anastomosis after pancreaticoduodenectomy (PD).

Patients and Methods: We performed EUS-guided transgastric treatment in three patients with obstruction of gastro-pancreatic anastomosis after PD, dilated duct in 1, retention pseudocyst in 2. Used equipments were curved linear arrayed EUS, 19 gauge needle devise, guide-wire and plastic tube stent.

Results: One patient who had dilated duct was performed EUS-guided pancreaticogastrostomy, and 2 patients who had retention cyst were performed EUS-guided transmural cystdrainage. The procedures were successfully done without complications. Two cases were not required further treatment. One case was surgically made fistula using plastic stent as a landmark.

Conclusion: EUS-guided treatment in the cases of dilated pancreatic duct/retention cyst due to obstruction of gastro-pancreatic anastomosis after pancreaticoduodenectomy is feasible with safety.

JPSY4-9

Interventional Pancreatic Fistulo-jejunostomy

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Background: In pancreatoduodenectomy (PD), it has been reported that complete exteriorization of pancreatic juice is the safe method for the high risk patients or pancreatic fistula with the arterial bleeding.

On the other hands, we often encounter the intractable pancreatic fistula which has no communication with jejunum.

Aim: We propose the interventional pancreatic fistulo-jejunostomy for those cases by which we can avoid the laparotomy for the pancreato-enteric anastomosis.

Methods: After the pancreatic fistula was completely made, we confirmed the spacial relation between the pancreatic fistula and the jejunal loop by the computed tomography. Then, the pancreatic fistula was punctured into jejunum with a 22Gy needle for percutaneous transhepatic biliary drainage under X ray fluoroscopy.

The jejunum filled by air under endoscopy was visualized as the gas image.

After penetration one guide wire was inserted into the jejunal lumen via the needle.

Another guide wire was inserted into the pancreatic duct.

An 8Fr. internal drainage tube (Cliny Internal Drainage Tube®, CREATE MEDIC CO.,LTD) was pushing into both the jujunal lumen and pancreatic duct through the wire as the 'lost tube'.

Results: 4 patients underwent this procedure. No complications was occurred during this procedure. No further pancreatic fistula was made.

The mean hospital stay after this procedure was 11 days.

Conclusions: The interventional pancreatic fistulo-jejunostomy was very useful technique for the intractable pancreatic fistula or normalization of exteriorized pancreatic juice.

JPS Video Symposium 1 Cutting Edge Endoscopic Procedures for Diagnosis and Treatment of Pancreatic Diseases

VSY1-1

Endoscopic Ultrasound-guided Drainage for Pancreatic Diseases

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Background: As a treatment for pancreatic pseudocysts, drainage procedure using endoscopic ultrasound (EUS) has been widely developed. EUS-guided drainage has also been applied to pancreatic duct drainage for obstructive pancreatitis.

Method: EUS-guided pseudocyst drainage (EUS-PCD) and pancreatic duct drainage (EUS-PD) was performed in 29 and 3 cases, respectively. After puncturing pseudocyst by a needle, a pig-tail stent was placed to bridge cysts and the digestive tract. If cysts were infected, we inserted a nasocystic catheter as an additional step to irrigate the cyst. EUS-PD was employed in cases with obstructive pancreatitis. We punctured the dilated pancreatic duct from the body of the stomach under EUS-guidance. After a guide wire was inserted into pancreatic duct from the needle, we placed a stent into pancreatic duct using a rendezvous technique if the wire passed through the stricture of the duct to duodenum. If the guide wire did not pass the stricture of pancreatic duct, we deployed the stent to bridge the duct and digestive tract after dilation of puncture hole.

Result: EUS-PCD: In 11 cases with infected pseudocyst, a nasocystic catheter and a pig-tail stent were deployed. A single pig-tail stent was deployed in other cases. One patient underwent surgery due to enlargement of infected cyst. 86% of pseudocysts reduced or disappeared. As complication, exacerbation of pancreatitis was found in 1 case. EUS-PD: Stent placement in main pancreatic duct from minor papilla using rendezvous technique was performed in 1 case. Two patients had a stent deployment in the puncture site. The stent placement was successful in all cases, but peritonitis due to leakage of pancreatic juice was appeared in a case, which was improved by conservative treatment.

Conclusion: EUS-guided drainage could be a first choice for treatment of pancreatic pseudocysts, and be expected as a new minimally invasive treatment for obstructive pancreatitis.

VSY1-2

The Role of Interventional EUS for Pancreatic Diseases

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Background: The interventional EUS has been considered as diagnostic modality and treatment options in pancreatic disease. From Jun.2001 to Dec.2009, a total of 421 patients of pancreatic abnormalities were performed interventional EUS in our hospital. We reviewed our cases, and retrospectively investigated the role of interventional EUS for pancreatic disease.

Strategy of Interventional EUS: For pancreatic cancer: For the diagnosis, we firstly performed EUS-guided fine needle aspiration biopsy (EUS-FNA) in patient without obstructive jaundice. Diagnostic value of EUS-FNA in pancreatic mass lesion (n=237); sensitivity, specificity, accuracy was 95.9%, 98.3%, 96.6%. We performed EUS-guided paracentesis in 8 patients to rule out malignant ascites coincidentally. Four patients were diagnosed for malignant ascites and could avoid unnecessary operation. In unresectable cancer, we could select second regimen, following gemcitabine, according to the result of chemosensitivity test using specimen obtained by EUS-FNA. Some chemo-resistant patients were enrolled for EUS-guided fine needle injection with dendritic cells. EUS-guided celiac plexus neurolysis (EUS-CPN) relieved pain in 18/23 patients. EUS-guided biliary drainage (EUS-BD) for malignant biliary obstruction was successful in 5/6 patients. EUS-CPN and BD contributed to patient's QOL. For pancreatic pseudocysts: We considered postnecrotic pseudocysts on acute/chronic pancreatitis were well candidate for EUS-guided cyst drainage (EUS-CD). EUS-CD was performed in 42 patients with pancreatic pseudocysts during Jan.2001 to Dec.2009. Procedural success rate was 100% and efficacy rate was 96.6%. Recently, we used prototype forward-viewing echoendoscope for EUS-CD in 2 patients. The procedures were technically successful in all 2 patients without complications. Further studies that include larger numbers of patients are required to evaluate the role of the forward-viewing echoendoscope for interventinal EUS.

Conclusion: These results demonstrated that the interventional EUS could apply for various field of practice in pancreatic disease. It still has a potential for development including local therapy and further studies is required.

VSY1-3

Interventional EUS for Pancreatic Disease

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Introduction: EUS-FNA has widely accepted procedure for the diagnosis and therapy of pancreatic disease.

Objectives: Pancreatic lesions were 251 of 378 which were performed EUS-FNA from July 2000 to May 2009.

Methods: 1) The accuracy of histopathological results of 196 pancreatic masses was evaluated. 2) DOP-PCR CGH analysis was done for 16 pancreatic cancer patients using tissues obtained by EUS-FNA. 3) 11 patients were evaluated the sensitivity for GEM with HSP27 immunostaining. 4) EUS-guided pancreatic cyst drainage (EUS-CD) was performed for 25 lesions (17 men and 7 women, mean age 57.2 years). Mean size was 84mm (38–200mm). We punctured with 19G needles. About lately 12 pseudocysts, stents and nasocystic catheter were placed simultaneously. 5)EUS-guided choledochoduodenostomy (EUS-CDS) was performed for 4 pancreatic cancer patients (2 men and 2 women, mean age 64.5 years). We punctured with 19G needles and placed a straight plastic stent. 6) 2 pancreatic cancer patients underwent dendritic cell injection therapy by procedure of EUS-FNA. 7) The antiproliferative activity of combined administration with GEM and IFNgamma was evaluated in vitro and in vivo. GEM-resistant cells were transplanted on nude mice, then IFNgamma was injected within tumor, and GEM was administered systemically.

Results: 1) The accuracy, sensitivity, and specificity of EUS-FNA in solid pancreatic masses were 95.2%, 95.2%, and 95.5%. 2) Genetic alterations were identified same as surgical and autopsy tissues. 3) Patients with high HSP27 expression had worse prognosis. 4) 23 of 25 lesions (92%) were decreased or disappeared. 5) All EUS-CDS were successful. Especially, our handmade plastic stents were useful to prevent slipping out. 6) No adverse event was occurred after DC injection therapy. 7) The sensitivity for GEM was improved in vitro. And tumor growth was tended to be inhibited in vivo.

Conclusion: EUS-FNA has unlimited potential as therapeutic and diagnostic EUS for pancreatic diseases.

VSY1-4

How to Treat the Pancreatic Pseudocyst. Is Endoscopic Transpapillary Drainage the Best Treatment?

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Introduction: It is still controvercial how to treat the pancreatic pseudocyst. In 17 years, 95 cases of chronic pancreatitis with pseudocyst were treated. ENPD and ESP were the first choice for their treatment in our hospital.

Aims: Evaluation of the efficacy and safety of endoscopic transpapillary drainage (ENPD and ESP).

Objects and Methods: 95 cases consisted of 86 alcoholic, 6 idiopathic, 1 autoimmune, 1 hereditary, and 1 hyperparathyroidism. 68 cases had pancreatic stone and 27 cases were non-calcified chronic pancreatitis. Pseudocyst located in head 39 cases, body 19 cases, body and tail 8 cases, tail 28 cases and 1 case in out of pancreatic parenchyma. Stone removal alone was conducted in 17 cases, operation in 4 cases, percutaneous method alone 2 cases, and transmural method alone 1 case. 71 cases were treated by ENPD and ESP (with percutaneous and transmural methods in some cases). In this group, pseudocysts located in head 22, body 18, body and tail 7, and tail 24, and ERP revealed the connection between main pancreatic duct and pseudocyst in all 71 cases. The effect of the endoscopic transpapillary drainage (ENPD and ESP) mothods and their prognosis were evaluated.

Results: The success rate of ENPD and EPS was 98.6%(71/72) without any problems after the procedures. Pseudocyst relapse were 3 and re-placement of EPS was done.

Conclusions: When ERP has revealed the connection between lesions and the pancreatic duct, endoscopic transpapillary drainage is indicative. We would like to stress that this method is the best treatment of pancreatic pseudocyst, because it repairs the broken pancreatic duct and reduces normal pancreatic juice flow and makes good prognosis.

On the other hand, medically untreatable huge abscesses especially its inflammation spreading to the spleen are indicative of operation.

VSY1-5

The Value of Cytology Using Endoscopic Naso-pancreatic Drainage (ENPD) for Early Diagnosis of Pancreatic Cancer

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Backgrounds: We evaluated the value of cytology in pancreatic juice using ENPD for early diagnosis of pancreatic cancer retrospectively.

Materials and Methods: As the indication for ENPD, the case with localized irregular stenosis of the main pancreatic duct, and the elevation of serum pancreatic enzymes was chosen. From the beginning of 2007 to the end of 2009, ENPD was performed in 16 cases. A 5Fr. ENPD catheter was inserted into the main pancreatic duct over the irregular stenosis for one day to collect the pancreatic juice for 2 to 6 times.

Results: 11 out of 16 cases demonstrated positive in cytology using ENPD. The surgical therapy was performed in these 11 cases. Pathological finding revealed that 4 out of these11 cases were diagnosed as the ductal carcinoma in situ located in the pancreas body. All 4 cases demonstrated the dilatation of the main pancreatic duct from body to tail of the pancreas. However, the apparent tumor lesion was not detected by abdominal CT and EUS in these cases. The sensitivity, specificity, and overall accuracy of ENPD were 100%, 75%, and 93%, respectively. The complication of ENPD was recognized in one case with acute pancreatitis.

Conclusions: These results suggested that the method of cytology in pancreatic juice using ENPD may contribute to the early diagnosis of pancreatic cancer in cases with irregular stenosis of main pancreatic duct.

VSY1-6

Endoscopic Treatment Via the Minor Papilla by the Rendezvous Technique

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Objective: Endoscopic diagnosis and treatment with the rendezvous technique using the minor papilla via the major papilla are increasingly performed in cases where approach via the major papilla is technically difficult or where the main pancreatic duct has a bend or stricture. We present video records of cases treated endoscopically via the minor papilla using the rendezvous technique.

Patients and Methods: The subjects were 13 patients treated with the rendezvous technique for pancreatic diseases until September 2009. Per the rendezvous technique i) a guide wire is inserted from the major papilla toward the santrini duct and passed through the minor papilla into the duodenal lumen, ii) it is retrieved with a snare, basket, or biopsy forceps inserted into the same channel, iii) and then the catheter is inserted again using the guide wire remaining in the minor papilla. The issues we reviewed were 1) disease, 2) treatment, and 3) complications.

Results: 1. Disease included chronic pancreatitis in 12 cases and anomaly of pancreatobiliary ductal union combined with protein plaque in the accessory pancreatic duct in 1 case. 2. Of the 12 cases of chronic pancreatitis, endoscopic pancreatic stent (EPS) with/without minor papilla sphincterotomy was performed in 8 cases and ENPD was performed in 4 cases. In the case of protein plaque in the santrini duct, balloon dilatation of the minor papilla successfully removed the protein plaque. 3. Complications were minor; there was one case of pancreatitis and this resolved with conservative treatment.

Conclusion: In the endoscopic diagnosis and treatment of pancreatic diseases, the rendezvous technique using the minor papilla can be an effective method for cases where approach via the major papilla is technically difficult.

VSY1-7

A Novel Technique for Treating Infected Pancreatic Necrosis: Endoscopic Necrosectomy Based on the NOTES Approach

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Infected pancreatic necrosis (IPN) is potentially lethal. Conservative treatments are usually ineffective, and surgical necrosectomy with drainage is often required. However, it is associated with the high mortality rate. Recently, a minimally invasive endoscopic necrosectomy based on the natural orifice transluminal endoscopic surgery (NOTES) approach was developed.

Methods: Between February 2002 and October 2009, 10 IPN patients underwent endoscopic treatments at our institution. During the early period (until March 2006), a transmural stent and a nasocystic catheter were placed after puncturing the necrotic cavity under endosonographic guidance. Thereafter, the necrotic cavity was irrigated daily through the nasocystic catheter. During the later period (since April 2006), further aggressive treatment, NOTES-based endoscopic necrosectomy was additionally performed . First, balloon dilation (maximum diameter, 18 mm) of the transmural tract was performed, and an endoscope with a water-jet system was introduced through the gastrointestinal wall into the necrotic cavity. Subsequently, forceful irrigation and suction were performed, and the necrotic tissue was removed using a 5-prong forceps under direct visual control.

Results: During the early period, 6 patients underwent endoscopic drainage and irrigation, but the infection resolved completely in only 1 patient, whereas inflammation persisted or recurred in the others. Therefore, complementary percutaneous drainage (n=2) or surgical necrosectomy with drainage (n=3) was performed; the median duration of therapy was 15 weeks (range, 14–16 weeks) and 18 weeks (range, 17–20 weeks), respectively. During the later period, the remaining 4 patients were successfully treated by endoscopic necrosectomy. The median number of endoscopic necrosectomy sessions was 5.5 (3–6); median duration of therapy, 7 weeks (3–8 weeks); and median duration of follow-up, 14 months (2–43 months); no recurrence was observed during the follow-up period. No patient had any complications.

Conclusions: This technique is highly effective and safe for IPN treatment.

VSY1-8

Laparoscopic Ultrasonography-guided Biopsy for Pathological Diagnosis in Advanced Unresectable Pancreatic Cancer

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Background: It has been reported that patients considered for treatment protocols for locally unresectable pancreatic cancer should be stages laparoscopically before initiation of therapy. Staging laparoscopy is important for detect occult lesions such as peritoneal and superficial liver metastasis in pancreatic cancer. In addition to visual inspection, biopsy of suspicious lesion under laparoscopic ultrasonography (LUS) can be obtained. We evaluated the usefulness of LUS-guided biopsy for particular pathological diagnosis in unresectable advanced pancreatic cancer.

Method: Between July 1, 2006 and December 31, 2009, data from all consecutive patients undergoing elective staging laparoscopy for advanced unresectable pancreatic cancer were retrospectively analyzed. LUS-guided tru-cut biopsy was performed using the 18G needle that was introduced through the anterior abdominal wall right above the pancreatic tumor. All punctures were performed under LUS guidance with laparoscopic view of aspect.

Results: Thirty-six patients were identified who underwent staging laparoscopy. Mean age of these patients was 66-year old and male ratio was 0.65. Liver inspection by LUS was attempted to all patients. LUS-guided biopsy was performed in twenty patients. Single-incisional laparoscopic approach was introduced in three patients. Acquired samples were diagnosed as adenocarcinoma in nineteen patients (95%). Pathological differentiation type of adenocarcinoma was identified in fourteen patients (70%). LUS-guided biopsy revealed moderate differentiated adenocarcinoma in 70-year old male who was diagnosed as chronic pancreatitis by endoscopic ultrasound guided fine-needle aspiration. Although one patient had small abdominal abscess due to pancreatic fistula that was cured by conservative treatment, there were no uncontrorable bleeding and another complications after puncture of the tumor.

Conclusions: LUS-guided biopsy contributes to acquire enough volume of the tissue safely for certain pathological diagnosis with differentiation type of the tumor which we need to decide treatment strategy for advanced unresectable pancreatic cancer.

VSY1-9

Endoscopic Surgery for Islet Cell Tumor of the Pancreas

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Introduction: Since January 2004, we have conducted laparoscopic distal pancreatectomy (Lap-DP) and laparoscopic pancreaticoduodenectomy, which amount to more than 50 cases. The patients who underwent Lap-DP include 13 cases of islet cell tumor of the pancreas. We demonstrate the surgical techniques and clinical outcomes of laparoscopic spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein (Lap-SPDP) for the pancreatic neuroendocrine tumor.

Patients & Procedure: A total of 13 patients with islet cell tumor of the pancreas (5 insulinomas and 8 non-functioning tumors) who underwent Lap-DP from January 2004 to October 2009 were enrolled. Six men and 7 women, the mean age was 52 years (31–85 years old). The average BMI was 23.1 kg/m2 (17.1–28.2 kg/m2). The tumor was located at the body of the pancreas in 8 patients and at the tail in 5 patients. The average size of the tumors was 2.6cm (1.3–7.0 cm). Pancreatic transection was performed by endoscopic linear stapler in all 13 cases. When preservation of the spleen was proposed, Warshaw's procedure was not employed and the splenic artery and vein were conserved in all of 9 patients. The average follow-up periods was 30.1 months (2–69 months).

Results: Median operating time was 285 minutes (225–635 minutes), and median blood loss was 170 ml (10–1020 ml). No transfusions were given during or after surgery in all cases. In all patients, oral intake was started within five days of surgery, and the median value was 2 days after surgery. Pancreatic fistula was found in 53.8% (gradeA: 46.1%, grade B: 7.6%, grade C: 0%). The median hospital stay was 8 days (7–10 days), and none of the patients died in the perioperative period.

Conclusion: We emphasize that Lap-DP might be feasible and safe procedure in islet cell tumor arising in the distal pancreas.

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VSY2-1

Significance of Dissection Including the Root of the Mesentery for Pancreatic Head Carcinomas Arising from the Ventral Pancreas Domain

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Curative resection has been shown to be one of the key factors influencing the survival of patients with pancreatic head carcinomas. Even after resection, the 5-year survival rates are approximately 20%, with a median survival rate of approximately 18 months. Many patients develop local and/or distant recurrences after R0 resection, which could reflect the presence of microscopic residual disease at the time of resection. Esposite reported that the medial (68%) and the posterior (47%) margins were most commonly involved after conventional pancreatoduodenectomy for pancreatic head carcinomas. We discovered the lymphatic spread and nerve plexus invasion of pancreatic head carcinomas can be divided into two patterns by tumor location based on the two anlagen of the pancreas, the ventral or dorsal pancreas. When the tumor is confined to the ventral pancreas domain (40%), the lymphatic spread and nerve plexus invasion are limited to areas along the superior mesenteric artery (SMA) besides peripancreatic lymph nodes. And the anterior renal fascia acts as a barrier against the lymphatic spread and nerve plexus invasion of carcinomas. On the basis of these results, we developed a modified procedure of pancreatoduodenectomy for pancreas head carcinomas mainly confined to the ventral pancreas domain. There are mainly two different points in our procedure from the standard pancreatoduodenectomy. The first point is the dissection plane; posterior dissection is performed behind the anterior renal fascia from anterior to the inferior vena cava before removing the pancreas which is started from the original portion of the jejunum. The second point is the area of dissection around the mesentery; dissection area around the mesentery including from the lower level of the third portion of the duodenum to the root of the SMA.

VSY2-2

Non-touch Isolated Pancreaticoduodenectomy with a Mesenteric Approach for Pancreatic Head Cancer

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We have been performing non-touch isolated pancreaticoduodenectomy with a mesenteric approach for pancreatic head cancer since 1981. In this procedure, we never touch the pancreas head region before treating its influent and effluent vessels by a mesenteric approach. First, we assess tumor infiltration of the vessels and nerve plexus in accurate detail by intra-portal endovascular ultrasound (IPEUS) for patients with suspected invasion of the portal vein (PV) or the second portion of the pancreatic head nerve plexus. The mesenteric approach enables us to perform lymph node dissection around the superior mesenteric artery (SMA) and the superior mesenteric vein (SMV) safely and to determine the feasibility of resection. In addition, this procedure makes subsequent portal vein reconstruction easier. Ligation of the inferior pancreaticoduodenal artery is usually followed by dissection of the right side nerve plexus around the SMA. Portocaval bypass is created using an antithrombogenic catheter (Anthron Bypass Catheter) for patients suspected to require PV/SMV resection. After ligation of the gastroduodenal artery and PV/SMV resection, we mobilize the pancreatic head region from the retroperitoneum. Imanaga's procedure or modified Child's procedure is used for reconstruction. PV/SMV reconstruction is conducted by two-point mounting end-to-end continuous anastomosis. There were 161 patients with pancreatic cancer underwent this procedure from January 2001 to June 2009, including 109 (68%) patients requiring PV/SMV resection. Mean operative time was 477.7 minutes and mean estimated blood loss was 1317ml. There were no postoperative deaths. Among the 109 patients underwent PV/SMV resection, 28 (25.7%) required blood transfusion. We believe this procedure is safe and effective for decreasing of blood loss during operation and prevention of scatter of tumor cells.

VSY2-3

Pancreaticoduodenectomy Combined with Portal Vein Resection and Reconstruction for Pancreas Head Cancer

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We have performed aggressive surgical resection for a radical operation including resection and reconstruction of portal vein in order to improve the surgical results of pancreas head cancer. Between 1990 and 2009, the subjects in this study were 149 patients who underwent pancreaticoduodenectomy for pancreas head cancer, excluding 7 cases of arterial resection and 9 cases of hepatic metastases. Among these, combined portal vein resection was performed in 76 patients (51.0%). Portal vein reconstruction was performed by end-to-end anastomosis with a running suture in 59 patients, and by auto-vein graft in 17 patients. The auto vein grafts utilized were from the left renal vein in 15 patients, umbilical vein in 1, and inferior mesenteric vein in 1. An left renal vein graft can be obtained easily without making an additional skin incision during pancreatic surgery, and the diameter of the left renal vein graft usually matches well with the portal vein. Combined portal vein resection did not increase the risk of surgery and postoperative complication following pncreaticoduodenectomy. Multivariate analysis revealed that resection margin and adjuvant chemotherapy had independent factors on survival after surgical resection for patients with pancreas head cancer. Combined portal vein resection for histlogically curative surgery in patients with pancreas head cancer involving the portal vein might have a beneficial effect on prognosis. Our detailed procedure of portal vein reconstruction using left renal vein will be presented in the video.

VSY2-4

Oblique Transection of the Pancreas Head in Extended Distal Pancreatectomy with en Bloc Celiac Axis Resection (DP-CAR) for Advanced Pancreas Body Cancer

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Introduction: Advanced pancreatic body cancer often extends to the head of the pancreas as well as involving the common hepatic artery and/or the celiac axis. Distal pancreatectomy with en bloc celiac axis resection (DP-CAR) with oblique transection of the parenchyma of the pancreas head enables resection with negative margin for such proximally extended lesions in the condition that the gastroduodenal artery (GDA) could be preserved.

Objective: To establish the surgical technique of DP-CAR with extended parenchymal resection of the pancreas head.

Methods: GDA was encircled at its origin as well as the proper and common hepatic arteries. After dissection of the common hepatic artery, GDA was dissected distally to expose the anterior and posterior superior pancreatoduodenal arteries (ASPDA and PSPDA), and the right gastroepiploic artery (RGEA) as ligating and dividing small tributaries arising from the GDA and ASPDA. After GDA, ASPDA including RGEA were mobilized laterally and ventrally, transection of the pancreatic parenchyma was able to be started from the portion distant enough from the tumor, and continued obliquely towards the right side of the portal vein. During the procedure, surgeons had to pay special attention to prevent the lower bile duct and even its epicholedocal plexus from being injured. As the transection plane was usually so broad that no special procedure like suture closure was applied on it.

Results: Since 1998, among 50 patients who underwent DP-CAR, the extended oblique transection of the pancreas head was performed in 12 patients. Seven of 12 patients developed pancreatic

fistula postoperatively, however recovered with median duration of 25 days of drainage.

Conclusions: DP-CAR with oblique transection of the pancreatic parenchyma and mobilization of the GDA was successfully performed for the lesion which extended towards the head of the pancreas.

VSY2-5

Is Limited Pancreatic Resection Feasible for Renal Cell Carcinoma Metastatic to the Pancreas?

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Objectives: To validate the feasibility of limited resection to metastatic renal cell carcinoma (RCC) to the pancreas.

Methods: A total of 15 patients (9 men, 6 women) with a median age of 72 years (range 48 to 80) underwent pancreatic surgery. The initial pathologic findings were all renal cell carcinoma, with a left-sided tumor occurring in 4 and a right-sided in 10 and bilateral in 1 patient. The median interval from nephrectomy to the pancreatic surgery was 101 months (range 0 to 228). Solitary metastasis at the pancreas was confirmed in 9 patients, and other six carried multiple metastases.

Results: Surgical removal was accomplished by standard procedures (PD=4, DP=6, TP=1) and limited resection (MP=2, DpPHR=1, partial resection=1). There was no perioperative mortality. At the end of follow-up, seven patients were alive at 6.4 to 79.4 months, and the five-year survival was estimated at 80.8%. Pathological examination revealed that clear capsules of the metastatic tumors without micro vessel and lymphatic involvement were found in the patient with less than 30mm in tumor diameters (n=11), while micro vessel involvement or an extra-capsular invasion was found in 4 cases with over than 35mm.

Conclusions: Limited pancreatic resections might be procedures of choice in single and small metastasis in the pancreas.

VSY2-6

Pancreatic Head Resection with Segmental Duodenectomy (PHRSD) for Intraductal Papillary Mucinous Neoplasms (IPMN) of the Pancreatic Head

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We proposed pancreatic head resection with segmental duodenectomy (PHRSD) for benign or low-grade malignancy tumor of the pancreatic head region as a function-preserving operation instead of pylorus preserving pancreatoduodenectomy (PpPD). This operation is simple, easy and safe procedure compared with duodenum preserving pancreatic head resection (DpPHR).

Laparotomy is done by upper midline skins incision. The gastrocolic and duodenocolic ligament is divided. Intraoperative US study is very important to identify the tumor. By conserving the right gastric artery and gastroduodenal artery, 5 to 7 cm of the first portion of the duodenum is preserved with good arterial circulation. The anterior superior pancreatoduodenal artery and posterior superior pancreatoduodenal artery are ligated and divided. In addition, by conserving the anterior inferior pancreatoduodenal artery, the third portion and anal side of the second portion of the duodenum are preserved with good arterial circulation. Resection of the pancreatic head with 3 to 4 cm of segmental duodenectomy including minor and major papilla completes PHRSD. The distal pancreas is examined by ultrathin pancreatoscope. Reconstruction of the alimentary tract is then performed with pancreatogastrostomy, end-to-end duodenoduodenostomy and end-to-side choledochoduodenostomy.

PHRSD is simple, easy, safe and function-preserving operations for benign or low-grade malignancy tumor of the pancreas. We performed this operation in 70 cases, and there has been no mortality to date. In this video, PHRSD for the branch type of IPMN of the pancreatic head is presented.

VSY2-7

How I Do It – Pancreaticojejunostomy (Duct to Mucosa Anastomosis)

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Background: Significant advances in surgical technique and critical care management have substantially reduced the mortality associated with pancreatic surgery. However, pancreatic anastomotic failure has been a source of significant morbidity and potential mortality after pancreatic head resection.

Purpose: The aim of the present study was to improve management of the pancreatic remnant for reducing pancreatic anastomotic failure after pancreatic head resection.

Material & Method: From July 2004 to December 2009, 46 patients underwent pancreaticojejunostomy using the described technique. Pancreaticojejunostomy after pancreaticoduodenectomy was performed in all cases using a two-layer technique consisting of an outer full thickness pancreas-to-seromuscular jejunal anastomosis with 5-0 polypropylene continuous sutures and an inner duct-to-mucosal anastomosis with 4–6 interupted sutures using a 6-0 polydioxanone stitch with 2.5–3 X power ocular loupes. Stents are palced in all cases using 3.5–5F infant feeding catheter into the jejunum for external drainage. Incidences of pancreatic anastomotic failure and complications were analyzed.

Results: There was 2.2% (1/46) mortality and 16.3% (8/46) morbidity. The rate of pancreatic anastomotic failure was only 6.5% (3/46).

Conclusion: The end to side, duct-to-mucosa pancreaticojejunostomy with external stent technique is effective in reducing the leakage rate after pancreaticoduodenectomy.

VSY2-8

Laparoscopic Spleen Preserving Distal Pancreatectomy with Special Referrence to Vessel Preservation

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Aim: To demonstrate our method to preserve spleen with its artery and vein in laparoscopic distal pancreatectomy (LDP).

Backgrounds: Spleen preserving distal pancreatectomy is becoming more common in the field of the LDP. Preservation of splenic vessels is one of the most ideal methods to avoid perigastric venous dilatation after LDP, although it is more complicated than the Warshaw's method. It is urgent to establish the critical techniques to preserve splenic vessels in LDP.

Methods: There are few branches of splenic vein (SPV) in the pancreatic tail or on the SMV. However, between SMV and pancreatic tail, SPV is embedded in the pancreatic tissue, and many short branchs drain from pancreas to SPV. Therefore, we are applying two methods to preserve SPV. For extensive resection of the pancreatic body, we transect the pancreas over SMV at first, and the pancreas is turned over from SMV toward the tail. Short branches of SPV are sealed by a vessel sealing system. For the limited resection of the pancreatic tail, the pancreas is turned over from the tail toward the transection line, and the pancreas is cut at the end. It is quite difficult to start removal of the pancreas from SPV in the middle of the SMV and pancreatic tail.

Results: We encountered no splenic infarction or perigastric venous dilatation after vessel preserving LDP.

Conclusion: Splenic vessel- preserving LDP is complicated, although its outcome is ideal. The point to start removal of the pancreas is one of the pivotal points of this technique.

VSY2-9

Laparoscopic Distal Pancreatectomy in Our Institution

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Introduction: Since the approval of laparoscopic pancreatic resection by the ethics committee of Nippon Medical School in January 2004, this procedure has been introduced and performed in our department. We have conducted laparoscopic distal pancreatectomy (Lap-DP) and laparoscopic pancreaticoduodenectomy (Lap-PD), which amount to more than 50 cases to date. Although Lap-PD underwent in limited cases of such tumors as were localized at the papilla Vater or inferior bile duct, Lap-DP has been performed as standard procedure for the patients who had a lesion in the distal pancreas. We demonstrate the techniques and clinical outcomes of Lap-DP. We also introduce a new device, sponge spacer, for laparoscopic surgery.

Patients and Methods: A total of 45 patients who underwent Lap-DP between January 2004 and December 2008 were enrolled. 13 men and 32 women, the mean age was 54.8 years (14–85). The tumors were located in the distal panceas; 22 cystic diseases, 12 endocrine tumors, 6 invasive ductal cancers which were less than T2, and others. The average size of the tumors was 4.5cm (1.3–17.0).

Results: One patient who was intraoperatively diagnosed as pancreatic cancer with invasive growth to peripancreatic tissues was converted to open surgery. Thirteen patients were performed spleen-preserving Lap-DP with splenic vessel conservation. The pancreas was resected using an endoscopic linear stapler in all patients. The mean operation time was 316 min (150–635). The mean blood loss was 246 ml (0–1020) and there was no patient with blood transfusion. Pancreatic fistula occurred in 35.5% of Grade A, 6.6% of Grade B and zero of Grade C. There were no other postoperative complications. The mean postoperative hospital stay was 11.4 days (6–43) in these patients.

Conclusion: We conclude that Lap-DP is so feasible that this procedure will be standard operation for the cases of left pancreatic diseases.

VSY2-10

Laparoscope-assisted Central Pancreatectomy

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A central pancreatectomy (CP) is a parenchyma-sparing procedure. First, we analyzed the perioperative course, the frequency of postoperative onset of diabetes mellitus, and long-term change of body weight. Second, the surgical procedure of laparoscope-assisted CP (LACP) is introduced in this study.

Clinical outcomes of CP: The rate of postoperative complications including grade B/C pancreatic fistula was no different between CP and distal pancreatectomy (DP). Only one patient undergoing a CP (4.7%) developed new onset of mild diabetes. The body weight in the DP group was significant lower than that in the CP group. A CP is a safe procedure for the treatment of low-grade malignant neoplasms in the pancreatic body; the rate of onset of diabetes is minimal, and the body weight improves early in the postoperative course.

Surgical procedure of LACP: LACP has emerged as an attractive minimally invasive alternative for selected patients. To establish the less invasive surgery of CP, thus we have introduced the LACP.

Patient: A 19-year-old woman with an incidentally identified 4-cm cystic lesion in the pancreatic body. Two 5-mm and two 10-mm ports were placed in upper quadrant ports. The gastrocolic ligament was divided, and the pancreas was exposed by retracting the stomach upwards. The lesion was resected with a margin of at least 1 cm to both cut pancreatic ends. The distal pancreatic transaction was performed by use of Harmonic scalpel, and the duct was isolated and transected by scissors. The resected pancreas was then placed in a retrieval bag and extracted through the right upper quadrant enlarged 10-mm port incision. Reconstruction of the distal pancreatic remnant was extracorporeally performed by a duct-to-mucosal pancreaticojejunostomy. LACP can be safely performed in selected patients, and this procedure may be an optimal alternative to open surgery.

VSY2-11

HALS-DP as a Standard Method for Distal Pancreatic Tumors

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Background and Aim: Laparoscopic distal pancreatectomy (LADP) has been applied to many cases in pancreatic surgery, but it is not yet a standard method for pancreatic malignant tumors. We developed anterolateral approach with handassisted maneuver as a standard method for pancreatic disease including malignancy and now present the details.

Methods: For the last 7 years, 32 patients were treated with DP for pancreatic tumors. HALS with transperitoneal anterolateral approach was performed in 10 patients (group A). Other cases consisted of open laparotomy (group B). The patients' features, the operative details and the postoperative outcome in both groups were compared.

Operative Procedure: In preoperative estimation by CT scan and ultrasonography, location of the tumor and splenic artery (SA) should be identified. The site of Gelport is marked by ultrasonography before operation. Skin incisions for 3 ports and one Gelport are made. First, the lower pole and the back side of spleen is dissected from the retroperitoneum and then splenic artery is clipped at the marking. The lateral side then the upper pole of spleen is detached from the retroperitoneum, followed by enough isolation of pancreatic tail and body from the it (Portal vein should be visible). Finally, pancreas is cut with conventional method without GIA and the stump can be sutured through Gelport. Further lymph node dissection can be fully performed using operator's left hand.

Results: In group A, average hospital stay was 10 days, while 16 days in group B. Operation time, intraoperative blood loss did not show any difference. In the aspects of intraoperative and postoperative complication, there were none in the two groups.

Conclusions: In the cases of pancreatic tumor including malignancy, HALS with transperitoneal anterolateral approach significantly facilitates the surgical procedure and reduces the operational risk, while maintaining the advantages of conventional laparotomy.

VSY2-12

Usefulness of Hand-assisted Laparoscopic Distal Pancreatectomy for Benign and Low-grade Malignant Tumors of the Pancreas

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Laparoscopic pancreatic surgery (LPS) has now developed as a clinical setting. We introduced LPS in March 2007. The most important point is to select patients that are appropriate for LPS based on precise pre- and intraoperative diagnoses, and prevent complications such as pancreatic fistula. Indications are benign, borderline and low-grade malignant tumors and invasive ductal adenocarcinoma is contraindication at present. We put safety as the main priority on introducing LPS, and started from laparoscopic-assisted distal pancreatectomy, in which the body and tail of the pancreas were mobilized from retoroperitoneum laparoscopically and transected extraperitoneally under direct vision. We gradually progressed to intraperitoneal hand-assisted laparoscopic distal pancreatectomy (HALS-DP) using a liner stapler and splenic artery-, vein- and spleen-preserving distal pancreatectomy (HALS-SPDP). We report experiences in our institutions, indications for LPS, and the procedure.

The number of subjects with IPMN, MCN, SCN, LEC and NET were 5, 1, 2, 1 and 2, respectively. We performed 1 laparoscopic-assisted distal pancreatectomy (extraperitoneal resection), 7 HALS-DP, 1 HALS-SPDP, 1 tumor enucleation and 1 full laparoscopic-DP. The mean operative time was 325 minutes, and the hemorrhagic volume was 395 ml. No case required transfusion or conversion to open surgery. Notably, 2 cases, those were attempted with full laparoscopic technique, were converted to HALS-DP because of severe adhesion between tumor and vessels while maintaining less invasiveness and safety. Postoperative pancreatic fistula (grade B of the ISGPF classification) occurred in 3 (27%) patients. No other complication was observed. The mean postoperative number of days taken to initiate oral food intake was 2.2, and the average length of the hospital stay was 10 days.

A hand-assisted procedures were safely and efficiently especially for initial induction and experience of LPSs. We would like to perform more minimally invasive laparoscopic operations and expand the indications while confirming the safety.

VSY2-13

Minimally Invasive Surgery for Pancreatic Disease

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Since the introduction of laparoscopy, application on laparoscopic surgery for pancreas is increasing these days. There are several kinds of laparoscopic surgical procedure including distal pancreatectomy, pancreaticoduodenectomy, central pancreatectomy, enucleation, etc. Although, laparoscopic pancreaticoduodenectomy is still controversial due to its difficult techniques, laparoscopic distal pancreatectomy is frequently used as an optional treatment method for the lesions in body and tail of pancreas, when the lesion is considered benign or premalignant. Laparoscopic enucleation is an also good treatment modality when the lesion is presumed to be benign and small such as insulinoma. Central pancreatectomy is moderately difficult in terms of technique, and it is occasionally used for the lesion in the neck to preserve the volume of the pancreas as much as possible. The application of laparoscopic technique to malignancy is still contraindicated and still there are few reports on this disease entity

We retrospectively analyzed of the clinical outcome of 78 patients who underwent laparoscopic pancreas surgery from June 2004 to October 2009. Operation types were 55 cases of distal pancreatec-

tomy, 10 cases of pancreaticoduodenectomy, 6 cases of central pancreatectomy, 4 cases of enucleation and 3 other operations. Among them, 8 patients were confirmed as malignant disease. Among them 3 patients had ductal adenocarcinoma, 3 patients had malignant IPMT, one endocrine carcinoma and one mucinous adenocarcinoma. One patient out of 3 patients with ductal carcinoma has died due to liver metastasis, which was missed at preoperative work-up, and remaining 2 patients are still alive without any recurrence. The patient with invasive endocrine carcinoma is still alive for 52 months with recurrence of tumor at postoperative 21 months. In summary 7 out of 8 patients are still alive, with one recurrence. Our experiences show that laparoscopic pancreas surgery is becoming attractive option for pancreas disease.

VSY2-14

Laparoscopic Pancreaticoduodenectomy -Can LPD Be One of Therapeutic Options for Pancreatic Neoplasms?

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Background: Although many reports have described laparoscopic pancreatic surgery, only limited series and case reports concerning laparoscopic pancreaticoduodenectomy (LPD) have been published recently. We here review our experience with LPD, and discuss the role of this procedure in treatment of pancreatic neoplasms.

Methods: Thirty patients with periampullary disease underwent LPD. Seventeen of these 30 patients had pancreatic neoplasm, including 10 IPMNs, 4 pancreatic cancers, and 3 pancreatic endocrine tumors.

Results: In all 17 patients with pancreatic neoplasm, the operation were performed without serious complications. In one patient, cancer invasion to the portal vein was detected and portal resection and reconstruction was performed through a small midline incision. Although mean operative time of LPD was longer than that of open PD, mean blood loss were similar. No significant differences in the incidence of complications or hospital stay were noted between both groups. Surgical margin and number of lymph nodes found in the resected specimen did not differ between both groups.

Conclusions: LPD is feasible, safe, and beneficial for pancreatic neoplasms except pancreatic cancer, and may be one of therapeutic options for carefully selected patients with pancreatic cancer. Clearly, a larger cohort needs to be evaluated in a prospective, randomized study to elucidate appropriate indications and effects of the present procedure.

VSY2-15

Robot-assisted Function-preserving Minimally Invasive Pancreatectomy in Benign and Borderline Malignant Tumor of the Pancreas

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Background: Function-preserving minimal invasive pancreatectomy is thought to be ideal approach for pancreatic benign and borderline malignant lesions requiring pancreatectomy. In particular, great efforts to preserve spleen and pancreas parenchyma are increasing on the basis of this concept. However, conventional laparoscopic approach is not that easy. It must require extensive surgeons' learning-curves (experiences and techniques) due to several disadvantages that conventional laparoscopic surgery has. Robot surgical system was recently introduced to overcome these limitations to provide precise and safe laparoscopic surgery.

Materials and Methods: From March 2006 to December 2008, total 40 patients underwent laparoscopic pancreatectomy with intention to preserve spleen or pancreas parenchyme by a single pancreatic surgeon. Twenty-two patients were done by conventional laparoscopic approach (LP group) and the rest 18 patients by robot-assisted surgery (RP group).The perioperaitve clinicopathologic variables (age, gender, length of resected pancreas, tumor size, tumor location, bleeding amount, operation time, length of hospital, complication, mortality)were compared between two group, as well as spleen-preservation rate.

Results: The younger patients preferred robot-assisted surgery to conventional laparoscopic surgery (55.7±14.0 years vs. 44.1±16.5 years, $p=0.020$), and the mean operation time was longer in Robot group (271.6±120.0 min. vs. 365.8±129.4 min, $p=0.024$). From the view point of intention-to-preservation of spleen, the spleen-preserving rate of Robot group was considerably superior to that of Lap group (fail/success, 8/14 vs. 1/17, $p=0.027$). However, robot surgery cost the patients about 8000$ (8047.9±2066.3$) which was approximately twice the conventional laparoscopic group (4115.6±1865.4$). There were no significant differences in other clinicopathologic variables.

Conclusion: Robot-assisted pancreatic surgery can provide increased chance for not only spleen preservation but also far advanced laparoscopic surgery. More experiences are mandatory to exactly address the role of robot surgery in far advanced laparoscopic era.

Forum 01 Acute Pancreatitis Basic, Diagnosis

F-001

Organ Failure and Pancreatic Infection as Determinants of Mortality in Patients with Acute Pancreatitis: A Rationale for a 'Critical' Category of Classification

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Background: There is no consistency between the individual studies in the literature on whether organ failure (OF) or infected pancreatic necrosis (IPN) is the main determinant of severity in acute pancreatitis. We aimed to statistically aggregate the available data and determine the pooled influence of OF and IPN on mortality in patients with acute pancreatitis.

Methods: The search for relevant observational studies was undertaken in the MEDLINE, EMBASE, and Scopus electronic databases as well as in the proceedings of major gastroenterology meetings. The summary estimates presented as risk ratio (RR) and 95% confidence interval (CI).

Results: Fourteen studies comprising 1478 patients with acute pancreatitis were meta-analyzed. A total of 600 patients developed OF and 179 of them died (mortality - 30%); 314 patients developed IPN and 102 of them died (mortality - 32%). In a stratified analysis, patients with OF and IPN had a significantly higher risk of death in comparison with patients with OF and no IPN (RR 1.94; 95% CI 1.32 to 2.85; P=0.0007) and in comparison with patients with IPN and no OF (RR 2.65; 95% CI 1.30 to 5.40; P=0.0007). By contrast, patients with OF and no IPN did not have a significantly higher risk of death in comparison with patients with IPN and no OF (RR 1.44; 95% CI 0.53 to 3.93; P=0.48).

Conclusions: In patients with acute pancreatitis, the absolute influence of OF and IPN on mortality is comparable and thus the presence of either indicates severe disease. The relative risk of mortality doubles when OF and IPN are both present and indicates extremely severe, or critical acute pancreatitis.

F-002

Cerulein Induced Acute Pancreatitis Suppress the mTOR Activity

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Background and Aim: Acute pancreatitis has long been considered to be an autodigestive disorder, in which inappropriate activation of trypsinogen to trypsin within the pancreatic acinar cells leads to the development of pancreatitis. We previously reported that autophagy activates trypsinogen within the pancreatic acinar cells. Though autophagy is negatively regulated by mammalian target of rapamycin (mTOR), it is still uncertain how autophagy is regulated in the pancreatic acinar cell. So, we focus on the intracellular signaling in the state of acute pancreatitis.

Methods: ICR mice were induced acute pancreatitis by hourly intraperitoneal injections of a supramaximal stimulating concentration of cerulein for 12 hours. We investigated the molecular events caused by cerulein treatment using western blotting.

Results: (1) We first showed that the levels of LC3-II, localizes to autophagosome membranes, were strongly increased in the cerulein-induced pacreatitis. (2) Western blotting showed the mTOR decreased in the cerulein-induced pancreatitis. Otherwise, AKT (upstream molecules), eIF4E-binding protein and the ribosomal protein S6 (downstream effector molecules of mTOR), were phosphorylated significantly. (3) ERK1/2 and STAT3, other proliferation signal molucules were also phosphorylated in the cerulein treated mice.

Conclusion: Inhibition of mTOR occurred despite the fact that the AKT-mTOR signaling pathway was activated. There is a possibility that mTOR degradation is a cause of the induction of autophagy. Further work is necessary to evaluate the mechanism of mTOR protein degradation.

F-003

Can Gut Permeability Be Modulated to Prevent Infection of Pancreatic Necrosis? Effects of Cannabinoids, Cannabinoid Receptors and Pro-inflammatory Cytokines on a Novel Inflammatory in vitro Model

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Most deaths from acute pancreatitis are associated with infection of pancreatic necrosis. The healthy gut provides a barrier against bac-

teria, antigens and environmental toxins whilst efficiently absorbing nutrients, with its integrity regulated mainly by tight intercellular junctions (TJ). Splanchnic inflow decreases early in shock, leading to TJ functional impairment and increased permeability, permitting abnormal macromolecular absorption. This opens up the paracellular route for bacterial translocation, thus infecting pancreatic necrosis. Endocannabinoids and cannabinoid receptors (CBR) are ubiquitous in the gut, and cannabinoids benefit certain gastrointestinal conditions. The aim was to investigate their effect on intestinal permeability in vitro using a CaCo-2 monolayer model.

CaCo-2 cells were grown to confluence in multiwell microporous membranes over 18 to 21 days. TJ integrity was assessed from transepithelial electrical resistance (TEER), whereby decreases indicated increased permeability. EDTA 50um provided 20% decreased permeability to simulate a shock effect. Cannabinoids were applied, and CBR and related antagonists added: AM251 (CB1), AM630 (CB2), O-1918 (proposed CBR), capsazepine (TRPV1), GW9662 (PPARgamma), and GW6471 (PPARalpha). Inflammation was mimicked by interferon gamma (IFNg) and TNF alpha (TNFalpha).

Phytocannabinoids reversed EDTA induced TEER falls in a concentration-dependent manner. Endocannabinoids worsened TEER falls both after EDTA, and when applied alone, in a concentration-dependent manner. Phytocannabinoids inhibited the effect of endocannabinoids. Only CB1 antagonists inhibited these effects. IFNgamma and TNFalpha also reduced TEER, and endocannabinoids potentiated their effect.

These data show for the first time that cannabinoids and cytokines can directly modulate intestinal permeability and that phytocannabinoids can restore normal permeability, whereas endocannabinoids increased permeability and worsened the effect of pro-inflammatory cytokines. Cannabis-based medicines may have therapeutic benefit in preventing infection of pancreatic necrosis.

F-004

Protective Effect of Vasoactive Intestinal Peptide (VIP) on Oxidative Stress-induced Pancreatic Acinar Cell Damage

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Introduction: Vasoactive intestinal peptide (VIP) has various effects, of which its anti-inflammatory effect and cytoprotective effect have attracted attention recently. We previously reported that VIP attenuated experimental acute pancreatitis (AP) by inhibition of cytokine production from inflammatory cells (*Pancreas* 2005). There is increasing evidence of oxidative stress occurring on the pancreatic damage; however the effect of VIP on its process is unknown.

Aim: To evaluate the effect of VIP in pancreatic acinar cells (acini) on pancreatic injury induced by oxidative stress.

Methods: To induce oxidative stress, acini isolated from Lewis rats were incubated with various concentrations of hydrogen peroxide (H_2O_2) and the effect of VIP was analyzed as follows. 1) Visualization and quantification of intracellular reactive oxygen species (ROS) using CM-H_2DCFDA as fluorescent dye. 2) Cell damage (using MTS assay and flow cytometry). 3) Monocyte chemoattractant protein (MCP)-1 production. 4) The secretion of 8-hydroxy-2'-deoxyguanosine (8-OHdG), which is a marker of DNA damage induced by ROS.

Results: H_2O_2-induced intracellular ROS in acini were increased in time- and dose-dependent manner. VIP at the concentration of 0.1 to 100nM significantly inhibited ROS production from acini. Addition of 100nM VIP reduced ROS production the most by 42% compared to H_2O_2 100 μM alone. In the cell viability assay, H_2O_2 above 100 μM was markedly cytotoxic to acini and VIP reduced cell death at six hours after H_2O_2 induction. Furthermore, the treatment of acini with H_2O_2 increased both MCP-1 production and 8-OHdG secretion, and VIP reduced its levels in the culture supernatant.

Conclusion: The damage of acini was associated with oxidative stress. These results demonstrate that VIP inhibits ROS production in acini exposed to oxidative stress, which results in reduced cell death and chemokine production. Therefore, we concluded that VIP has a protective effect on acini from oxidative stress-induced cell injury.

F-005

Direct Lymphatic Connections Between the Intestine and Pancreas: Do They Exist?

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Purpose: Critical illness is associated with toxic changes to mesenteric lymph (ML) and induces bacterial translocation. Toxic ML can exacerbate acute pancreatitis and translocated bacteria may infect pancreatic necrosis. It is unknown whether ML is able to reach the pancreas directly via lymphatics and thereby exert an effect on the organ. This study aimed to identify and characterise lymphatic connections between the intestine and pancreas.

Methodology: In diabetic (n=29) and non-diabetic (n=25) rats, four lymphatic preparations were used: retrograde cannulation of the mesenteric duct (MD) or thoracic duct (TD), and antegrade MD cannulation with TD drainage or ligation. Gadodiamide, colloidal carbon, resin, fluorescent microscopheres or fluorescent-labelled E. coli were perfused into the lymphatics. Lymphatic pressures were monitored during perfusions. Lymphatic connections were identified visually, and with fluorescence microscopy, MRI and bacterial culture.

Results: Mean baseline lymphatic pressures were 2.2 (SEM 2.3) cmH2O, and during perfusions with TD drainage or ligation were 7.0 (SEM 3.7, $p>0.05$) and 26.6 (SEM 17.7, $p<0.001$) cmH2O respectively. Four anatomical arrangements of pancreatic lymph drainage into the MD were identified. When lymphatic valves were absent or incompetent perfusates passed retrograde from the MD through pan-

creatic lymph nodes into pancreatic parenchyma. Pancreatic enhancement was seen on MRI. Bacteria were cultured from the pancreas but not from blood, lung, liver, kidney or spleen.

Conclusion: Functional lymphatic connections were identified between the intestine and pancreas through pancreatic lymph nodes when valves were absent or incompetent. Given the pathogenic role of toxic ML and bacterial translocation, these findings identify new therapeutic strategies for acute pancreatitis.

Forum 02 Pancreatic Cystic Tumor

F-006

New Large Pseudocyst Developing Post Cystogastrostomy Surgery – Probable Causes and Treatment Options

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Background: EUS guided aspiration and pig tailing of pancreatic pseudocyst have been described. We describe one such case of new pseudocyst developing 4 months post cystogastrostomy surgery, which completely resolved after single EUS guided aspiration along with minor papilla stenting.

Clinical History: A 54 years old chronic alcoholic and DM patient presented with pain and lump in epigastrium since 2 months. At investigation he was found to have a 19 by 7 cms pseudocyst in the body and tail of pancreas along with a terminal CBD stone. He had raised serum lipase levels with normal serum amylase. Patient Underwent an ERCP with CBD stone removal and stenting followed by surgical cystogastrostomy and cholecystectomy. He had an uneventful recovery and was discharged from the wards. Four months post surgery he presented with recurrence of symptoms. CT scan and MRCP showed a large psedocyst 20 by 10 cms anterior to the stomach and mostly arising from the head region with atrophy of rest of the pancreas. There was no obvious communication with the PD demonstrated. A EUS guided aspiration of 1.3 liters of clear fluid through the stomach was performed. Patient was planned for a EUS guided cystogastrostomy later on. One week later at EUS and ERCP there was a complete resolution of the pseudocyst and a pancreas divisium was noted for which a minor papilla stenting was performed. Three months post procedure the patient is asymptomatic and CT scan is suggestive of preserved pancreatic head with atrophy of the body and tail region with no new collection.

Conclusion: Alcohol or pancreas divisium could be the cause of new pseudocyst forming post surgery in the presented case. In such difficult location and large symptomatic collection a EUS guided aspiration or Cystogastrostomy should be considered as a viable treatment options.

F-007

A New Classification System for Primary Intraductal Neoplasms of the Pancreas

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There has been a lot of debate about the classification system of primary intraductal neoplasms of the pancreas represented by intraductal papillary mucinous neoplasms (IPMNs) and intraductal tubular neoplasms (ITNs). They are differentiated based on a histological proliferative pattern whether it is papillary or tubular. ITNs are further subdivided into intraductal tubular adenoma (ITA) and intraductal tubular carcinoma (ITC). We have recently reported an interesting entity, intraductal tubulopapillary neoplasm (ITPN). ITPNs show many characteristics different from IPMNs; 1) macroscopically, solid and nodular appearance obstructing pancreatic ducts, 2) no overt production of mucin, 3) tubulopapillary proliferative pattern on histology, 4) frequent micro-necrotic foci, 5) exhibiting uniform high grade atypia (without any low grade area), 6) negative for MUC5AC and MUC2, 7) negative for fascin, 8) negative for trypsin (a distinctive feature from acinar cell carcinoma that can show intraductal tubulopapillary pattern), 9) no mutation in KRAS gene. These features are also different from pancreatic intraepithelial neoplasia (PanIN), a precursor lesion of invasive ductal adenocarcinoma of the pancreas. Based on these observations, we conclude that ITPN comprises a distinctive entity encompassing ITC as a morphologic variant. Consequently, we propose a new classification system for primary intraductal neoplasms based on the feature of overt mucin production rather than on the histological proliferative pattern (papillary or tubular). In this system, primary intraductal neoplasms are categorized into IPMNs (mucinous phenotype) and ITPNs (non-mucinous phenotype). Therefore, both IPMNs and ITPNs can show tubular, papillary or tubulopapillary proliferative pattern but they are distinctive for the overt production of mucin. In this concept, today's ITAs should be included in IPMN family because of their mucinous nature. We believe that this new concept is a simple, precise and useful classification system for primary intraductal neoplasms of the pancreas.

F-008

A Case of Invasive Ductal Carcinoma Derived from Branch Duct Intraductal Papillary Mucinous Neoplasm Showed Almost No Change in Size During Three and a Half Years

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We report a case of invasive ductal carcinoma of pancreas derived from intraductal papillary-mucinous neoplasm (IPMN) after three and a half year observation. A 80-year-old man was admitted to our hospital because of pancreatic nodules that were observed for three and a half year in another hospital. Abdominal CT scan showed a 55mm-sized cystic tumor in the pancreas head and a 40mm-sized cystic tumor in the pancreas body, and endoscopic ultrasonography revealed a 15-mm mural nodule in the pancreatic head cystic tumor. We diagnosed as double branched type IPMN (highly carcinoma suspected), and subtotal pancreatectomy (preserving pancreas tail) was carried out. Histopathological examination revealed invasive ductal carcinoma derived from IPMN. Recently, it appears that asymptomatic IPMN without main duct dilation (>6 mm), those without mural nodules, and those <30 mm in size have a low risk of prevalent cancer and is commonly decided to follow rather than resect. In our resected case, when the pancreatic cystic masses was detected at first, it was decided to follow because of aged, asymptomatic and double masses of pancreatic head and body. However, these masses appear to grow slightly, the patient was referred to our hospital. An intramural nodule of the pancreatic head mass was firstly found by endoscopic ultrasonography (EUS), therefore it was a high likelihood of malignancy and we decided to resect. Although this case showed invasive ductal carcinoma in the pathological findings, Magnetic Resonance Cholangio-Pancreatography (MRCP) revealed no remarkable change during three and a half years. EUS is useful to detection for mural nodule even if it is not clear by enhanced CT or MRCP.

F-009

Indication of Resection for Intraductal Papillary Mucinous Neoplasm (IPMN): A Prospective Study in a Single-institution

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Background: Since consensus hasn't been built for any resection criteria for IPMN, indication for surgery is made by each institution's criteria at present.

Objective and Method: In our hospital, indication for IPMN surgery is made in cases where lesion location is of main pancreatic duct type, cyst diameter is more than 25mm, main pancreatic duct diameter is more than 7mm, height of mural nodule is more than 4mm, and results of pancreatic fluid cytology and biopsy are positive. Targets were surgically-operated 51 cases out of 176 cases who were diagnosed with IPMN based on the above mentioned criteria in our hospital from May 1999 to September 2009.

Results: Of the 12 cases of main pancreatic duct type for which surgical operation was performed, 2 cases of adenoma (17%), 1 case of border line (8%), 7 cases of non-invasive (58%) and 2 cases of invasive carcinoma (17%). Of the 33 cases of branch type for which surgical operation was performed, 24 cases of adenoma (73%), 6 cases of border line (18%), 3 cases of non-invasive carcinoma (9%). The mean values of height of mural nodule in preoperative imaging findings were 2.2mm, 4.7mm and 6.3mm in adenoma, border line and non-invasive cases respectively. Pathological findings of 6 cases of branch pancreatic duct type which were indicated surgery since imaging findings were changed or symptom was recognized after strict observation were 3 cases of non-invasive carcinoma (50%) and 3 cases of adenoma (50%). In all of the non-invasive carcinoma cases, size of mural nodule was increased.

Conclusion: We consider it to be reasonable that there is an indication for surgery of IPMN with non-invasive carcinoma in such cases of; 1) main pancreatic duct type, 2) branch pancreatic duct type with more than 5mm of nodule, 3) observation group of branch pancreatic duct type with increased nodule, and 4) those with subjective symptom (pancreatitis).

F-010

Indication of Laparoscopic Distal Pancreatectomy for the Pancreatic Neoplasms

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Background: Laparoscopic surgery is now widely applied for various pancreatic neoplasms. Some institutions have already applied laparoscopic surgery for intraductal carcinoma of the pancreas on trial. Laparoscopic pancreatic surgery has not been approved for the national health insurance in Japan and the consensus on indication for laparoscopic pancreatic surgery is not clearly defined.

Aim & Objectives: Eleven cases of laparoscopic pancreatic surgery for pancreatic neoplasms were performed in Kobe University Hospital from March 2007 to October 2009. We investigate 10 cases of laparoscopic distal pancreatectomy retrospectively.

Results: Mean operation time, blood loss and hospital stay were 336 minutes, 395 ml and 10.4 days respectively. Pathologic diagnosis were IPMNs (adenoma:4, CIS:1), serous cystic neoplasms (2 cases), well differentiated neuroendocrine carcinoma, MCN, lymphoepithelial cyst respectively. Pathological examination of resected specimens revealed disease free pancreatic cut end margin and dissected peripancreatic tissue margin in all cases. All but one case of well differentiated neuroendocrine carcinoma of the pancreas are in good condition without recurrence or severe complications to date. A case of neuroendcrine carcinoma was diagnosed NET with biopsy and highly suspected carcinoma preoperatively. In a view of the prognosis with coexist lung carcinoma, we applied laparoscopic distal pancreatec-

tomy as a minimally invasive surgery to maintain his quality of life. Metastatic lesions to the brain and bone were apparent 4 months after laparoscopic distal pancreatectomy but primary organ whether lung or pancreas was not clearly diagnosed.

Conclusion: The short term results of laparoscopic distal pancreatectomy for the pancreatic neoplasms were satisfactory. Laparoscopic pancreatic surgery will play important role for benign, borderline and low-grade malignant tumors. On the other hand, application for the malignant disease especially intraductal carcinoma should be careful at present.

F-011

A Case of Giant Serous Microcystic Adenoma of the Pancreas Safely Resected with Preoperative Arterial Embolization

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Serous microcystic adenomas are rare and account for 1–2% of exocrine pancreatic tumors and 25% of cystic neoplasms. Recently, due to improvements in imaging techniques, they have been identified more frequently. A 63-year-old woman visited her doctor because of a gastric deformity detected by gastro-camera checkup, in 1999. CT of the abdomen revealed a cystic lesion measuring 6.0cm in diameter, diagnosed as a serous microcystic adenoma of the pancreatic head. During follow-up, the tumor progressively increased in size, measuring 6.0cm in diameter in 1999 and 13cm in 2008, though remaining asymptomatic. While the risk of malignant transformation seemed to be low even in the long-term, some cases of serous cystadenocarcinoma were recently reported. In this case, assessment of the relationship between the tumor and adjacent vascular structures, such as massive drainage vein development on the surface or tumor flow into the portal and superior mesenteric veins and the celiac and superior mesenteric arteries, was critical in determining preoperative resectability. The risk of intra-operative massive hemorrhage was felt to be considerable given the extent of veins on the surface of the tumor, as well as the size and location of the primary pancreatic mass. Therefore she underwent preoperative embolization of tumor feeding arteries from the celiac axis (gastroduodenal, splenic, and dorsal pancreatic arteries). Estimated blood loss was 570ml, and tumor resection with pancreatico- duodenectomy was performed without blood transfusion. Final pathology confirmed a serous microcystic adenoma. The patient is alive and disease-free. With preoperative partial embolization of tumor feeding arteries and intra-operative resection of the right gastric and inferior pancreatoduodenal arteries, the tumor blood supply was essentially stopped without preoperative tumor necrosis, and blood loss was thereby reduced. Preoperative partial embolization of feeding arteries is useful for resection of hypervascular giant tumors of the pancreas.

F-012

A Case of Gastrointestinal Bleeding from a Ruptured Pseudoaneurysm Within the Pancreas Pseudocyst Through Pseudocyst-duodenum Fistula

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A 74-year-old woman with a known pseudocyst of the pancreas was admitted to our hospital due to hematemesis and shock. Following admission, computed tomography (CT) was showing 9 cm pseudocyst with 9 mm pseudoaneurysm, which was supposed to be ruptured. It was also suggested that gastrointestinal hemorrhage could resulted from the pseudocyst-duodenum fistula on CT. Arteriography was done via the celiac artery, which was revealing two 10mm pseudoaneurysms in the posterior superior pancreaticoduodenal artery adjacent to the pseudocyst. Interventional therapy was performed using microcoils. Three days after the therapy, obstructive jaundice was found with 9.1 mg/dl of serum total bilirubin. Jaundice might be caused by occlusion of fistula by coagulated blood or expansion of the cyst. Percutaneous transhepatic gallbladder drainage was performed. Following these therapeutic procedures, the patient condition was getting better. Endoscopic examination was showing obvious fistula with bile spillage in the duodenal bulb. Under endoscopy, contrast media was injected into the fistula and radiography was taken to confirm pseudocyst-duodenum fistula and microcoils in the pseudocyst. Usually rupture of a pancreatic pseudocyst is known to be a particularly serious complication. Mortality rate is supposed to be quite poor if hemorrhage has occurred. Here we reported a rare and rescued case of gastrointestinal bleeding from a ruptured pseudoaneurysm within the pancreas pseudocyst through pseudocyst-duodenum fistula.

F-013

A Case That Seemed to Be Pancreatic Mucinous Cystadenocarcinoma (MCC)

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Case: Patient is 70-year-old woman. Chief complaint: Upper abdominal pain. Blood test findings: Serum amylase was slight high. Imaging findings: Upper gastrointestinal endoscopy; No abnormality was found. Contrast CT; A 2.5-cm unilocular, round cystic lesion was observed in the tail of the pancreas, but capsule was not pointed out, and overall contrast effect was poor. MRI; The lesion showed overall low signal in the T1WI, high signal with partial low signal internally in the T2WI, overall low signal in the diffusion-WI. EUS; A septal wall was observed in the interior of the lesion, and a partially nodular

protruding lesion was observed. ERCP; No mucinous effusion was observed in Vater's papilla. There was no dilatation of the pancreatic duct or mucus plug in the pancreatic duct. Retention of contrast agent in the lesion was observed. PET/CT; Significant FDG-Uptake was not observed systemically, including the lesion. Course: The tail of the pancreas and spleen were excised. Intraoperative echo showed direct communication between the lesion and the main pancreatic duct.

Pathological Findings: A 2-cm cystic lesion was found which had no capsule and was multilocular, with a fairly thick septal wall. The content had little mucus, and it was filled with a white crystalline substance. The main pancreatic duct passed through the lesion. The cystic epithelial cells were a monolayer with mild atypia, and only a few cells contained mucin. Fusiform-shaped cells were densely present in the stroma, which were estrogen receptor / progesterone receptor positive, and seemed to be an ovary-like stroma. Nodular protrusions from growth of the stroma were also observed. Ductal structures were also found in the stroma, which like the cystic epithelium showed mild cellular atypia, and were p53-positve, and thus it was diagnosed as minimally invasive adenocarcinoma.

Forum 03 Pancreatic Cancer Surgery

F-014

Palliative Distal Pancreatectomy for Patients With Metastatic Pancreatic Cancers

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Background: The advent of gemcitabine hydrochloride (GEM) has revolutionized the treatment strategy for pancreatic cancer. We have performed palliative distal pancreatectomy (DP) in patients (pts) with cancer of the body or tail of the pancreas, even if metastases to the peritoneum, liver, or para-aortic lymph nodes were detected during surgery, for the purpose of volume reduction. Here we report the results and discuss the usefulness of this method.

Patients and Methods: Between 2001 and 2009, we treated 277 pts with pancreatic cancer. In this series, we excluded pts with intraductal papillary mucinous carcinoma. One hundred and five pts (38%) had tumors located in the body or tail of the pancreas, among whom 58 pts (55%) received DP, while 27 pts (26%) had unresectable disease due to distant metastasis. Patients were divided into three groups, pts with metastatic cancer who underwent DP (group A, n = 12), pts without metastases who underwent DP (group B, n = 45), and pts without any surgical treatment (groupC, n = 27). We compared the surgical outcome (mean operating time, complications, and hospital stay) between group A and B, and compared survival among all three groups.

Results: The surgical outcome was not significantly different in group A and B (mean operating time was 262 and 210 minutes, the complication rate was 17 and 20%, and the mean hospital stay was 22 and 23 days respectively). The median survival time (MST) was 11.3 months in group A, 28.7 months in group B, and 5.5 months in group C. MST was significantly longer in group A than group C ($p = 0.006$).

Conclusion: Palliative DP is technically safe. It appears to be a promising method for pancreatic cancer pts with distant metastases to obtain longer survival and better quality of life.

F-015

Clinical Significance of Bypass Surgery for Gastrointestinal Outlet Obstruction in Patients with Unresectable Pancreatic Cancer

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Background: Gastrointestinal outlet obstruction in patients with unresectable pancreatic cancer often causes disability of ingestion that leads to decrease in quality of life (QOL) and to discontinue of the treatment by an oral anti-cancer drug. Bypass surgery for such patients is a gold standard despite of several options including nasogastric tube, percutaneous gastrostomy,and a metal stent those. Operation, however, may deteriorate patients' QOL and prognosis without improvement of oral intake. OBJECTIVE: The aim of this study was to evaluate the clinical benefit of bypass surgery from the view point of the relationship between a degree of oral intake after surgery and prognosis.

Patients and Methods: We reviewed our pancreatic surgery database between November 2006 and December 2009. Twenty patients underwent bypass surgery. We defined patients with oral intake 50% or more after surgery as Group A including 13 pts, lower than 50% as Group B, including 7 pts. We compared induction of oral anti-cancer drugs and survival between these two groups. Prognostic factors were also analyzed.

Results: This study included 7 female and 13 men. The median age was 65 years ranging from 47 to 85 years. The primary pancreatic lesion was located in the head in 14 patients, in the body and the tail in 6. We performed gastro-jejunostomy was in 11 patients, duodeno-jejunostomy was in 8, jejuno-jejunostomy was in 1. Average hospitalization period was 21 days. Median survival time (MST) after the operation was 208 days ranging from 22 to 898 days. Ratio of patients treated with oral anti-cancer drug was 54% in Group A, 14% in Group B. MST of Group A was significantly longer than Group B (152 vs.51 days). Preoperative jaundice was the only prognosis factor among clinicopathologic factors.

Conclusions: Better oral intake after bypass surgery prolongs the survival of patients with unresectable pancreatic cancer. Careful consideration of bypass surgery must be done for patients with preoperative jaundice.

F-016

Comparative Study of Results Between PPPD and SSPPD for Pancreatic Head Malignancies

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Purpose: Pylorus preserving pancreaticoduodenectomy (PPPD) has advantages of postoperative nutrition and this procedure can be applied for pancreatic head malignancies as a radical operation. However, delayed gastric empty (DGE) is a frequent complication leading to a longer fasting period and hospital stay. On the other hand, subtotal stomach-preserving PD (SSPPD) may be an alternative option to preserve nutritional status and to shorten period of fast. By the historical study in our series, we compared postoperative results between PPPD and SSPPD in peri-pancreatic head malignant diseases.

Subjects: Subjects were 28 cases in PPPD and 27 in SSPPD since 2000.

Results: Mean age was 66 y.o in PPPD group and 68 y.o in SSPPD group. Diseases were pancreatic carcinoma in 12, bile duct carcinoma in 9, ampullar carcinoma in 6, IPMC in one in PPPD group, and pancreatic carcinoma in 19, bile duct carcinoma in 5, ampullar carcinoma in 2 and gallbladder carcinoma in one in SSPPD group. Pancreatic carcinoma was more frequent in SSPPD group ($p=0.04$). Operating time was longer in SSPPD group than that in PPPD group (660 and 539 min.) ($p=0.02$). Blood loss was more in SSPPD group than PPPD group (1810 and 1306ml) ($p=0.048$). Resection of portal vein was undergone in 14% in PPPD group and 26% in SSPPD group. Period of NG tube placement and period of fast was shorter in SSPPD group than PPPD group (6 vs. 15days, and 9 vs. 19days, respectively: p less than 0.01). Grade C of DGE by ISGPF was 7% in SSPPD group and 48% in PPPD group. Postoperative complications and nutritional status were not different between groups.

Conclusions: Nevertheless of higher rate of advanced pancreatic carcinoma in SSPPD group, DGE was significantly avoided by this procedure and, therefore, SSPPD is useful option for pancreaticoduodenectomy.

F-017

Reducing Intraoperative Blood Loss and Operative Time During Pancreaticoduodenectomy by Using LigaSureTM Vessel Sealing System

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Introduction: Recent advances in surgical instruments enable us complex surgical procedures safer. Since April 2007 we introduced LigaSureTM vessel sealing system (LVSS) during pancreaticoduodenectomy (PD) routinely instead of conventional tie and cut technique. In this study we tested if routine use of LVSS during PD would reduce intraoperative blood loss and transfusion.

Methods: A total of 168 patients who underwent PD between Oct 2005 and Dec 2009 were included in this study. All procedures were performed by one of the same HBP surgical team member. A retrospective comparison was performed between 84 consecutive patients undergone PD with LVSS (Group A) and 84 historical cohort without using LVSS (Group B) in terms of peri-operative data including blood loss, transfusion, operative time, morbidity and mortality.

Results: Two groups were comparable in terms of patient's demographics, type of disease, and type of procedure. The 30-day mortality was 0.6% (1 out of 168). Median OR time was significantly shorter in Group A compared with Group B (401 vs. 443min., $p<0.01$). Median intraoperative blood loss was significantly less in Group A (1158g vs. 1663g, $p<0.01$). Frequency of intraoperative transfusion of PRBCs was also significantly less in Group A (53% vs. 82%, $p<0.01$). Median units of transfusion was different as well between the groups (2.1 vs. 4.4 units, $p<0.01$). This trend is more prominent in a subgroup of malignant disease. Overall morbidity, POPF (any grade) and LOS were not different.

Conclusions: Although the limitation of retrospective observation, using LigaSureTM vessel sealing system during PD would contribute to reduction of operative time, blood loss, and transfusion, which makes surgical procedure much safer.

F-018

Posterior Epigastric Artery Is the Key Vessel to Preserve Pancreatic Function Following Pancreaticoduodenectomy with Resection of Splenic Artery and Splenectomy After Total Gastrectomy

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It is well known that the quality of life is severely impaired after total pancreatectomy for pancreatic diseases. We successfully preserved pancreatic function of the patient with pancreatic cancer following pancreaticoduodenectomy with resection of splenic artery and splenectomy after total gastrectomy.

The patient is fifty six years old male who underwent total gastrectomy for gastric ulcer twenty years ago. He had suffered from abdominal discomfort and visited local clinic. He was referred to our hospital because of pancreatic mass. Abdominal CT scan revealed pancreatic head tumor invading portal vein, 5cm in diameter, and pancreatic body tumor invading splenic artery, 2cm in diameter. Serum levels of CEA and Span-1 were 28.1 ng/ml and 180U/ML. He underwent endoscopic ultrasound guided fine needle aspiration biopsy for pancreatic masses and both of the tumors were histologically proven as adenocarcinoma. Moreover chest CT scan revealed primary solitary lung cancer of the right lobe, 2cm in diameter. He was diagnosed as double pancreatic cancer and primary lung cancer. After preoperative systemic chemotherapy with gemcitabine and TS-1, surgery for the pancreatic cancers was done before treatment of the lung cancer, considering his limited life expectancy. We planed to preserve pancreatic function as long as the resected margin of the pancreas was no malignant. To keep the blood flow to the remnant pancreas after resection of the splenic artery and splenectomy, we preserved the posterior epigastric artery which arises from the mesocolon to the pancreas. We performed pancreaticoduodenectomy with resection of portal vein and splenic artery and splenectomy. Postoperative course was uneventful and pancreatic function was completely preserved. He had been free from insulin and antihyperglycemic agent since operation. Postoperative abdominal angiography revealed that posterior epigastric artery was preserved.

F-019

Pancreatic Duct Holder for Facilitating Duct-to-mucosa Pancreatojejunostomy After Pancreatoduodenectomy

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Background: Duct-to-mucosa pancreatojejunostomy may prevent pancreatic fistula after pancreatoduodenectomy. However, the anastomosis may be technically difficult, particularly in cases where the remnant pancreas is soft with a small main pancreatic duct. We devised a pancreatic duct holder for facilitating duct-to-mucosa pancreatojejunostomy (Am J Surg 2009).

Methods: The holder has a cone-shaped tip. One-third of circle of the tip is cut away, which makes a slit. As the tip is inserted gently into the pancreatic ductal lumen, the pancreatic duct can be adequately expanded to 3–5 mm with the cone-shaped tip, even in patients with a small pancreatic duct. The holder provides a good surgical field for anastomosis. A slit of the tip allows needle insertion. The holder, which is inserted into a small opening of the jejunum, facilitates stitches of the jejunum also. A total of 114 patients underwent pancreatoduodenectomy followed by pancreatojejunostomy using two layers including duct-to-mucosa and the pancreatic parenchyma-to-the jejunal seromuscular layer. Duct-to-mucosa anastomosis was performed with (n = 37) or without (n = 77) the holder.

Results: The holder allows eight stitches in duct-to-mucosa anastomosis, even in patients with a non-dilated pancreatic duct (the diameter of 2 mm or less at the pancreatic stump).

The incidences of pancreatic fistula (ISGPF Grade B/C) tended to be lower after anastomosis with (6% for non-dilated and 5% for dilated pancreatic duct) than without the holder (14% and 6%, respectively).

Conclusion: The pancreatic duct holder is a simple and useful tool for facilitating duct-to-mucosa pancreatojejunostomy. Use of the holder may prevent pancreatic fistula.

F-020

Single Drain Is Enough for Pancreatic Reconstruction After Pancreaticoduodenectomy

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Purpose: Pancreatic fistula after pancreaticoduodenectomy (PD) is one of the crucial complications. We had placed several drains close to pancreatic reconstruction after PD because of not only information of pancreatic leakage but also treatment of pancreatic fistula, if it happened. Recently, reduction of the drain has been recommended from the viewpoint of Surgical Site Infection (SSI). The aim of this study was to clarify where the number of the drain close to pancreatic reconstruction after PD affect postoperative course or not.

Methods: Between April 2005 and December 2009, 117 consecutive patients underwent PD for periampullary disorders in Kumamoto University Hospital. We placed single drain in 31 (single-drain group) and multiple drains in 86 (multi-drain group). We compared incidence of pancreatic fistula and SSI, period of drain insertion, and postoperative hospital stay between the two groups.

Results: This study included 58 men and 59 women. The median age was 70 (32–85). Pancreatic cancer, including IPMN was in 59, bile-duct cancer in 31, neuroendocrine tumor in 7, ampullary or duodenal cancer in 10 and others in 10. We performed conventional PD in 8, pylorus preserving PD in 26, and substomach preserving PD in

83. Pancreaticojejunostomy was in 41 and pancreaticogastrostomy was in 76. No significant difference of patients' characteristics, including age, gender, disorders and intraoperative factors, including operation time, bleeding amount was observed between the two groups. There was no significant difference about incidence of SSI and pancreatic fistula between the two groups. Average period of drain insertion was 13.3 days in single-drain group, significantly shorter than 28.5 in multi-drain group. Moreover, average postoperative hospital stay was 23.1 days in single-drain group, significantly shorter than 37.7 in multi-drain group.

Conclusion: Single drain for pancreatic reconstruction after PD tends to period of drain insertion and postoperative hospital stay without increase of complications.

F-021

Distal Pancreatectomy: Analysis of Techniques for Closure of the Pancreatic Remnant and Complications

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Background: Several techniques have been described to achieve perfect closure of the pancreatic remnant associated with distal pancreatectomy (DP). However, the morbidity remains high. Pancreatic fistula (PF) is the most common major complication to occur after DP, ranging in frequency from 5% to 40%. The aim of this study was to analyze the occurrence of clinical complications and the techniques for closure of the pancreatic remnant.

Methods: A retrospective review was performed of the medical records of 57 patients who underwent DP in Sapporo Medical University Hospital between April 2001 and July 2009. They were subdivided according to the method used to close the pancreas remnant: 1) the suture group comprised 18 patients, 2) the staple alone group comprised 15 patients, 3) the stapler covering with polyglycolic acid felts comprised 24 patients.

Results: Overall pancreatic fistula rate was 23% in this series and intraabdominal abecess rate was 35%. In the suture group, 29% developed a PF and 47% developed an intraabdominal abecess. In the staple alone group, 26% developed a PF and 26% developed an intraabdominal abecess, and in the stapler covering with polyglycolic acid felts group, 13% and 25%, respectively.

Conclusion: These findings support the advantages of using a stapler closure in distal pancreatectomy. Moreover, the stapler covering with polyglycolic acid felts is considered to be a simple and safe method that decreased pancreas-related complications such as fistula.

F-022

Identification of a Risk Factor for Pancreatic Fistula After Distal Pancreatectomy Using a Stapler: The Thickness of Pancreatic Stump Is an Important Determinant

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Background: In spite of the recent progress in both surgical techniques and postoperative managements, the incidence of pancreatic fistula after distal pancreatectomy remains high. In order to reduce the incidence of pancreatic fistula, several surgical techniques, including a hand-sewn closure and a staple closure, have been introduced to close the pancreatic stump. Numerous previous studies have tried to identify the superiority of these two techniques, yet the conclusion is still controversial. Rather, choosing the suitable technique in each patient depending on the patient's characteristics seems to be the best way to reduce the incidence.

Methods: Forty-six patients who underwent distal pancreatectomy at Osaka University Hospital were enrolled in the present study. Distal pancreatectomy with a hand-sewn closure of the pancreatic stump was performed in 26 consecutive patients during the first period, whereas a staple closure using echelon 60 was performed in 20 patients in the second period. When using a stapler, the closure jaw was clamped carefully and slowly taking more than 5 minutes at a fixed speed. The incidence of pancreatic fistula and the patients' characteristics including the texture and the thickness of the pancreatic stump were investigated.

Results: Seven patients (27%) developed pancreatic fistula in the hand-sewn group, while it was 5 patients (25%) in the stapler group. Neither the texture nor the thickness of the pancreas was a risk factor for pancreatic fistula in the hand-sewn group. In the stapler group, a thick pancreas, but not a hard pancreas, was a significant risk factor. Especially, no patients with thin pancreas developed pancreatic fistula in the stapler group.

Conclusions: A thick pancreas, but not a hard pancreas, is a risk factor for postoperative fistula of the pancreas when the stump is closed by a stapler.

Forum 04 Pancreas Complication

F-023

Fatty Liver After Pancreatoduodenectomy and Total Pancreatectomy

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Metabolic syndrome or nonalcoholic fatty liver (NASH) are clinically highlighted. Fatty liver sometimes occur after pancreatoduodenectomy (PD). However, reasons of fatty liver after PD are not still obscure.

Recently we performed PD (150 cases) and total pancreatectomy (5 cases) for periampullary neoplasms. Among them, eight cases of postoperative fatty liver after PD or total pancreatectomy were studied and discussed literally. Postoperative fatty liver was diagnosed with CT as diffuse low density area in the liver.

Diagnoses of postoperative fatty liver cases were three intraductal papillary mucinous neoplasm (IPMN) (4 cases), bile duct cancer (2), carcinoma of the papilla of Vater (1), and pancreas cancer (1). Seven cases were female and one was male. Postoperative serum albumin, cholinesterase, and total cholesterol were decreased compared to preoperative levels. On the contrary, endocrine (glucose tolerance) function was well maintained. Typical CT imaging of fatty liver after PD or total pancreatectomy will be presented.

Fatty liver changes are also found in short bowel syndrome or jejuno-ileal bypass. Imbalance between synthesis and secretion of hepatic triglycerides was considered for the reason. We speculate triglycerides are not secrete to blood because of impairment of apoprotein.

Postoperative nutritional support will be necessary for prevent fatty liver change after PD or total pancreatectomy.

F-024

Analysis of Factors Inducing Hepatic Steatosis After Pancreaticoduodenectomy

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Background: About one third of the patients after pancreaticoduodenectomy are observed hepatic steatosis due to the dynamic alteration of the nutritional state. However, there has been no analysis reported from the point of surgical procedure. Here we investigated the factors inducing the hepatic steatosis after pancreaticoduodenectomy such as the extent of the dissection, operation time, blood transfusion and nutritional state before and after operation.

Methods: From April 2007 to March 2009, 92 patients underwent pancreaticoduodenectomy in our hospital. The hepatic steatosis was evaluated with density ratio between liver and spleen (L/S ratio) in the plain computed tomography after 6 months of the operation. The factors analyzed for the steatosis were body weight change, diabetes mellitus before and after operation, liver damage before operation (ICG), duration of the operation, blood transfusion, amount of diet after surgery, extent of lymphnode and neural dissection, diarrhea after surgery and cancer or benign tumor.

Results: When we set the L/S ratio less than 0.9 as hepatic steatosis, 12 out of 92 patients were diagnosed as such. Sixty six patients were operated due to cancer and the rest 26 were due to IPMN or endocrine tumor. All of the 12 patients with hepatic steatosis were cancer patients, especially of pancreatic cancer. When we examined in detail, none of the factors including body weight change, diabetic state, operation time, liver damage, blood transfusion, diet after surgery was related to the hepatic steatosis. However, hepatic steatosis was apparently obvious in the group with neural and the lymphnode dissection around SMA/hepatoduodenal ligament and the diarrhea in relation ($p=0.021$ and $p=0.045$), suggesting the lymphatic flow around the hepatoduodenal ligament as well as nutritional state is important for preventing hepatic steatosis.

Conclusions: One of the factors for the hepatic steatosis after the pancreaticoduodenectomy could be the extent of the lymphode/neural dissection in operation.

F-025

The Change of NAFLD Ratio After Pancreatoduodenectomy According to a Method of Reconstruction, R-Y vs B-II

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Aim: PD is the operation with big damage for patient. We often encountered patients who showed poor intake or weight loss and some patients had sever fatty liver. In this study, we examined the postoperative NAFLD according to different reconstruction methods.

Materials and Methods: Thirty two patients who had undergone PD between January 2008 and Oct. 2009 were included in this study. Weight, Lab data, blood cell count, trace element were evaluated in preoperation, 1 week, 3 week, and 3 months POD. NAFLD was defined as that neither HU value was less than 40HU nor spleen/liver HU ratio was more than 1.5 using abdominal CT three months after operation. One of the two reconstruction methods, R-Y or modified Traverso's method (B-II) was selected.

Results: There was no postoperative death. There were 16 male and 16 female patients. Reconstruction with method of R-Y was performed in 16 patients. Reconstruction with method of B-II was performed in 16 patients. In all of 32 patients, Weight, TP, Alb, Zn, Cu, pre-alb were decreased in 1, 3 weeks and 3 months compared with before operation ($P<0.001$). There was no difference in start of oral intake in both groups. Ten of the 32 patients had NAFLD three months after operation, R-Y group was 4 and B-II group was 6. However, HU level in B-II method was significantly lower than R-Y group. In addi-

tion, Liver function test, AST, ALT, GTP, ALP, in B-II group were significantly higher than in R-Y group one week after PD ($P<0.05$). However, in R-Y group, low level of TP and Alb remained after three months. All of the B-II group patients were recovering in the same period.

Conclusion: NAFLD ratio was not different in R-Y and B-II methods. B-II method was effective for recovering nutrient condition.

F-026

Usage of Polyethylene Glycolic Acid Felt with Fibrin Sealant to Prevent Postoperative Pancreatic Fistula in Pancreatic Surgery

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The purpose of this non-randomized retrospective study was to report our new procedures using polyethylene glycolic acid (PGA) felt with fibrin sealant to prevent severe pancreatic fistula in patients undergoing pancreatic surgery. From 2000–2008, 54 and 63 patients underwent pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), respectively. Of those patients, we applied PGA felt with fibrin sealant to 18 PD patients and 26 DP patients. In PD patients, the PGA felt was wrapped around the pancreatic suture site, while in DP patients the PGA felt was wrapped around the predictive division site. In PD, the pancreatic parenchyma was sutured penetratingly using straight needles with 4-0 monofilament non-absorbable threads through the PGA felt and the seromuscular layer of the jejunum. After anastomosis between the pancreatic main duct and the jejunal wall using 4 to 12 stitches with 6-0 monofilament absorbable threads, the previous 4-0 threads were tied and the pancreaticojejunostomy finished. In DP, we used staple devices that gave a staple line consisting of a triple row of closely placed staples. The pancreaticojejunostomy site in PD patients and the cut stump in DP patients were coated with fibrin sealant. We compared the occurrence rates for severe postoperative pancreatic fistula (POPF) that occurred after PD or DP both with and without our new procedures. Before introduction of our procedures, severe POPF developed in 14 of 36 PD patients (39%) and 10 of 37 DP patients (27%). By contrast, after introduction of our procedures the incidence of POPF was only one in both of 18 PD (6%) ($P=0.016$) and 26 DP (4%) ($P=0.017$) patients. In summary, our procedure using PGA felt with fibrin sealant may reduce the risk of severe POPF.

F-027

The Effectiveness of the Synbiotics Early Enteral Nutrition/Nutrition Support Team Program in Pylorus-preserving Pancreaticoduodenectomy

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Purpose: Pylorus-preserving pancreaticoduodenectomy (PpPD) have a risk of mulnutrition, metabolic disorders, resulting in severe and often fatal complications such as anastomotic leakage, and/or delayed gastric emptying (DGE). Perioperative nutritional management by early enteral nutrition with synbiotics (S-EN) / nutrition support team (NST) thought to be effective for resolving those problems. However, its evidence is not yet clear. Therefore, we determine the usefulness of the S-EN/NST program in PpPD.

Patients & Methods: PpPD (mucosa-to-mucosa anastomosis, no stent or lost stent method) was performed in 33 patients from '01 April. Synbiotics (antibiotics-resistant Lactobacillus, L-glutamine, dietary fiber, an oligosaccharide was given preoperatively, and semi-digestion liquid diet with synbiotics was given with 20 ml/h through 6.5Fr naso-jejunum feeding tube after ICU admission. NST actively supported S-EN. Furthermore, specialized rehabilitation for the early ambulation, in parallel with the education for patients were performed. One the first post-operative day, gait training was started, and the pedometer wearing was conducted. The mortality, morbidity (Clavien classification $\geqq$ IIIa, ISGPF $\geqq$ grade B), starting date of oral intake, intravenous drip infusion period, postoperative hospitalization and body weight ratio were compared.

Results: There were no differences between each group including pancreatic duct diameter (SEN/NST group 3.2 ± 2.1mm, $N=14$, control group 3.6 ± 2.0mm, $N=19$). The mortality, morbidity of the SEN/NST group was 0.0, 0.0%, whereas a control group was 5.3, 26.3%. Also, starting date of the oral intake [5 (2–13) vs. 10 (5–18)], intravenous drip infusion period [11 (7–21) vs. 20 (9–36)], postoperative hospitalization period [13.5 (9–30) vs. 35 (21–50)], and body weight ratio [100.9 (94.9–111.0) vs. 94.3 (86.0–97.4)] of the SEN/NST group were better than those of control group.

Conclusions: S-EN/NST program in PpPD was very useful for perioperative nutritional management and improvement of the disease outcome itself as well.

F-028

Accelerated Liquefaction of Pancreatic Necrosis Using Proteolytic Enzymes: A New Paradigm

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Purpose: Treatment of infected pancreatic necrosis requires specialised open or minimally invasive intervention. Accelerated dissolution of necrotic tissue with enzymes may assist its removal. The aims of this study were to: 1) characterise the architecture and composition of normal and necrotic pancreatic tissue to identify targets for dissolution; 2) determine the ex-vivo efficacy of enzymatic dissolution.

Methodology: Normal cadaveric pancreas (n = 3) and necrotic pancreas (n = 10, patients undergoing necrosectomy for acute pancreatitis) was collected. Samples were analysed by microscopy and Fourier transform infrared spectroscopy (FTIR). Tissue was incubated for 24 hours at 37°C in treatment solutions (saline control, collagenase, trypsin/chymotrypsin, or bromelain). Change in wet and dry mass, architecture and composition was determined. Change in tissue mechanical properties (peak force and work of extrusion) were determined using a texture analyser.

Results: Necrosum lacked normal cellularity and extracellular matrix elements, with an absence of vascular structures. Collagen dominated necrotic tissue architecture, with marked heterogeneity in its pattern of deposition. Saline incubated tissue gained wet weight and lost 20% of its dry weight. There was no significant difference in weight change between treatment solutions. Collagenase and bromelain reduced the peak force of extrusion ($p < 0.05$), and all three enzymes reduced the work of extrusion compared with saline alone ($p < 0.05$).

Conclusion: Significant architectural and compositional changes exist between normal and necrotic pancreatic tissue. Enzyme treatment had mechanical advantages over saline alone during tissue extrusion, giving evidence that enzymatic dissolution is feasible.

Forum 05 Chronic Pancreatitis Treatment 1

F-029

Start with Jaundice and Various Symptoms Come After Steroid Therapy; A Case Report of AIP

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Introduction: It is well known that various symptoms come with autoimmune pancreatitis (AIP). We report an AIP case with atypical symptoms; verbal and swallowing disturbances on acute onset.

Case Report: 81 year old man referred to our hospital for examinations of the cause of jaundice. His jaundice improved by PTBD at a previous hospital but his CBD had a stricture. Particular values of laboratory data on admission were ALP; 713U/L, GGT; 142U/L, ChE; 214U/L, BS; 247mg/dL, HbA1c; 6.9%, CRP; 2.3mg/dL, CA19–9; 39.4U/mL, RF(-), ANA(-), IgG; 1637mg/dL, IgG4; 195mg/dL. An enlargement from pancreatic body to tail was shown by abdominal ultrasound, but no dilatation of MPD. Abnormal texture of fat tissue around pancreatic tail and obstruction of portal vein were shown by CT scan. T1 weighted MRI image showed low intensity and a delayed enhanced swollen pancreas. Stricture of MPD at pancreatic head and an irregular wall of distal MPD were shown by ERP but no dilatation of distal MPD. No atypical cells were detected by repeated bile cytology. We diagnosed him as AIP and steroid therapy began with 10mg prednisolone daily. Three months later, pancreatic enlargement improved but slight breathlessness and coughs appeared. Shortly afterwards, dyspunea put him into readmission and bilateral pleural effusion, diffuse shadow and cardiomegaly became apparent. ECG showed atrial fibrillation with tachycardia (150/min). Medication for congestive cardiac failure and other complications helped his recovery and he was discharged 18 days later with 5 mg prednisolone every other day. After three months, he suddenly could not speak well and had swallowing difficulties. Otolaryngologist found no abnormality and symptoms disappeared naturally. Afterwards, steroid therapy was stopped by patient's discretion and he is well now.

The origin of these various symptoms is questionable of whether it was because of AIP or steroid therapy side effects?

F-030

59 Cases of Pancreatic Diseases Treated by Endoscopy via Minor Papilla – its Safety and Efficacy

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Introduction: In the past 8 years we have experienced 59 cases treated via minor papilla endoscopically; pancreatic stone - 48 (39 alcoholic, 3 idiopathic, 3 divisum, 2 hereditary, 1 hyperparathyroidism), non-calcified chronic pancreatitis with the Wirsung duct narrowing - 6, symptomatic non-calcified divisum - 2, ventral pancreas dysplasia - 1, and carcinoma in the Wirsung duct - 2.

Aims and Methods: Evaluation of the safety and efficacy of treatment via minor papilla. The procedures consisted of guide wire (+) EPST - 48, guide wire (-) EPST - 1, Rendezvous method - 5, Rendezvous precut method - 2, free hand method - 2, EPDBD (balloon dilation) alone - 1. The indications of this treatment were in such conditions as severe narrowing of the Wirsung duct (47), divisum (5), continuous pain by impacted fragments (3), stones in the Santorini duct (2), dilation of the orifice of minor papilla;IPMN (1), and ventral pancreas dysplasia (1).

Results: These procedures were successful in all cases and no major problems occurred. In the pancreatic stone group, the stone-free-rate was 90% (43/48), pain-free-rate 100% (45/45). In other groups, pain disappeared in all cases.

Conclusions: The treatment of pancreatic disease via minor papilla is a safe and useful method when the treatment via major papilla is difficult in such cases as above. In these cases, pancreatic juice is drained mainly through the Santorini duct, so careful procedures to the minor papilla are necessary.

F-031

Modified Fully Covered Self-expandable Metallic Stents with Anti-migration Features for Benign Pancreatic-duct Strictures in Advanced Chronic Pancreatitis; With a Focus on the Safety Profile and Reducing Migration

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Background: Fully covered self-expandable metallic stent (FCSEMS) placement has recently been tried in the management of refractory pancreatic-duct stricture associated with advanced chronic pancreatitis. The major limitation of FCSEMSs was frequent migration.

Objective: To assess the safety, migration rate, and removability of modified FCSEMSs with antimigration features used for treatment of benign pancreatic-duct strictures.

Design: Prospective study.

Patients: Thirty-two patients with chronic painful pancreatitis and dominant ductal stricture.

Interventions: Transpapillary endoscopic placement of FCSEMSs (Bumpy type, Taewoong, Seoul, Korea) in the pancreatic duct, with removal after 3 months.

Main Outcome Measurements: Technical success, functional success, and adverse events associated with placement of metal stents.

Results: FCSEMSs were successfully placed in all patients through a major (n = 27) or minor (n = 5) duodenal papilla. All patients achieved pain relief during stent placement. There was no occurrence of stent-induced pancreatitis or pancreatic sepsis. No stent migrated and all stents were easily removed. Follow-up ERCP 3 months after stent placement showed resolution of ductal strictures in all patients. Pancreatogram upon FCSEMS removal displayed “de novo” focal pancreatic-duct strictuers in five patients, but all were asymptomatic.

Limitations: No long-term follow-up

Conclusions: Temporary 3-month placement of FCSEMSs was efficacious at resolving pancreatic-duct strictures in chronic pancreatitis, with an acceptable morbidity profile. Modified FCSEMSs can prevent stent migration, but may be associated with de novo ductal strictures.

F-032

ESWL of Pancreatic Stones in Treating Children with Chronic Pancreatitis

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Objectives: Extracorporeal shock wave lithotripsy (ESWL) of pancreatic stones is a treatment option for patients with chronic pancreatitis (CP), when pancreatic stones cannot be removed by endoscopic procedures during retrograde cholangiopancreatography (ERCP).

The aim of the study was to evaluate if ESWL of pancreatic stones is effective in treating children with chronic pancreatitis.

Methods: 11 children (6 girls and 5 boys; mean age 11.2 years, range: 5.5 to 17 years) with severe CP, hospitalized since 1998 to 2009, were treated by ESWL for endoscopically irretrievable obstructive stones. The medical records of these patients were reviewed for data on the presentation, diagnostic findings, ESWL and endoscopic treatment. ESWL was performed with an electromagnetic lithotriptor. The etiology of chronic calcifying pancreatitis were gene mutations (PRSS1, CFTR) in all but one patient.

Results: 11 patients had 13 endoscopic-ESWL sessions. ESWL was administered twice in two children. Pancreatic stones fragmentation was achieved in all patients. The procedures were well tolerated by all children. There were no complications or failures related to ESWL. Early pain relief occurred in all cases. At a mean follow-up of 61 months (range: 14–90 months) pain improved in 7 children (63.6%). Acute episodes of CP after endoscopic-ESWL treatment were observed in 3 patients (27.3%). Recurrence of endoscopically irretrievable pancreatic stones was revealed in 3 cases.

Conclusions:

1. Extracorporeal shock wave lithotripsy is a safe and effective therapy in treating children with chronic pancreatitis and irreversible pancreatic stones.

2. Extracorporeal shock wave lithotripsy should be considered complementary and not alternative therapy to endoscopic drainage.

F-033

Pancreatic Pseudocysts in Children with Chronic Pancreatitis

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Chronic pancreatitis (CP) in children is uncommon. Pancreatic pseudocysts (PP) are a serious complication of CP. The reported paediatric experience with PP is small and little is known about the treatment of pseudocysts in children.

The aim of our study was to evaluate management of pancreatic cysts in children with CP.

Patients and Methods: Between 1995 and 2009, 148 children with CP were hospitalized in the Department of Gastroenterology; The Children's Memorial Health Institute. We retrospectively reviewed the outcome of treatment in 23 children (15,5%) with a diagnosis of PP.

Results: Eight children (34,8%) were treated by observation. One child (4,3%) underwent endoscopic cystogastrostomy. PP resolved after drainage. Eight patients (34,8%) underwent endoscopic guided drainage procedure (ERCP). Four children after endoscopic stenting had clinical and radiologic resolution of their PP. Nine patients (39,1%) were treated by surgical drainage or resection. Four children underwent Jurasz's operation. PP resolved after cystogastrostomy in all cases. There were no complications or failures related to surgical procedures. Some patients fell into more than one category.

Conclusions: 1. Endoscopic or surgical drainage of PP in children with CP is a safe procedure. 2. Small cysts can be managed by a period of observation.

Forum 06 Acute Pancreatitis Treatment

F-034

Three Cases of Infected Walled-off Pancreatic Necrosis Treated with Transmural EUS-guided Drainage and Endoscopic Necrosectomy in a District General Hospital

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Introduction: Endoscopic necrosectomy has recently emerged as an alternative to surgery for the management of infected walled-off pancreatic necrosis (WOPN).

Methods: Three patients with severe acute pancreatitis complicated by CT-confirmed WOPN underwent transluminal EUS-guided drainage and endoscopic necrosectomy. Two of the 3 patients had biliary pancreatitis. The technique includes transgastric and/or transduodenal EUS-guided puncture using curvilinear-array echoendoscope (GF-UCT2000, Olympus) by traditional single guidewire approach with 19-gauge needle (EchoTip Ultra, COOK Endoscopy). The puncture site is dilated by 6Fr Soehendra biliary catheter and a biliary balloon catheter of 6mm in diameter, and then a 7Fr double pigtail stent is inserted. The pseudocyst is recannulated using a catheter and guidewire, followed by insertion of the 6Fr nasocystic catheter and continuous saline irrigation. Approximately one week after drainage, step-wise wire-guided dilation is performed using a transluminal endoscopic balloon dilator (CRE balloon, Boston Scientific) up to 18mm. A gastroduodenoscope is directly inserted into the cyst cavity, and necrotic tissue is irrigated by spraying water and removed by grasping forceps and basket catheter. Initial endoscopic drainage and endoscopic necrosectomy were performed 2 to 4 weeks and 4 to 7 weeks after the episode of pancreatitis, respectively.

Results: Two patients (19-year-old male and 72-year-old male) were successfully treated by endoscopic necrosectomy. The number of session is 7 and 8, respectively, and the follow-up CT did not reveal any recurrence of abscess. Disappointedly, a 72-year-old female patient died of upper GI bleeding due to Mallory-Weiss tear three days after the fourth necrosectomy.

Conclusions: Endoscopic necrosectomy can be performed safely and effective for the primary treatment of WOPN.

F-035

Surgical Treatment for Severe Acute Pancreatitis: A Summary of 9 Cases

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Background & Aim: Surgical intervention for acute pancreatitis is primarily indicated for necrotizing pancreatitis and pancreatic abscess. However, multiple organ insufficiency remains an obstacle to favorable surgical results, and previous reports documented poor postoperative outcomes. In the present study, we evaluated our experience of surgical treatment for severe acute pancreatitis.

Method: The study cohort consisted of 9 patients who underwent necrosectomy with lavage of the abdominal cavity for uncontrollable necrotizing acute pancreatitis and/or pancreatic abscess between 1998 and 2008. Indications for surgical treatment were determined by sustained inflammatory response and imaging findings (necrotozing pancreatitis, pancreatic abscess, and infected pseudocysts) in the abdominal cavity after the intensive medical treatment by gastroenterologists. Our methodology was an extensive resection of necrotic tissue preserving intact pancreatic parenchyma, as well as insertion of multiple drainage tubes in the abscess cavities: after the operation, irrigation of abscess cavities with saline was continued until the inflammatory response became controllable.

Results: According to the Japanese guidelines for acute pancreatitis (version 3), the median score for severity of the pancreatitis was 4 (range 3–6) and CT grading was 1 in 2 patients, 2 in 2 patients, and 3 in 5 patients, respectively. The median interval between the onset of the pancreatitis and operation was 49 days (range 5–96 days). The median operation time was 525 minutes (range 170–820 minutes), and a median of 11 drainage tubes (range 5–14 tubes) was inserted. Postoperative continuous irrigation was performed for a median of 75 days (range 26–170 days). As a result, all patients survived and discharged from our hospital 104 days (median, range 53–184 days) after the operation.

F-036

A Case of Severe Acute Pancreatitis Complicating Duodenal Perforation

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We experienced a case of duodenal perforation due to severe acute pancreatitis which was successfully treated by percutaneous drainage. A 32-year-old man was transferred to our emergency center due to acute respiratory and renal failure due to alcoholic pancreatitis. Abdominal computed tomography (CT) showed swelling of the pancreas and fluid collection around the pancreas. Mechanical ventilation and hemodialysis was performed, and respiratory and renal condition was improved. He was transferred to the previous hospital to treat pancreatitis without a break. However, three days after that, he was re-transferred to our hospital due to shock and unconsciousness. Abdominal CT showed a lot of fluid collection around the pancreas and kidneys and Grade V pancreatitis was diagnosed. Mechanical ventilator and continuous hemodialysis was performed again. Percutaneous drainage of the fluid around the pancreas tail and left kidney was performed on the 13th hospital day. Abdominal CT on the 25th hospital day showed a development of right retroperitoneal abscess with large amount of air. Duodenal perforation at the 2nd portion was diagnosed by gastrointestinal contrast study. Percutaneous drainage was done for this abscess. This abscess cavity was washed every day with saline twice a day. Abscess cavity got smaller gradually but duodenocutaneous fistula was still remained. Although the fistula was refractory, endoscopic closure of the duodenal orifice successfully let it close on the 167th hospital day.

F-037

Comparison of Nasogastric Feeding and Nasojejunal Feeding for Severe Acute Pancreatitis

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Background: Several studies have shown that enteral nutrition may reduce infectious complication in severe acute pancreatitis (SAP).

Aim: The aim of this study was to evaluate methods of feeding in enteral nutrition (EN) for SAP.

Methods: We compared the effects of nasogastric feeding (NG) with those of nasojejunal feeding (NJ) for SAP in terms of mortality, total hospital stay and incidences of several complications. We retrospectively investigated 48 patients with SAP (median age, 49 years old; 38 male and 10 female patients) who were admitted to Showa University Hospital from November 2002 through October 2009. When an abdominal pain disappeared, we started EN at 20–25 mL/h (250–300 kcal/day) using a nasogastric or nasojejunal feeding tube. We gradually increased ingestion rate of feeds every 24–48 h to a final rate of 40–50 mL/h (1,000–1,200 kcal/day). We fed an elemental feed (Elental®) or an immuno-activating feed (Impact®).

Results: We performed NG in 22 patients and NJ in 26 patients. There were no significant differences in median age, sex distribution and severity of SAP between the groups. There were significant reductions in a period from the admission to the start of a meal (11 vs. 16 days, $p = 0.006$), a total hospital stay (24 vs. 32 days, $p = 0.009$) and the duration of administration of antibiotics (11 vs. 15 days, $p = 0.005$) between NG group and NJ group. There were no significant differences in incidences of organ dysfunction, infectious complications and mortality between the groups.

Conclusion: The results suggest that NG is as useful as NJ for SAP. Further randomized studies are necessary to compare NG with NJ for SAP.

F-038

Efficacy of Nutrition Support Team Supporting Synbiotics Enteral Nutrition in the Severe Acute Pancreatitis

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Purpose: To clarify whether nutritional support team (NST), which supports early enteral nutrition using synbiotics (S-EN), improves the outcomes of severe acute pancreatitis (SAP) patients.

Patients & Methods: In SAP defined by the new ('08) Ministry of Health, Labour and Welfare criteria, semi-digestion liquid diet was carefully given through naso-jejunal feeding tube with antibiotics-resistant Lactobacillus, L-glutamine, oligosaccharide and a dietary fiber (as synbiotics), soon after the intestinal function recovered. After the establishment of NST in our hospital in September, 2005, NST intervened in all SAP patients, round once a week is routinely carried out since then, and NST actively supported S-EN. 67 SAP patients ('92-'10) were divided into 2 groups whether S-EN supported by NST was performed. The secondary pancreas infection rate (IR), mortality (MT), and duration of hospitalization in the surviving patients (HP) were compared.

Results: No differences in severity, such as the new ('08) Ministry of Health, Labour and Welfare prognostic score, existed between two groups (5 point). IR of NST group (N=20, 15.0%) was better than that of control group (N=47, 27.7%), although MT was not different (30.0% vs. 19.1%). Furthermore, HP of NST group (median; 38 days) was shorter than that of control group (54 days).

Conclusions: S-EN might be, theoretically, effective for controlling the patient with SAP, but results of clinical trials are still controversial. One of the reasons is that enforcement of uniform protocol is difficult because of a complicated clinical course and/or a weak intestinal function in SAP. Therefore, the team approach such as NST must be effective, especially for prevention of pancreatic infection and shortening the duration of hospitalization.

F-039

Polymeric or Elemental Nutritional Formula in Patients with Severe and Critical Acute Pancreatitis? A Meta-analysis of Randomized Trials

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Introduction: While the benefits of enteral nutrition in severe and critical acute pancreatitis are well-established, the optimal composition of enteral feeding formula is largely unknown. The aim of the present study was to compare the effect of elemental versus polymeric formula in patients with severe and critical acute pancreatitis.

Methods: Three databases (Scirus, MEDLINE, Cochrane Controlled Clinical Trials Register) and the proceedings of major pancreatology conferences were searched for randomized controlled trials on either elemental or polymeric enteral feeding versus parenteral feeding in acute pancreatitis. Given the lack of trials on direct comparison of elemental versus polymeric formulas, they were compared using the methodology of indirect meta-analysis. The summary estimate was presented as a relative risks (RR) with corresponding 95% confidence interval (CI).

Results: A total of 6 randomized controlled trials were meta-analysed. The use of elemental versus polymeric formula in patients with severe and critical acute pancreatitis was not associated with a significant difference in feeding intolerance (RR 2.26; 95% CI 0.32 –15.27; P=0.41), total infectious complications (RR 0.23; 95% CI 0.03–1.86; P=0.25), and mortality (RR 0.89; 95% CI 0.28–4.90; P=0.12).

Conclusion: The use of elemental versus polymeric formulas is associated with similar risk of feeding intolerance, infectious complications and mortality in patients with severe and critical acute pancreatitis. Thereby, it seems that the use of more expensive elemental formula does not provide a significant advantage over relatively cheap polymeric formula.

Forum 07 Chronic Pancreatitis Treatment 2

F-040

Long-term Outcome of Treatment for Pancreatolithiasis with Extra-corporeal Shockwave Lithotripsy

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To elucidate long-term outcome of treatment for pancreatolithiasis using extra-corporeal shockwave lithotripsy (ESWL), we retrospectively analyzed 100 patients with pancreatolithiasis treated in our hospital from 1992 to 2009. Their mean age was 56 years, and the male:female ratio was 5:1. Etiology was alcohol-related in 73 patients, idiopathic in 20, and other in 7. Fifty-one patients had a single stone. The largest calculus was smaller than 10 mm in diameter in 37 patients, and 10 mm or greater in 63. Fragmentation of stones was achieved in all patients, and the complete stone-clearance rate after ESWL alone or ESWL in combination with interventional endoscopy was 89%. Effects on outcome of age, gender, etiology, number of stones, size of stones, distribution of stones, and presence of strictures in the main pancreatic duct were assessed statistically by univariate and multivariate analyses. An etiology (other than alcohol-related) and presence of stones (in over 2 regions) had significant negative effects on stone clearance. Patients were followed for a mean of 51 months, during which time 32 (36%) had stone recurrence. Early recurrence (within 1 year) was high in patients with ductal strictures, while later recurrence was more likely in patients with strictures. Recurrence was noted in 18% of alcohol-related patients and 24% of patients with pancreatic atrophy. Exocrine pancreatic function improved in 26 patients (40.6%), was unchanged in 19 (29.7%), and worsened in 26 (29.7%).

F-041

Standard Steroid Treatment for Autoimmune Pancreatitis

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Objective: To establish an appropriate steroid treatment regimen for autoimmune pancreatitis (AIP).

Method: A retrospective survey of AIP treatment, focusing on steroid treatment, was conducted in 17 centers that participated in this study in Japan. The main objective of this study is to clarify the rate of remission and relapse.

Results: Of 563 cases of AIP, 459 (82%) with AIP received steroid treatment. The remission rate of patients with AIP was significantly higher in patients who received steroid treatment (98%) than in those not given steroid treatment (74%, 77/104; $p<0.001$). The reasons for AIP treatment were obstructive jaundice (60%), abdominal pain (11%), associated extrapancreatic lesions except the biliary duct (11%), and diffuse enlargement of the pancreas (10%). There was no significant difference between the period necessary to achieve remission and the initial dose (30mg/day vs 40 mg/day) of prednisolone (PSL). Maintenance steroid treatment was performed after remission in 377 (82%) of 459 steroid-treated patients, and steroid treatment was stopped in 104 patients (28%). The relapse rate of patients with AIP on maintenance was 23% (63/273), which was significantly lower than that of patients who stopped maintenance treatment (34%, 35/104; $p=0.048$). 56%(55/99) relapsed within 1 year and 92%(91/99) relapsed within 3 years from the start of steroid treatment. Of the 89 relapsed patents, 83(93%) received steroid re-treatment, and steroid re-treatment was effective in 97% of them.

Conclusions: The major indication for steroid treatment in AIP is the presence of symptoms. We recommend PSL at a dose of 0.6mg/kg/day for the initial dose, which should be reduced to a maintenance dose over a period of 3–6months. Maintenance treatment with low-dose steroid can reduce but can not eliminate relapses.

F-042

Corticosteroids Correct Aberrant CFTR Localization in the Duct and Regenerate Acinar Cells in Autoimmune Pancreatitis

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Background: Corticosteroids are now widely accepted as a treatment for autoimmune pancreatitis (AIP). However, the molecular mechanism by which steroid treatment improves AIP remains largely unknown. The aim of this study was to elucidate cellular mechanisms by which corticosteroids improve both pancreatic exocrine function and histopathology in AIP.

Methods: Pancreatic exocrine function was evaluated by the secretin-stimulated function test and pancreatic biopsies were processed for histological analysis at the time of diagnosis and 3 months after initiation of steroid treatment. Expression and localization of proteins was assayed by immunohistochemistry. Analysis of IgG4-positive plasma cells was used to verify inflammation in AIP.

Results: The number of IgG4-positive plasma cells in pancreatic sections was decreased by steroid treatment, indicating reduced inflammation. Fluid, bicarbonate (HCO3-), and digestive enzyme secretions were all impaired in most patients with AIP. Corticosteroids improved both HCO3-; and digestive enzyme secretion. A large fraction of CFTR, which plays a central role in pancreatic duct HCO3-;

secretion, was mislocalized to the cytoplasm of duct cells prior to treatment. Corticosteroids corrected the localization of CFTR to the apical membrane, accounting for the improved HCO3- secretion. Steroid treatment resulted in regeneration of acinar cells, accounting for restored digestive enzyme secretion.

Conclusions: Corticosteroids reduce inflammation and restore both digestive enzyme and HCO3-; secretion in patients with AIP by regenerating acinar cells and correcting CFTR localization in pancreatic duct cells. Mislocalization of CFTR may explain aberrant HCO3- secretion in other forms of pancreatitis.

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F-043

Biliary and Pancreatic Ductal Hypertension Surgical Therapy in Chronic Pancreatitis Patients

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Background and Aim: main pancreatic and biliary duct obstruction are the first rate complications in chronic pancreatitis (CP). Surgical therapy is the leading way of their treatment. Contemporary drainage and resection techniques have a few important drawbacks that made us look for a new way of therapy in CP.

Methods: We analysed 28 patients in 12–24 months after longitudinal total pancreatowirsungoduodenopapillotomy with formation of longitudinal total Roux-en-Y pancreatojejunoduodenostomy. The new technique idea is a 1–2 cm posterior-medial incision of the intrapancreatic part of the common bile duct during pancreatowirsungoduodenopapillotomy. There were 25 men, average age: 50 years. They all had sings of pancreatic and biliary hypertension because of strictures and calculi of Wirsungeal duct, compression of CBD by enlarged and cystic transformed pancreatic head at US, CT-scan and ERCPG. The majority of them had also segmental portal hypertension and duodenostasis.

Results: Mortality rate was 0% in this group. 96,4% of the patients were pain released. None of them had clinical evidence of pancreatic or biliary hypertension. Pancreatic head size decreased in 93,4% of the patients. All the patients had normal duodenal passage, the normal size of the portal vein, the common bile duct, spleen. The patients also had normal parameters of bilirubin, alkaline phosphatase and Y-glutamiltransferase.

Conclusion: longitudinal total pancreatowirsungoduodenopapillotomy with simultaneous posterior-medial incision of the intrapancreatic part of CBD and formation of longitudinal total Roux-en-Y pancreatojejunoduodenostomy is an effective tool for biliary and pancreatic ductal hypertension surgical therapy, pain relief, restoring of duodenal passage and physiologic passage of bile and pancreatic juice to duodenum.

F-044

Adult Choledochal Cyst with Chronic Pancreatitis – An Uncommon Presentation

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Background: Incidence of adult choledochal cyst is rare. We report a case of large Type 1 choledochal cyst associated with chronic pancreatitis with multiple pancreatic ductal calculi presenting with obstructive jaundice. This case is highlighted to describe the surgical technique the patient underwent and also because of the rare presentation of the disease.

Clinical History: A 45 years old diabetic female patient was undergoing investigations for chronic upper abdominal pain and obstructive jaundice. Blood investigations revealed a direct hyperbilirubinaemia. Abdominal imaging (CT scan and MRCP) revealed a large Type 1 choledochal cyst with multiple pancreatic ductal calculi and atrophy of pancreatic tissue. An ERCP was performed to palliate the jaundice, during which biliary stricture and growth was ruled out. Patient then underwent an exploratory laparotomy, where complete choledochal cyst excision with removal of all pancreatic ductal calculi was done. For the anastamosis first the Roux loop was taken through the window in the mesocolon and a side to side pancreaticojejunostomy was performed and then the same loop was taken anterior to the stomach and an end to side Hepaticojejunostomy was performed. About 40 cms distal to the Hepaticojejunostomy a Jejeuno-Jejunal anastamosis was performed. Histopathology confirmed the diagnosis of choledochal cyst. Patient had an uneventful postoperative recovery and is fine at one year after surgery.

Conclusion: Occurrence of choledochal cyst with chronic pancreatitis is very uncommon and presents a surgical challenge. Performing a pancreaticogastrostomy with a Roux en Y Hepaticojejunostomy is one possible option. The technique described here is another such modification which could be performed with good outcome.

Forum 08 IPMN Diagnosis 1

F-045

Stromal Hyalinization in Intraductal Papillary Mucinous Neoplasms

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Background: Stromal hyalinization, which is observed in several tumors such as ovarian clear-cell carcinomas and basaloid-squamous carcinomas, has been suggested to be caused by deposition of basement membrane material. The aim of this study was to examine stromal hyalinization in intraductal papillary mucinous neoplasms (IPMNs).

Methods: A total of 76 IPMN cases were identified from the files of the Department of Pathology, Tokai University School of Medicine. All the cases were surgically-resected cases at Tokai University Hospital. IPMNs were classified into the following subtypes: intestinal type (IPMN-I: 44 cases), gastric type (IPMN-G: 22 cases), pancreatobiliary type (IPMN-PB: 4 cases), and oncocytic type (IOPN: 6 cases). Immunohistochemical studies for laminin and type-IV collagen were conducted to detect cases of stromal hyalinization.

Results: Stromal hyalinization was observed in 3/6 cases (50.0%) of IOPN. However, stromal hyalinization was not observed in the other subtypes. Stromal hyalinization was observed in the stroma of the tip of the papillary structure in IOPN. Stromal hyaline surrounded capillaries and connected to basement membranes of capillary walls. Some lesions showed connections between basement membranes of capillary walls and those of tumor cells via expanded stromal hyaline. Immunohistochemical studies revealed that stromal hyalinization was diffuse and strongly positive for type-IV collagen but negative or weakly positive for laminin.

Conclusions: Stromal hyalinization in IOPN is considered to be the thickened basement membrane material of capillaries. Stromal hyalinization could be as a clue to diagnosis of IOPN because stromal hyalinization was only observed in IOPN. Tumor cells of IOPN contain numerous mitochondoria in cytoplasm. Therefore, we assumed that stromal hyalinization in IOPN is related in some way to the mitochondrial function of tumor cells.

F-046

Natural History of Intraductal Papillary Mucinous Neoplasms of the Pancreas Based on EUS Morphological Changes, Focusing on Coexistent Invasive Ductal Cancer and Malignant Transformation of IPMN Itself

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Background/Aims: Branch-duct type intraductal papillary mucinous neoplasms (BD-type IPMN) of the pancreas have been reported to have a relatively favorable prognosis, but their natural course has not been clarified. We investigated the malignant alteration of BD-IPMN based on morphological changes in a long-term follow-up.

Patients and Methods: The subjects consisted of 143 patients who underwent contrast-enhanced endoscopic ultrasonography for the initial diagnosis after January 2001 with more than 6 months follow-up. The occurrence of invasive ductal cancer and the malignant transformation rate (MT-R) of BD-type IPMN itself were evaluated. Additionally, based on the morphological changes in patients who underwent surgery, predictive factors for malignant transformation were evaluated regarding imaging findings and clinicopathological factors.

Results: Follow-up observation was performed in 143 patients (median:41.6 months). Morphological changes were observed in 30 patients who underwent surgery. IDC occurred in 5 patients (3.5%) including 3 unresectable cases. The age-standardized incidence ratio of IDC was 19.0 (95% CI, 2.4–35.7). MT-R was 6.3%(9/143), and the 5-year MT-R was 10.7%. Thirty five (24.4%) of 143 patients exhibited the enlargement of mural nodules (MN). No invasive IPMN was observed in the operated patients at the appearance of new MN. As factors predicting MT, the size of the main pancreatic duct (MPD), MN, the nodule-growth-rate during the just past year, the occurrence of symptoms and history of other organ malignancy were significant.

Conclusion: The malignant alteration of BD-type IPMN was not infrequent. The observation of morphological changes of MPD and MN, mainly on EUS, may be useful for predicting malignant transformation of BD-type IPMN itself.

F-047

Treatment Strategy for Intraductal Papillary Mucinous Neoplasm of the Pancreas Based on Malignant Predictive Factors

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Noninvasive intraductal papillary mucinous neoplasms (IPMNs) have a favorable prognosis; however, the prognosis of invasive intraductal papillary mucinous carcinoma (invasive IPMC) is poor. Identification of predictive factors for differentiating IPMC from benign IPMNs would assign providing appropriate treatment. In the present study, clinical data, preoperative imaging findings, cytologic findings, tumor markers in serum and pancreatic juice were assessed to identify the significant predictors of malignant IPMN. Between July 1999 and January 2006, 54 patients with IPMN were surgically treated at Wakayama Medical University Hospital. Histologic examination showed 25 to be malignant, consisting of 14 cases of carcinoma in situ and 11 invasive adenocarcinomas, and another 29 to be benign IPMN. In result, age of 70 years or older, presence of mural nodules, mural nodule size of 5mm or larger, and carcinoembryonic antigen (CEA) level in pancreatic juice of 110 ng/mL or higher (as obtained by preoperative endoscopic retrograde pancreatography) were predictive of a malignant IPMN by univariate analysis, and a CEA level of 110 ng/mL or higher in pancreatic juice was identified as the only independent predictive factor for the malignant entity (odds ratio, 29.8; 95% confidence interval, 2.8–313.9). The presence of jaundice or body weight loss, main pancreatic duct type, presence of mural nodules, mural nodule size of 5mm or larger, and CEA level in the pancreatic juice of 110 ng/mL or higher were all predictive of invasive IPMCs by univariate analysis. Of the pathological factors analyzed, the presence of a cancer component, found in 25 cases (46%), was a predictor of the prognostic outcome (P=.004), and the presence of an invasive component, found 11 cases (20%), was a strong predictor of shorter survival (P<.001) In conclusion, measurement of the CEA level in the pancreatic juice is a useful diagnostic method to distinguish malignant from benign IPMNs.

F-048

Atypical Epithelial Cells in Fluid Aspirated from Mucinous Cysts of the Pancreas are a Powerful Predictor of Malignancy

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Objectives: Distinguishing benign from malignant pancreatic mucinous cysts is important for patient management. Malignancy is often suspected from the presence of a mural nodule (MN) and dilated main pancreatic duct (MPD) noted radiologically. Cytological evaluation of aspirated fluid is controversial. We hypothesized that the finding of atypical epithelial cells in aspirated cyst fluid would be a more sensitive predictor of malignancy than these two radiological features.

Methods: We retrospectively reviewed clinical, radiological and cytological data on a cohort of 112 patients with histologically confirmed mucinous cysts of the pancreas (mucinous cystic neoplasm (MCN) or intraductal papillary mucinous neoplasm (IPMN) evaluated in a single institution tertiary medical center between 1993 and 2008. All patients had cysts with histological classification according to contemporary nomenclature and all cysts were aspirated pre-operatively by endoscopic ultrasound. Cytology slides were available for re-review in all cases. Radiological parameters were retrieved from medical records. Neoplasms were grouped as benign (low grade and moderate dysplasia) and malignant (in-situ and invasive carcinoma) and categorical variables compared using Chi Square and Fisher's Exact Test with significance at $p=0.05$.

Results: Atypical epithelial cells (AEC) on cytology distinguished benign and malignant mucinous cysts ($p<0.0001$) similar to MN and dilated main MPD (both $p<0.0001$), but with far more sensitivity (72%) compared to MN (39%) and dilated MPD (46%) by univariate and multivariate analysis, even for small branch duct IPMN (67% vs. 22% for both MN and dilated MPD).

Conclusions: AEC in aspirated cyst fluids are a powerful predictor of malignancy in mucinous cysts of the pancreas.

F-049

Intraductal Papillary-mucinous Neoplasms of the Gastric and Intestinal Types May Have Less Malignant Potential Than the Pancreatobiliary Type

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Objectives: Intraductal papillary-mucinous neoplasms (IPMNs) of the pancreas are classified into four types; gastric, intestinal, pancreatobiliary, and oncocytic; on the basis of their morphology and immunohistochemistry. We classified IPMNs at our institute and used this classification to determine the clinicopathological features, prognosis, and malignant potential of the four types.

Methods: Sixty one patients with IPMN who underwent surgery between 2000 and 2007 were evaluated retrospectively.

Results: There were 24 tumors of the gastric type, 22 intestinal, 12 pancreatobiliary, and 3 oncocytic. Patients with the intestinal or gastric type had a better prognosis than those with the pancreatobiliary type. The intestinal and pancreatobiliary types had almost the same frequencies of carcinoma, but the intestinal type tended to have a lower frequency of invasive carcinoma than the pancreatobiliary type. Patients with invasive carcinomas derived from intestinal-type IPMNs tended to have a better prognosis than those whose invasive carcinomas were derived from the pancreatobiliary type.

Conclusions: IPMN of the gastric and intestinal types may have lessmalignant potential than that of the pancreatobiliary type. Invasivecarcinomas derived from intestinal-type IPMNs may be less invasiveand slower growing than those derived from the pancreatobiliary type.

F-050

Management of IPMNs by Endoscopic Ultrasonography

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Background: Intraductal papillary mucinous neoplasm (IPMN) is often accompanied with ductal pancreatic cancer. IPMN-related carcinomas consist two types; carcinomas derived and distinct from IPMNs. Among several imaging examinations, endoscopic ultrasonography (EUS) is superior to any other modality with respect to spatial resolution. We employed EUS for diagnosis as well as follow-up of IPMNs, and evaluated its role in characterization of mural nodules and detection of concomitant carcinomas.

Patients and Methods: Between April 1999 and March 2009, EUS was performed in 317 patients who had been suspected of having IPMNs. Forty-one patients with histopathologically proved IPMNs (hyperplasia, n=1; adenoma, n=24; non-invasive carcinoma, n=6; invasive carcinoma, n=7; derived carcinoma, n=3) underwent surgery after EUS, MDCT and MRCP. Ninety-three patients were followed up mainly by EUS twice a year for more than 12 months.

Results: EUS, MDCT and MRCP achieved depiction of mural nodules in 92% (35/38), 26% (10/38) and 16% (6/38) of cases, respectively. Thirty-five lesions depicted by EUS included 22 benign lesions (hyperplasia, adenoma) and 13 carcinomas (non-invasive, invasive). Twenty-five lesions were detected only by EUS, 6 cases of which were non-invasive or invasive carcinoma. The average height of mural nodules measured preoperatively by EUS was 4±3mm in hyperplasia and adenoma, 10±4 mm in non-invasive and invasive carcinoma. The height of mural nodules in carcinoma was significantly higher than in benign lesion. Among 93 patients who were followed up, no IPMN-derived carcinoma occurred but 3 concomitant carcinomas distinct from IPMN were complicated during follow-up period.

Conclusion: EUS is useful to detect mural nodules of IPMNs and ductal pancreatic carcinoma distinct from them. Higher mural nodules measured by EUS indicate malignancy. Periodic follow-up by EUS in patients with IPMNs may play an important role in early detection of pancreatic carcinomas.

Forum 09 Endocrine Tumor, Other Pancreatic Tumor

F-051

Pitfalls in the Assessment of Ki-67 Index in Pancreatic Endocrine Neoplasms

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Ki-67 has been advocated as a prognostic factor for pancreatic endocrine neoplasms (PENs). Technical and interpretational aspects of Ki67 have not been clarified. To distinguish bening from malignant behavior, some employ 2% as the cut-off, others use 5%. Optimum method with best predictive value hasn't been determined. Another question is the impact of tumor heterogeneity especially in evaluation of limited specimens. In this study, we compared Ki-67 by different measurements.

Design: 70 PEN's were evaluated: male/female 0.9; mean age 52 (23–82); 20 functioning; 6 multifocal; mean size 3.9cm (0.6–17); and 29 (41%) metastasizing. In areas containing >2000 cells, Ki-67 was assessed in high labeling (Ki-67(h)) and in random (Ki-67(r)) areas.

Results: Ki-67(h) ranged from 0.3 to 23.7 (5.4%). By using the cut-off 2% advocated by WHO, there were significant differences in size (2.5 vs. 4.7cm), mitotic count (>2/10 HPF, 0 vs.15%), vascular invasion (25 vs. 67%) and metastasis (25 vs. 50%) between PENs with Ki-67(h) <2% (n=24) and those with Ki-67(h)>2%. Few cases were Ki-67(h) <1% (n=7) and none had metastasis. On the other hand, tumor heterogeneity appeared to be an important factor. Ki-67(r) was less than Ki-67(h) in all cases (0.1–18.7; 2.6%). Ki-67(h)/Ki-67(r) ratio ranged from 1.1 to 7.7 (3.1). PENs with Ki-67(r) <2% (n=45) outnumbered those with Ki-67(r)>2%. In terms of relation with metastasis, the cut-off 2% was not significant, but there was a significant difference between PENs with Ki-67(r) <0.5% (n=18) and those with Ki-67(r)>0.5% (11 vs. 52%).

Conclusions: This study confirms the association of Ki67 with signs of aggressive behavior in PENs including size, metastasis, mitosis and vascular invasion. It also illustrates that intratumoral heterogeneity is an important factor. Depending on the area of tumor chosen, 30% of the PENs could be placed erroneously into the "benign behavior" category. The data may be informative especially in small samples like biopsy.

F-052

A Case Report of Glucagon-Producing Multiple Pancreatic Neuroendocrine Tumors That Involved Pancreatic Cystic Lesions

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A 59 year-old female who had previous history of a surgical resection of pancreatic cyst and diabetic mellitus presented with abdominal distension. The blood chemistry data including tumor markers were within normal range. Abdominal ultrasonography showed an 8mm size hyperechoic heterogeneous pancreatic tumor and two cystic lesion at the tail of the pancreas. The tumor and the cystic lesions showed enhancement on early phase of CT, a marked distension of the stomach was also seen. Gastrointestinal endoscopy revealed pyloric stenosis which seemed to be caused by accompanying gastric ulcer and duodenal ulcer scars. EUS revealed another 6mm size hyperechoic tumors at the pancreatic body, and the finding also showed a thick capsule in one of the cystic lesions. ERCP was not possible due to severe stenosis of the pyloric ring. At this point, we suspected pancreatic endocrine tumor with cystic lesions and pyloric stenosis. Plasma hormones were measured. A significant increase in plasma glucagon (17000pg/ml) was seen, however gastrin level was normal. With clinical diagnosis of glucagonoma with pancreatic cyst and pyloric stenosis, distal pancreatectomy and total gastrectomy was performed. Pathologic finding revealed that both the 6–8mm size tumors and the cystic lesions were well differentiated neuroendocrine tumors. They were immunohistochemical positive for glucagon and SSTR2A. We have experienced a case of glucagon producing multiple pancreatic endocrine tumors that involved cystic change, and we report the case with literature reviews.

F-053

Successful Control of Intractable Hypoglycemia by Radiopharmaceutical Therapy with Strontium-89 in a 57-year-old Woman with Malignant Insulinoma and Bone Metastases

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Context: Insulinomas are rare tumors that arise from the pancreatic islet cells that produce insulin. Approximately 5% to 10% of the tumors are cancerous, and control of insulin secretion and hypoglycemia may be difficult in patients who have a malignant insulinoma. Malignant insulinomas generally respond poorly to traditional chemotherapy regimens. Streptozotocin is the only drug approved by whom for the treatment of pancreatic islet cell tumors, but it is not covered by national health insurance in Japan.

Setting and Patients: This report describes the case of a middle-aged woman with liver and bone metastases after distal pancreatectomy and splenectomy for a malignant insulinoma and severe hypoglycemia. Octreotide, diazoxide, and transarterial embolization to treat the liver metastases failed to raise her blood glucose level, and she required constant glucose infusion (about 1000 kcal/day) and oral feeding (about 2200 kcal/day) to control her hypoglycemia and elevated insulin levels.

Intervention: 110 MBq (2.0 MBq/kg) dose of strontium (Sr)-89 was administered by intravenous injection.

Results: Three weeks after the Sr-89 injection, it was possible to begin to wean the patient from the constant glucose infusion and to maintain euglycemia and lower circulating insulin levels. About six weeks after the injection, it was possible to completely stop the constant glucose infusion even though previous treatment had failed.

Conclusions: Although this therapy may be indicated in patients with multiple painful bone metastases detected on a bone scan, Sr-89 therapy may also be useful as a means of arresting tumor growth and controlling hypoglycemia in patients with a malignant insulinoma and bone metastases. To the authors' knowledge this is the first report to provide evidence that Sr-89 can be useful in controlling intractable hypoglycemia in malignant insulinoma with bone metastases.

F-054

Solid Pseudopapilary Neoplasm of the Pancreas: Sixteen Cases Study in Our Institution

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Purpose: Solid pseudopapillary neoplasm (SPN) of the pancreas, which predominantly affects young women, is a relatively indolent entity with favorable prognosis. The aim of this study is to evaluate the clinicopathological features and surgical management of this rare disease in our institution.

Methods: We retrospectively evaluated about the clinical and histological characters of sixteen SPN patients treated in Tohoku University Hospital from January 1994 to December 2009.

Results: The 16 cases included 14 female and 2 male patients, and the average age was 35.1 years. Majority of the patients have no symptom about the disease (10/16: 62.5%), but some patients have abdominal pain (n=4), palpitation (n=1), and back pain (n=1). The neoplasm was localized in the pancreatic body (n=8), tail (n=5), head (n=2). Residual 1 patient admitted with multiple liver metastases after distal pancreatectomy. The median diameter of these lesions was 51.3 mm. All patients underwent surgical exploration, including 7 distal pancreatectomies, 4 middle pancreatectomies, 2 pancreaticoduodenectomies, 2 enucleations, and 1 partial resection of the liver. Three of these procedures were carried out laparoscopically. The resection margin was R0 in 13 patient and R1 in 3. Four patients were diagnosed as malignant SPN histologically, due to lymph node involvement, invasive or metastatic characters. There were no surgical mortalities, and postsurgical complications occurred in 10 patients (62.5%). The median postsurgical stay was 32.3 days. Only 1 patient with liver metastases received chemotherapy, but had recurrence in the remnant liver 3 months after liver surgery. Another 15 patients had disease-free survival at a median follow-up of 77.2 months.

Conclusions: SPN is a rare neoplasm and has low malignant potential in general, however there are some malignant cases with a possibility of recurrence. Thus, malignant SPN patients should be treated with attention after surgical treatment.

F-055

A Case of Solid Pseudopapillary Neoplasm Presenting with Strong Fluorodeoxyglucose Uptake on Positron Emission Tomography Mimicking Malignancy

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Solid pseudopapillary neoplasms (SPNs) are rare pancreatic tumors, mostly affecting young women. SPNs are now considered low-grade malignant neoplasm with low metastatic rate and high overall survival.

A 65-year-old woman was told she had a tumor in the pancreas when she was in her 30's, but left it untreated for over 30 years. In 2009, she consulted a physician for abdominal pain. Radiological findings proved a large tumor in the pancreas and she was transferred to our hospital. Physical examination revealed an abdominal mass in right upper quadrant. In the laboratory tests, the levels of serum amylase and tumor markers were within the normal range. Abdominal MRI showed a large tumor which had calcification and necrosis in it. Contrast-enhanced MRI showed solid and cystic components with an early or delayed phase, which was compatible with SPN. It is interesting to note that 2-deoxy-18F-fluoroglucose positron emission tomography (FDG-PET) showed a strong uptake in the tumor where standardized uptake value max was 11.4. Therefore, malignant SPN was strongly suspected but neuroendocrine neoplasm and acinar cell carcinoma were also considered. Then we performed a percutaneous tumor biopsy. The specimen was suggestive of SPN and consequently pylorus preserving pancreaticoduodenodectomy (PpPD) was performed. Histologically, the neoplasm was mostly composed of sheets of spindle cells. Contrary to our expectations, no cellular atypia, mitosis, vascular invasion and inflammatory cells infiltration were identified. Immunohistochemically, the tumor cells were positive for alpha1-antitrypsin, CD10, synaptophysin and progesterone receptor but negative for chromogranin A and alpha1-antichymotrypsin which are typical findings of SPN.

It is well-known that imaging features of SPN are solid and cystic components, intratumoral hemorrhage and calcification in the tumor. Until now, however, findings of FDG-PET with pathological association have not been fully investigated. We present a rare case of SPN showing strong FDG uptake on PET mimicking malignancy.

F-056

Value of EUS and EUS-FNA for Diagnosing Metastatic Pancreatic Cancer

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Background: Although rare, metastatic lesions of the pancreas represent a subtle cause of focal pancreatic lesions that are difficult to diagnose by imaging alone. In addition, few reports describe EUS and EUS-FNA findings of such lesions. Here, we examined the ability of EUS and EUS-FNA to diagnose pancreatic tumor metastasis.

Methods: This retrospective, single-center study compared the features of all pancreatic metastases diagnosed using EUS and EUS-FNA over an 11-year period with those of primary pancreatic cancer as a control.

Results: Of 21 patients who underwent EUS, 14 underwent EUS-FNA and/or 11 were operated. The primary lesions were renal cell cancer (6), lung cancer (4), sarcoma (3), malignant lymphoma (2), malignant melanoma (2), ovarian cancer (1), orbital cavity cancer (1), colon cancer (1), and breast cancer (1). Primary and metastatic sites were concurrently discovered in four patients. Pancreatic metastases were more likely to be multiple, well-demarcated, heterogeneous ($p=0.001$) and with a halo-like low echoic margin ($p=0.002$) than controls. Primary cancers were more likely to have retention cysts ($p=0.01$) and atrophic parenchyma at the tail side ($p=0.03$). None of tumor size, site, MPD dilation at the tail side, calcification, and cystic degeneration significantly differed. EUS-FNA sampling adequacy was 92.8% (13/14) and all tumors were diagnosed as malignancies. Ten specimens were examined by immunohistochemical staining and/or genetic testing (k-ras) to confirm suspected diagnoses. One tumor that was a false negative (insufficient sample) was diagnosed at surgery as metastasis of renal cell cancer. No severe complications developed.

Conclusions: Pancreatic metastases are more likely to have multiple, well-defined margins, a heterogeneous echo pattern and a halo-like low echoic margin. Using EUS-FNA to diagnose pancreatic metastases can influence the choice of appropriate therapeutic strategies.

F-057

Spleen-preserving Distal Pancreatectomy with Conservation of the Splenic Artery and Vein

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We have been performed spleen-preserving distal pancreatectomy (SpDP) as a function preserving surgery.

Our technique of SpDP preserves both splenic vein and artery to avoid infarction of the spleen. After opening bursa omentalis, incise the Toldt's fascia. Branches of the splenic vein were ligated and cut toward spleen. Next, branches of the splenic artery was divided.

Parenchyma of the pancreas is sharply cut, and stump of the pancreas is sutured like fish mouth. We had never experienced postoperative bleeding due to pancreas fistula. Torsion of the spleen is not occur, even patient walk 1 postoperative day.

We consider indication of SpDP as benign lesion of the pancreas including intraductal papillary mucinous adenoma (IPMA).

Results: Operative time was longer than ordinal distal pancreatectomy (DP) 367 vs 288 min ($p<0.05$). Blood loss, rate of pancreatic fistula, hospital stays, preoperative platelet counts were similar between SpDP and DP groups. On the contrary, postoperative platelet counts are significantly lower in SpDP group (39.5) than DP (58.9). And postoperative hemoglobin after one month are higher in SpDP (11.9) than DP (11.4).

In conclusion, SpDP considered clinically important for preventing postoperative pulmonary or cerebral infarction and improving postoperative hemoglobin after one month. SpDP is useful and safety surgical procedure for benign pancreas neoplasms.

F-058

A Case of Inflammatory Pseudotumor of the Pancreas Associated with Lymphoplasmacytic Sclerosing Pancreatitis

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A 73-year-old woman with back pain was referred to our hospital for further investigation. Radiological findings revealed a 2-cm tumorous mass in the pancreatic head. As laboratory examination revealed slight elevation of the serum levels of gamma-globulin and IgG., that of IgG4 was within normal limit. Based on the preoperative diagnosis of non-functioning pancreatic endocrine tumor or solid pseudopapillary tumor predominantly composed of solid compartment, the pylorus-preserving pancreaticoduodenectomy was conducted. Histological examination of the resected specimen showed spindle cell proliferation showing SMA and vimentin positivity suggesting myofibroblastic differentiation. Severe atrophy and destruction of lobular structure and periductal lymphoplasmacytic infiltration and fibrosis, which are usually observed in autoimmune pancreatitis

(AIP), were seen in the tumor. Adjacent pancreatic tissue also showed mild interlobular fibrosis and atrophy of acinar tissue, and periductal lymphoplasmacytic infiltration. Immunohistochemical staining showed IgG4-positive plasmacytes in both of the tumor and adjacent pancreatic tissue. Based on these histological findings, the patient was diagnosed to have an inflammatory pseudotumor associated with AIP although radiological findings were inconsistent with the diagnostic criteria for AIP of Japan Pancreas Society.

Forum 10 Pancreatic Cancer Diagnosis

F-059

Gender Differences in the Association of Long-standing Diabetes with Pancreatic Cancer

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Aim: Type 2 diabetes is heterogeneous disease and long-standing diabetes is considered to be a predisposing factor for pancreatic cancer. In this study, we attempted to clarify the gender difference in the association of preexisting diabetes (Pre-DM) with pancreatic cancer.

Method: We reviewed the medical records of the total of the 924 patients with pancreatic cancer diagnosed between 1975 and 2008. Pre-DM was defined as having diabetes for at least 5 years prior to the diagnosis of pancreatic cancer. After limiting the patients with information regarding a family history of diabetes in first-degree relatives, we studied gender differences in clinical pictures of pancreatic cancer. Two hundred forty four men and 181 women were eligible.

Results: All Pre-DM observed belonged to type 2 diabetes. The frequency of Pre-DM was significantly higher in men than in women (16.8% vs. 8.3%; p=0.013). In men, no difference of age at the diagnosis of the pancreatic cancer was found between those with Pre-DM and those without (66.3 years vs. 64.8 years). On the other hand, women with Pre-DM were 6 years older than not only those without Pre-DM (72.3 years vs. 66.0 years; p=0029), but also men with Pre-DM (p=0.028). Median duration of diabetes was 10 years in men, and 18 years in women. Among men, the positive rate of a family history of diabetes was significantly higher in those with Pre-DM than in those without (51.2% vs. 11.3%), whereas such a difference was not found in women (26.7% vs. 18.1%)

Conclusion: The underlying mechanisms of predisposing Pre-DM to pancreatic cancer can be different between men and women.

F-060

Prognostic Biomarkers in Pancreatic Cancer

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Background: The most of pancreatic cancer metastasize even after curative resection and it makes its prognosis extremely poor. The aim of this study was to evaluate the prognostic biomarkers which could help predicting time to progression, treatment response, and overall survival on the basis of immunohistochemistry in pancreatic cancer.

Method: Two hundred forty five patients who underwent pancreatic cancer resection with the final diagnosis of pancreatic cancer were retrospectively reviewed by electronic medical records during the period 2002–2007. Among them, eighty-two patients had completely resected (R0) pancreatic adenocarcinoma and they were included in the study and the tissue microarray was made from the above patients. Immunohistochemical staining was performed with 19 antibodies according to the following categories: EGF, c-Met, VEGF, MMP, DNA repair gene families, and chemokines. OS and DFS were analyzed with a Cox model adjusted for clinical and pathological factors.

Results: The median OS in the group of patients who had high vs low expression of Epiregulin, TIMP3, VEGF, neuropilin and amphiregulin were 32 vs 22mo, 35 vs 18mo, 31 vs 22mo and 32 vs 22 mo respectively. (p=0.02, 0.002, 0.036, 0.04, 0.03) The ERCC1 expression could not affect OS and DFS, however, the patients who had long term survival more than 60 mo had significant high expression of ERCC1. The patients who present their disease progression in distant metastasis had significant higher expression of epiregulin or phospho c-met expression. (p=0.019, 0.04)

Conclusion: The presence of high expression of epiregulin and phospho c-met were associated with early distant metastasis in R0 resected pancreatic cancer patients. The pancreatic cancer patients with high expression of epiregulin, TIMP3, VEGF, neuropilin and amphiregulin had statistically significant longer OS. These biomarkers could give us an idea of starting point to understand the mechanisms of pancreatic cancer dissemination with further investigation.

F-061

Long-term Outcome of RT-PCR Based Detection of Minute Cancer Cells in Peritoneal Lavage Fluid During Surgery in Patients with Resectable Pancreatic Adenocarcinoma

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Background: Recent advances in molecular biochemistry enable the detection of cancer cells in the peritoneal cavity with superior sensitivity than that by conventional cytology. RT-PCR based identification (molecular diagnosis) of minute cancer cells in peritoneal lavage fluid has been shown to be a positive predictive factor for intrapenitoneal recurrence in several kinds of cancers including gastric, colon and ovarian cancers, however it has not been determined in pancreatic cancer.

Methods: In 59 patients with pancreatic adenocarcinoma, peritoneal lavage fluid was harvested just after a laparotomy. Half of the fluid was examined by cytology and the remaining half was used to measure carcinoembryonic antigen (CEA) mRNA expression. After surgical resection, patients were followed at least for 2 years or until pancreatic cancer-related death.

Results: Among 59 patients, only 1 were cytologically positive [CY(+)], while 15 were positive by RT-PCR [PCR(+)]. Postoperative recurrence was observed in 32 patients, including local recurrence in 12, peritoneal dissemination in 8, recurrence in the liver in 7, recurrence in the lung in 7 (2 patients had multiple recurrences). In 15 of PCR(+) patients, 11 showed intra-abdominal recurrence (peritoneal- or local-recurrence, excluding liver metastases) during the follow up (Positive Predictive Value; 73%), whereas 35 patients in 44 of PCR(-) patients did not show this mode of recurrence (Negative Predictive Value; 80%). Kaplan-Meier analysis demonstrated that the intra-abdominal recurrence rate was significantly lower in PCR(-) patients ($p < 0.0001$), while the recurrence rates in the distant organ were similar between the two groups. Postoperative survival rate was also significantly better in PCR(-) patients ($p = 0.043$).

Conclusions: The RT-PCR based cancer cell detection accurately predicts the intra-abdominal recurrence, and was a significant prognostic factor in patients with resectable pancreatic adenocarcinoma.

F-062

Role of 18F-fluorodeoxyglucose Positron Emission Tomography with Dual Time Point Evaluation in the Diagnosis of Small Pancreatic Cancer

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Background: Early detection is essential to allow a potentially curative resection for invasive ductal cancer of the pancreas. The aim of this study was to investigate the role of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the diagnosis of small pancreatic cancer.

Methods: This study involved 31 patients with proven invasive ductal cancer of pancreas. The patients were divided into tree groups according to the maximum diameter of the tumor, TS1(<2.0cm), TS2 (2.0–4.0cm), or TS3-4 (4.0cm). The relationships between the TS and various diagnostic tools, including FDG-PET with dual time point evaluation were analyzed.

Results: The tumors ranged 1.3 to 11.0cm in diameter. There were 5 patients classified as TS1, 15 patients as TS2 and 11 patients as TS3-4. The sensitivity of FDG-PET, CT and MRI were 100%, 40%, 0% in TS1, 93%, 93%, 89% in TS2 and 100%, 100%, 100% in TS3-4. The sensitivity of FDG-PET was significantly higher in comparison to CT and MRI in the patients with TS1 ($p < 0.032$). The SUV did not show a significant difference in relation to the TS. All of the TS1 tumor showed higher SUV in delayed phase compared with that in the early phase.

Conclusions: These results indicate that FDG-PET with dual time point evaluation is a useful modality for the detection and diagnosis of small pancreatic cancer.

F-063

Preoperative Detection of Liver Metastases Secondary to Pancreatic Cancer: Utility of Gadolinium-ethoxybenzyl-diethylenetriamine Pentaacetic Acid-enhanced Magnetic Resonance Imaging (Gd-EOB-DTPA MRI)

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Background: Utility of CTAP+CTHA (computed tomography during arterial portography combined with computed tomography-assisted hepatic arteriography) has been already reported to detect liver metastases secondary to pancreatic cancer before surgery. Recently Gd-EOB-DTPA MRI (Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging) is known to useful modality of detecting liver tumor.

Objective: The aim of this study was to evaluate utility of Gd-EOB-DTPA MRI for preoperative detection of liver metastases secondary to pancreatic cancer compared with CTAP+CTHA.

Methods: From May 2008 to December 2009, we retrospectively studied 24 patients with pancreatic cancer. Both CTAP+CTHA and Gd-EOB-DTPA MRI were performed on all patients. The presence of each lesion at diagnosis was defined as positive histological proof at operation or enlargement of the lesions during follow-up period on radiological examinations. The absence of liver metastasis at diagnosis was proved by intraoperative findings including ultrasound for operative cases and/or follow-up radiological examinations of more than 3 months.

Results: CTAP+CTHA diagnosed presence of liver metastases in 12 patients. Of the 12 patients 7 patients (58.3%) were diagnosed as presence of liver metastases with Gd-EOB-DTPA MRI. Twelve patients, those were diagnosed as absence of liver metastases with CTAP+CTHA, were also diagnosed as no liver metastases with Gd-EOB-DTPA MRI. Follow up MDCT revealed liver metastases clearly detected in 2 patients. In one patient, CTAP+CTHA had detected it, but Gd-EOB-DTPA MRI had not. In the other patient, neither modality could detect liver metastases. The sensitivity and the specificity of Gd-EOB-DTPA MRI versus CTAP+CTHA were 77.8% versus 88.9% and 100% versus 73.3%, respectively. The overall accuracy of Gd-EOB-DTPA MRI versus CTAP+CTHA was 91.7% versus 79.2%.

Conclusions: Gd-EOB-DTPA MRI showed better accuracy to detect liver metastases than CTAP+CTHA. Gd-EOB-DTPA MRI could be useful modality to detect liver metastases before surgery.

F-064

The Evaluation of MSX2 Expression Level in Brushing Samples During ERCP Differentiates Malignant from Benign Pancreatic Lesions

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Background and Aim: We have shown that MSX2 expression is found in pancreatic cancer and malignant intraductal papillary mucinous neoplasms (IPMNs) but not in nontumorous pancreatic tissues. Therefore, we investigated the expression level of MSX2 in ERCP brushing specimens to assess whether this expression would differentiate malignant from benign pancreatic lesions.

Materials and Methods: Cytologic brushing specimens were obtained from strictures of pancreatic duct during ERCP from 94 patients at Tohoku University Hospital. The brushing fluid was subjected to cytological diagnosis and RNA extraction. Final diagnosis was pancreatic carcinoma (n=57), IPMN (n=13) including 5 cases of carcinoma of IPMN (IPMC) and chronic pancreatitis (n=24). The expression levels of MSX2 mRNA were evaluated by one step real-time RT-PCR. The copy number of MSX2 in each sample was normalized to the respective GAPDH copy number. The cut off value was determined according to the ROC curve analysis.

Results: The mean expression levels of MSX2 (MSX2/GAPDH copy number) was observed in the following order: 0.011 + 0.002 (mean + standard error) in pancreatic cancer, 0.006 + 0.005 in IPMN and 0.004 + 0.002 in chronic pancreatitis. MSX2 expression level was significantly higher in pancreatic carcinoma than in chronic pancreatitis (P=0.04), but no significant difference was found between IPMN and pancreatic cancer or chronic pancreatits. On the other hand, MSX2 expression was significant higher in malignant lesions (pancreatic cancer and IPMC) than in benign lesions (benign IPMN and chronic pancreatitis) (P=0.001). The sensitivity and specificity of cytology and MSX2 expression for the detection of carcinoma in strictures are: 48.4% and 100%, 64.5% and 65.6%, respectively.

Conclusion: The sensitivity of MSX2 expression level for the diagnosis of malignant lesions was higher than cytology. This suggests that the evaluation of MSX2 in ERCP brushing sample would be useful tool to distinguish malignant from benign pancreatic lesions.

F-065

Diagnostic Value of Endoscopic Ultrasound Guided Fine Needle Aspiration in Patients with Pancreatic Lesions

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Background and Aim: Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) is used frequently for tissue diagnosis in pancreatic mass lesions. We aimed to evaluate the diagnostic accuracy and problem of EUS-FNA in patients with pancreatic lesions.

Patients and Methods: Between January 2001 and June 2009, 105 patients (70 men, mean age 62.73±22.6 years) with pancreatic lesions underwent EUS-FNA. EUS was performed with a linear echoendoscope and FNA was performed with Endosonopsy 21-gauge (Hakko) or ECHOTIP 22-gauge (Wilson-Cook) or NA-200H-8022 22-gauge (OLYMPUS). Ten to-and-fro needle movements were routinely applied for each of the aspiration procedures. Fine-needle aspirates were assessed immediately by an attending cytopathologist. The final diagnosis was based on definitive cytology, surgical pathology, and clinical follow-up.

Results: 105 pancreatic lesions were investigated, and their diagnoses were; 70 pancreatic adenocarcinomas, 1 metastatic renal cell carcinoma, 1 metastatic small cell carcinoma of the lung, 11 autoimmune pancreatitis, 9 tumor-forming pancreatitis, and 13 others. On average, 2.44 passes were performed for one pancreatic lesion. 87.6% of all samples were suitable for diagnosis. The sensitivity, specificity and accuracy of EUS-FNA were 83.5%, 100% and 87.6% respectively. There were no procedure related complications. We investigated the characteristics of 13 false negative lesions comparing with computed tomography; 4 lesions were located back side of the pancreas, 3 were mainly composed of cystic lesions, 5 were not larger than 10mm in size, and 1 was located at the tip of pancreatic tail.

Conclusion: EUS-FNA was useful for pathological diagnosis. There were three features of false negative cases; the lesions were small and not clear by EUS, the lesions were mainly composed of cyst, and the lesions were located deeply from the EUS view.

F-066

Effectiveness of EUS-FNA in Diagnosing Pancreatic Lesions

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Objectives: To evaluate the diagnostic effectiveness of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) performed in our department on pancreatic lesions.

Patients: From June 2005 to December 2009, 202 patients (216 lesions) whose pancreatic lesions were diagnosed with EUS-FNA were included. The number of the cases for each diagnosis was as follows: adenocarcinoma (PC), 153 lesions; neuroendocrine tumor (NET), 19 lesions; the autoimmune pancreatitis (AIP), 15 lesions; metastatic tumor, 10 lesions; and others, 19 lesions. In total, there were 207 mass-forming lesions.

Methods: For each lesion we compared the pathological diagnosis with the final diagnosis. Final diagnoses were made by considering all clinical information. Pathological diagnoses were made based on cytological or histological findings using samples obtained by EUS-FNA. We defined pathological diagnoses as accurate when either cytological or histological diagnoses matched up to final diagnoses.

Results: The pathological diagnostic accuracies for all lesions and mass-forming lesions were 90.7% and 90.3%, respectively. 1) The accuracies for lesions with diameters less than 20 mm, 20~40 mm, 40~60 mm and 60 mm or greater were 81.0%, 92.2%, 97.2% and 100%, respectively. 2) The accuracies for lesions of the pancreatic head, body and tail were 87.5%, 92.3% and 93.9%, respectively. 3) The accuracy for malignant lesions was 92.8% and for benign lesions was 85.7%. The accuracies for PC, NET, AIP and metastatic tumors were 94.1%, 68.4%, 93.3% and 70.0%, respectively. 4) The only major complication of EUS-FNA was severe pancreatitis, which occurred in one case.

Discussion: The accuracy of EUS-FNA the pathological diagnosis of pancreatic lesions was low when the lesion was small and localized in the pancreatic head. Future studies should focus on developing methods that improve the accuracy of difficult-to-diagnose lesions.

Forum 11 Multidisciplinary Approaches

F-067

Impact of Gemcitabine-based Neoadjuvant Chemoradiotherapy in Patients with Borderline Resectable and Unresectable Locally Advanced Pancreatic Adenocarcinoma

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Background: The National Comprehensive Cancer Network (NCCN 2009) acknowledges criteria for resectability as a unique substage of pancreatic adenocarcinoma. According to NCCN classification, we can selected resectable (R), borderline resectable (BR) and unresectable (UR) pancreatic cancer in locally advanced primary tumors. For selected patients with locally advanced pancreatic adenocarcinoma, gemcitabine-based neoadjuvant chemoradiotherapy (NCRT) may offer the potential for margin-negative (R0) resection, resulting in improvement of prognosis. We assessed the outcome of patients who received NCRT for BR and UR patients.

Patients: Between February 2005 and January 2010, we enrolled 85 consecutive patients with histlogical proven who underwent gemcitabine–based NCRT: 3-dimensional conformation radiotherapy (45 Gy ;1.8 Gy/day) and weekly intravenous infusion of gemcitabine (800 mg/m2 over 30 min) for 5 weeks including one-week break. The patients underwent restaging 4 to 6 weeks after NCRT were taken to surgery. Among 85 patients, 38 were BR and 35 were UR according to NCCN criteria assessed by triphasic MDCT.

Results: Completion rate of NCRT was 100% in BR, 94% in UR. In BR and UR patients, 13%(5/38),20% (7/35) cases were precluded from surgery due to distant metastasis at the time of restaging. The rates of resection were 74% (28/38) and 43% (15/35). The rates of R0 resection were 79% (22/28) and 40% (6/15) respectively.

In BR patient, the median survival time of resected patients were significantly longer than that of nonresected patients (24.9 months vs. 7.1 months, $P<0.001$). Interestingly even in UR patients, survival rate was improved in resected patients compared to nonresected patients. (16.0 months vs. 8.3 months, $P=0.007$).

Conclusion: NCRT for BR patients can provide the higher rate of R0 resection, resulting in improvement survival. Even for UR patients, NCRT can select the patients who are likely to benefit from aggressive resection.

F-068

A New Viewpoint of Multidisciplinary Therapy in Patients with Primarily Unresectable Pancreatic Cancer – Chemotherapy Followed by Radical Resection

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Although the prognosis of patients with unresectable pancreatic cancer is improved due to introduction of some new anticancer drugs, it has not been evaluated well yet. Here we show two successfully radical resected cases of primarily unresectable pancreatic cancer after systemic S-1+Gemcitabine chemotherapy and show a new strategy of multidisciplinary therapy against pancreatic cancer. Case1: A 63-year-old women was diagnosed as intestinal obstruction due to pancreatic cancer in pancreas tail with peritoneum dissemination. She underwent a partial resection of ileum that was cause of obstruction and then she was treated by S-1 (60mg/m2 for 14days)+Gemcitabine (1000mg/m2 on Day1 and Day8) chemotherapy for thirteen months. Meanwhile the main tumor got small. The serum CA19-9 level decreased from 2973 to 225 U/ml after 6 cycles, however, after 10 cycles it increased up until 402 U/ml after 13 cycles. We performed distal pacreatectomy with partial resection of stomach and transverse colon that were directly invaded. There were no peritoneum dissemination and no malignant cells in lavage ascites. We could perform radical resection. One year and five months after the second operation, she is alive, but unfortunately with recurrence on retroperitoneal area. Case2: A 64-year old man who was diagnosed as pancreas head cancer in his local physician was transferred to our hospital. In our hospital multiple liver metastases were pointed and he was treated by S-1+Gemcitabine chemotherapy. After three cycles of the chemotherapy the liver metastasis tumors were vanished and the serum level of CA19-9 decreased from 1166 to 8 U/ml. We performed pancreaticoduodenectomy and two month later there are no evidence of recurrence. We propose that we have to deliberate the possibility of operation for unresectable case of pancreatic cancer during the treatment of chemotherapy for prolonged prognosis.

F-069

Renal Function After Preoperative Chemoradiation with Full-dose Gemcitabine in Pancreatic Cancer

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Objective: We performed a combination of preoperative chemoradiotherapy (CRT) with full-dose gemcitabine (GEM) and postoperative liver perfusion chemotherapy (LPC) for T3-pancreatic cancer and showed to increase the long-term survival. Specific aims of this analysis were to assess long-term renal function after preoperative CRT.

Methods: Preoperative CRT consisted of concurrent radiotherapy (50 Gy in 25 fractions), and chemotherapy (GEM 1,000 mg/m2) intravenous, weekly for 12–15 weeks, three times during 4 weeks). Patients underwent restaging and, in the absence of disease progression, were taken to surgery. Postoperative LPC consisted of 5-FU (each 125 mg/body via both routes of hepatic artery and portal vein, daily for 28 days) or GEM (1,000 mg/m^2 via portal vein, weekly for 4 weeks). Renal function was assessed by the changes in estimated glomerular filtration rate (eGFR) prior to CRT and 3-years after CRT.

Results: A total of 105 patients were treated between 2002 and 2006. All patients received 50 Gy of radiotherapy, except for 2 patients whose treatment was stopped at 46 and 48 Gy. Surgical resection was performed in 67 (65%) of 105 patients and the 3-year survival for those who resected and unresected was 49% and 0%, respectively. Thirty-three (31%) of 105 patients survived for >3 years after CRT and were analyzed renal function. For these 33 patients, characteristics were: median age was 65 years (range, 41–81), 16 (48%) were female, and median planning target volume (PTV) of radiotherapy was 242 cm3 (range, 111–380). With a median follow-up of 46 months (range, 36–76), mean eGFR slightly decreased from 79.9 mL/min/1.73 m2 (range, 57.3–103.3, SD 11.6) before CRT to 76.5 mL/min/1.73 m2 (range, 40.5–110.4, SD 17.1) over 3 years after CRT.

Conclusions: Preoperative CRT with full-dose GEM in pancreatic cancer did not change in renal function at a 3 years follow-up.

F-070

Chemoradiotherapy in Patients with Unresectable Locally Advanced Pancreatic Cancer

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Backgrounds: Chemoradiotherapy using 5FU is a conventional option for the management of unresectable locally advanced pancreatic cancer. However, the role of chemoradiotherapy is still controversial.

Methods: Between 1997 and 2008, 76 patients with unresectable advanced pancreatic cancer received chemoradiotherapy using CDDP ± 5FU (in 31 patients) and S-1 (in 45 patients). Radiation dose was 50Gy in 25 fractions or 50.4Gy in 28 fractions. The gross tumor volume was the primary tumor, regional lymphnodes detected by CT. Planning target volume was defined as the GTV plus 15–20 mm. No prophylactic nodal irradiation was given. We retrospectively analyzed patients' outcomes.

Results: The median survival time was 13.6 months. One year, two year and three year survival rate were 56%, 26% and 16%, respectively. There were two patients surviving over 5 years without evidence of disease progression.

Conclusions: There are some long term survivors after receiving chemoradiotherapy in patients with locally advanced pancreatic cancer. Chemoradiotherapy seems to be an attractive option for patients who are interested in more aggressive therapies.

F-071

The Current Status of Treatment for Unresectable Pancreatic Cancer

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We evaluated the current status of treatment for unresectable pancreatic cancer by retrospectively reviewing our cases in a municipal hospital. Between April 2001 and December 2009, 36 patients were diagnosed as unresectable pancreatic cancer in our department (4 of them were not operated). All of them were intended to undergo systemic chemotherapy (gemcitabine and/or S-1). About tumor localization, survival time of unresectable cancer of pancreatic head (n=23) seemed to be longer than that of body and tail (n=9), though not significant. Patients of pancreatic head cancer without liver metastasis (n=15) tended to survive longer than with liver met (n=8), though not significant. Twenty operated patients were able to continue postoperative chemotherapy for 4 months or more (continuation group). The other 12 pts ceased the treatment by less than 4 months (stop group). When both groups were compared, survival time of the continuation group (median 13.3mo) was significantly longer than that of the stop group (median 3.6mo) ($p<0.001$). On the other hand, one of 4 patients, who were out of operative indication, could continue gemcitabne-treatment and survived more than 2 years. In summary, it may be important to continue chemotherapy as long as possible, even decreasing the dose or adopting irregular administration.

F-072

Curative-intent Resection of Pancreatic Cancer in This Decade. Kobe Experience

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Background: Prognosis of patients with pancreatic cancer (PC) is worse even after curative resection. Gemcitabine (Gem) has shown clinical benefit for the patients with advanced PC, and recent clinical trials have proved that adjuvant chemotherapy becomes a new standard. This is a single-institution observational study to analyze factors which affect long-term surgical outcome and include biweekly Gem in adjuvant setting.

Methods: We reviewed 152 patients with invasive ductal adenocarcinoma of the pancreas (JPS stage I: 6, II: 1, III: 35, IVa: 70, IVb: 40) who underwent surgical resection at our hospital between January 2000 and December 2009.

Results: The overall 5-year survival rate was 29% after resection and median survival time (MST) was 25 months. Long-term survival had significantly improved when compared to historical control data (116 pts, 5-year survival: 19%, MST: 12 mo).The survival analysis using a Cox proportional hazard model indicated that curative resection [risk ratio: 2.05 (95%CI: 1.32–3.14), $p=0.002$] and adjuvant chemotherapy [risk ratio: 0.57 (95%CI: 0.35–0.95), $p=0.033$] were the significant predictors of survival. 110 patients (72%) received curative resection (R0). 5-year survival rate was 39% and MST was 31 months in R0 group. Ten patients survived over 5-year and all of them underwent R0 surgery. Ninety-seven patient received post-operative chemotherapy with biweekly Gem (800mg/m); the regimen comprised a half-dose intensity of the CONKO-001 . Adjuvant chemotherapy was started at median of 33 days after surgery and was able to continue median of 177 days. 5-year survival rate was 27% and MST was 27 months in group of patients who received Gem. The results were equivalent to CONKO-001.

Conclusions: In this analysis, curative resection was the crucial factor determining long-term outcome. Adjuvant chemotherapy with biweekly Gemcitabine might contribute it as well.

F-073

Infectivity-enhanced Oncolytic Adenoviral Vectors Expressing Syngeneic IFN-alpha for Pancreatic Cancer

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Although interferon (IFN)-alpha shows great promise for combination therapy in various cancers including pancreatic cancer, its clinical utilization has been impeded by its systemic toxicity and poor tumor distribution. To enhance its efficacy without increasing toxicity, it is logical to express the IFN-alpha locally in the tumors. In this work, we applied IFN-alpha-expressing conditionally replicative adenovirus (CRAd) for pancreatic cancer. Host specific human and hamster IFN-alpha expressing Ads were used for the experiments, respectively. In vitro, IFN-alpha-expressing oncolytic Ads killed hamster and human pancreatic cancer cell lines at significantly lower dose compare to non-replicative IFN-alpha expressing vectors and oncolytic Ad without IFN-alpha. To study in vivo effect, we established subcutaneous human MiaPaca2 xenografts in nude mice and hamster HP1 tumors in immunocompetent Syrian hamsters, which permit human Ad replication. After single intratumoral injection of infectivity-enhanced vectors expressing hamster IFN-alpha, both replciative and non-replicative vectors showed anti-tumor effect in early time points, but the tumor re-grew in non-replicative vector group after day 12. After day 20, oncolytic Ad IFN-alpha significantly outperformed the non-replicative vector. Importantly, the hamsters treated with oncolytic IFN-alpha vector exhibited significant tumor shrinkage (and some disappearance). Such shrinkage was not evident in immunodeficient mice, suggesting that this is due to immunomodulatory effect of INF-alpha. These data indicate that infectivity-enhanced CRAd expressing syngeneic IFN-alpha is a powerful therapeutic modality for pancreatic cancer.

Forum 12 Imaging, Translational Research

F-074

Comparison Between CT and EUS in Diagnosis of Local Invasion of Pancreatic Cancer

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Purpose: To investigate the additional effects of EUS on the diagnostic accuracy of CT for pancreatic cancer.

Patients: Consecutive patients with pancreatic cancer who were examined by helical CT and EUS and underwent surgery in our hospital between April 2004 and December 2008.

Method: We retrospectively evaluated preoperative CT and EUS findings with regard to detectability, local invasion (S,RP,CH,DU,PV,A) and T factor, and compared these findings and pathological findings. CT evaluation: S,RP,CH,DU(+), no pancreatic parenchyma between subject and tumor; PV,A(+), contact with tumor. EUS evaluation: S,RP,CH,DU,PV,A(+), no pancreatic parenchyma or marginal echo between subject and tumor.

Investigation items: In CT, 1) rate of tumor detection, 2) accuracy of T factor, 3) accuracy of diagnosis of invasive factor, and 4) content of misdiagnosis of T factor, and additional effects of EUS on 1–3).

Results: 1) TS1, 94%; TS2-4, 100%. Additional effect of EUS: TS1, 6%; TS2-4, none. 2) T1, 33%; T2, 0%; T3, 50%; T4, 79%. Additional effect of EUS: T1, 33%; T2-4, none. 3) The pancreatic head (n=40) (S,RP,CH,DU,PV,A): 73%, 63%, 90%, 70%, 83% and 88%, respectively. Additional effect of EUS: DU, 13%; others, none. The pancreatic body or tail (n=21) (S,RP,CH,DU,PV,A): 67%, 76%, 95%, 90%, 66% and 52%, respectively. Additional effect of EUS: 14%, 5%, 5%, 5%, 10% and 10%, respectively. 4) Overdiagnosis, underdiagnosis and difficult to evaluate: S (8, 8, 1); RP (7, 11, 1); CH (3, 1, 1); DU (2, 11, 1); PV (11, 2, 1); and A (13, 0, 1).

Discussion: EUS is superior to CT in tumor detection. Although EUS is more effective in evaluating T factors of small tumors (TS1), CT is superior for larger tumors (TS2-4). These results would be due to the characteristics of EUS as offering excellent image resolution at short range and attenuation at long range.

F-075

Significance of FDG-PET for the Unresectable Patients with Pancreatic Cancer Who Received Chemo-radiation Therapy

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Background and Purpose: Image-diagnosis and tumor marker are generally employed for cancer patients as estimating methods of chemo-radiation (C-R) therapy. We examined the usefulness of (18) F-fluorodeoxyglucose-positron emission tomography (FDG-PET) as an assistant indicator in patients with pancreatic cancer who received C-R therapy.

Patients and Methods: Forty-four patients with unresectable pancreatic cancer who received C-R therapy were enrolled in this study. FDG-PET was performed in all patients before C-R therapy and the maximum standardized uptake values (SUVmax) were compared with clinicopathological factors and response after C-R therapy.

Results: For the accumulation of FDG in the main tumor before C-R therapy, the high SUVmax level was no significantly correlated with each category in TNM classification, tumor size, and CEA scores. Although, there was significant correlationship between SUVmax score and CA19-9 levels (>100 U/mL) ($p=0.02$). SUVmax level was significantly correlated with tumor marker response by C-R therapy ($p=0.05$). SUVmax score tended to have correlationship with tumor response by C-R therapy ($p=0.06$). The overall survival of the group in which SUVmax was less than 7. 0 was better than that of the group in which it was more than 7. 0 ($p=0.02$).

Conclusions: SUVmax level in FDG-PET might be an indicator for C-R therapy in pancreatic cancer.

F-076

Differential Diagnosis of IPMNs (Benign or Malignant) by Contrast-enhanced PET/CT

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Background: The differential diagnosis between malignant and benign IPMNs is important, and for this purpose, EUS, ERP, IDUS and/or POPS are mainly used in Japan. However, these diagnostic technologies are invasive, and also require a high degree of technical skill. In our cancer center, contrast-enhanced PET/CT, in which the whole-body is scanned first with simple CT, followed by FDG-PET and early- and late-phase CT, is routinely conducted in the preopera-

tive evaluation for pancreatic tumorous lesions. In the present study, we assess usefulness of contrast-enhanced PET/CT for the differential diagnosis of IPMNs.

Patients and Methods: PET/CT was conducted in 26 patients with IPMNs during Apr/06~Sep/09. Operation was performed in 14 patients (11 malignant, 3 benign), and findings on PET/CT were compared with histological findings in order to determine the accuracy in the differential diagnosis by PET/CT. SUVmax values on PET/CT were compared in 26 patients with benign (IPMA) and malignant IPMNs (IPMC, invasive carcinoma).

Results: IPMNs were classified into 4 groups according to the findings on PET/CT (presence or absence of contrast-enhanced nodules and FDG accumulation): A(n=4), nodule(-)&FDG(-); B(n=1), nodule(-)&FDG(+); C(n=5), nodule(+)&FDG(+); D(n=4), solid tumorous lesion with FDG(+) in addition to IPMNs. What histological types of IPMNs were included in these groups? A, 3 IPMA and 1 IPMC; B, 1 IPMC; C, 3 IPMC and 2 invasive carcinoma; D, 4 invasive carcinoma. In other words, FDG accumulation was observed in 9 of 11 malignant IPMNs, suggesting that FDG accumulation on PET/CT predict malignant IPMNs. In the remaining 2 without FDG accumulation, contrast-enhanced nodules and MPD dilatation were noted, respectively. These results indicate that the accuracy for the differential diagnosis of IPMNs by contrast-enhanced PET/CT is 100%. The SUVmax values in malignant IPMNs seem to be higher than those in benign ones.

Conclusion: Contrast-enhanced PET/CT is useful for the differential diagnosis of IPMNs.

F-077

Clinicopathological Study of Resected Cases of a Variant of Autoimmune Pancreatitis Forming a Localized Mass

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Aim: To elucidate the proportion of AIP in resected benign localized masses with a preoperative diagnosis of possible pancreatic cancer and histological findings which discriminate AIP from other diseases.

Methods: From 1988 to 2009, 12 patients with a benign localized pancreatic mass diagnosed as possible pancreatic cancer underwent resection at our center. We retrospectively evaluated histological findings and pancreatography of these cases.

Results: Out of the 12 patients, 9 (75.0%) proved to have localized AIP according to the histological diagnostic criteria for AIP by the Japan Pancreas Society. Histologically, 8 of these 9 patients showed marked thickening of the main pancreatic duct (MPD) wall. The remaining 1 patient, whose MPD was histologically normal, did not show narrowing nor obstruction of the MPD by pancreatography. In all 9 cases, the epithelium of the MPD was well preserved, and dilated branch ducts and protein plugs were rarely observed, while marked obliterative phlebitis was confirmed. All but one case showed abundant (>10 cells/HPF) IgG4-positive cells in the lesion. In the portion outside the mass, the lobular structure was well preserved in all the cases. Pancreatography showed localized stenosis or obstruction at the site of the mass in 7 cases, slight stenosis in 1 case with a 25-mm-diameter mass, and almost normal findings in the other case with a 10-mm-diameter mass. In the 3 cases which did not meet the criteria of AIP, typical histological findings of chronic pancreatitis such as dilated branch ducts and protein plugs were observed. Obliterative phlebitis was not confirmed. IgG4-positive cells in the mass were sparse.

Conclusions: In a variant of AIP showing a localized mass, confirmation of obliterative phlebitis would greatly contribute to distinguishing AIP from other conditions. Morphological changes in the MPD might be excluded from the requirement for establishing the diagnosis in some patient cohorts.

F-078

The Comprehensive Measurement of Serum Cell Signal Phosphoproteins Is Useful for the Detection of Pancreatic Cancer

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Introductions: Intracellular phosphoprotein activation significantly regulates cancer progression. However, the significance of circulating phosphoproteins in the blood remains unknown. There is an urgent need to discover highly sensitive markers for early detection of devastating pancreatic cancer. We investigated the serum phosphoprotein profile involved in pancreatic cancer by a novel approach that comprehensively measured serum phosphoproteins levels, and clinically applied this method to the detection of pancreatic cancer.

Materials & Methods: We analyzed the serum phosphoproteins that comprised cancer cellular signal pathways by comparing sera from pancreatic cancer patients and benign controls including healthy volunteers and pancreatitis patients in three independent sets.

Results: Hierarchical clustering analysis between pancreatic cancer patients and healthy volunteers revealed differential pathway-specific profiles. In particular, the components of the extracellular signal-regulated kinase (ERK) signaling pathway (p-ERK1/2; $P<0.00001$, p-MEK1; $P<0.0005$) were significantly increased, with a positive correlation in the sera from pancreatic cancer patients compared with healthy volunteers. The positive rate of p-ERK1/2 (82%) was found to be superior to that of CA19-9 (53%) for early stage pancreatic cancer. For the combination of these serum levels, the area under the receiver-operator-characteristics curves (AUC) were showing significant ability to distinguish between the two populations in independent validation set, and between cancer and non-cancer populations in another validation set.

Conclusions: The comprehensive measurement of serum cell signal phosphoproteins is useful for the detection of pancreatic can-

cer. Further investigations will lead to the clinical application of this method and the implementation of tailor-made molecular-targeted therapeutics.

F-079

Genetic Alterations Associated with Clonal Progression of Pancreatic Cancer Metastasis

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Introduction: Metastatic disease accounts for the poor outcome of patients with pancreatic cancer. Contrary to early pancreatic carcinogenesis, the molecular features of pancreatic cancer metastasis are relatively unexplored. We performed a comprehensive genetic analysis of pancreatic cancer metastasis using samples collected in association with our rapid autopsy program (J Clin Oncol, 2009;27: 1806).

Methods/Results: We previously sequenced 23,219 transcripts, representing 20,661 protein coding genes, in 7 metastases from 7 different autopsied patients (Science 2008;321:1801). Our previous in-depth evaluation indicated an average of 45 genetic alterations (range 34 to 62) per patient. For the present study, whenever a gene was found to harbor a mutation in the index sample from each of these 7 patients it was sequenced in the matched samples of primary cancer and in 2 additional metastases from different organs from the same patient. The majority of mutations were present in both the primary cancer and all 3 metastases (range 25 to 47 per patient). However, in all 7 patients we identified mutations that were specific to metastases (range 2 to 32 per patient). To account for tumor and clonal heterogeneity, we sequenced 62 candidate mutations in the samples microdissected separately from 33 different areas in one primary cancer, allowing us to map out the tography of these genetic alterations in the primary cancer. There were 32 mutations that were heterogeneous and these genetic alterations accumulated systematically during local progression. We identified the geographic location from which the peritoneal metastases and lung /liver metastases in this patient were derived by comparing these mutational signatures. We are currently analyzing tumor and clonal heterogeneity in 2 additional cases.

Conclusions: Heterogeneous mutations accumulate systematically during local progression, inducing a clonal expansion of neoplastic cells. A small yet significant subset of mutations appears to be metastasis specific and represent novel therapeutic targets.

Forum 13 Acute Pancreatitis Treatment, Diagnosis

F-080

CpG ODN Activates Pancreatic Stellate Cell Via Toll-like Receptor 9

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Background: Pancreatic stellate cells (PSCs) are known for collagen producing cells. Recently it is revealed that PSCs work as an immunocompetent cell. PSCs express toll-like receptors (TLRs) to recognize pathogen associated molecular patterns (PAMPs). TLR9 recognizes CpG DNA, whose motif is rich in bacterial DNA. The TLR9 function becomes clear in dendritic cells but until now it is not well known for its function on PSCs.

Aims: To clarify the possible role of CpG ODN as a trigger factor for overt pancreatic inflammation on PSCs.

Methods: PSCs were isolated from the male Lewis rat. The expression of TLR9 mRNA was evaluated using reverse transcription-PCR. Internalization of CpG DNA was analyzed using a confocal laser scanning microscope. PSCs were incubated with CpG ODN and then cell proliferation, migration and MCP-1 secretion were assessed.

Results: We confirmed the expression of TLR9 at the mRNA level by RT-PCR. After 1, 5 and 15 minutes of CpG ODN administration, CpG ODN was seen on the cell membrane surface, in the cytoplasm and translocating to the perinucleus of PSCs. In response to CpG ODN administration, PSCs proliferated at dose- and time-dependent manners. Interestingly, PSCs proliferated earlier than PDGF-induced proliferation, achieving a peak 6 hours after CpG ODN administration, suggesting that PSCs could respond readily for innate immunity. CpG ODN also induced PSCs migration. Contrary to our expectations, CpG ODN attenuated MCP-1 secretion at dose-dependent manner.

Conclusion: It is suggested that PSCs express TLR9 and internalize CpG ODN, and that PSCs proliferate at dose- and time-dependent manners after internalization of CpG DNA. Contrary to our expectations, CpG ODN attenuated MCP-1 secretion at dose dependent manner. In conclusion, bacterial DNA might be involved in regressein of pancreatic inflammation via TLR9 on PSC.

F-081

Clinicopathological Features of Seronegative Autoimmune Pancreatitis in Japanese Patients

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Backgrounds: Most cases of autoimmune pancreatitis (AIP) in Japan are seropositive lymphoplasmacytic sclerosing pancreatitis (LPSP). It is believed that seronegative AIP represents idiopathic duct-centric chronic pancreatitis (IDCP), but existing data is limited. The aim of this study was to elucidate the clinicopathological features of seronegative AIP in Japanese patients.

Methods: Between 1997 and 2009, we evaluated 50 patients with suspected AIP. Thirty-six patients had serological markers available, and were analyzed retrospectively. AIP was diagnosed according to the Asian Diagnostic Criteria. We compared the clinical features including other organ involvement (OOI), associated inflammatory bowel disease (IBD), relapse rates after corticosteroid withdrawal, and the pancreatic histology obtained by endosonography-guided sampling (fine-needle aspiration or trucut biopsy) between with seropositive and seronegative AIP patients.

Results: Thirty patients were seropositive (26 males, mean age: 64 years) and 6 were seronegative (4 males, mean age: 60). Thirty-two patients, including all seronegative patients received corticosteroids, and all responded. There was no significant difference between the two groups in gender, age and relapse rates. The incidence of OOI was significantly higher in seropositive group than seronegative group (21 of 30 vs. 1 of 6 patients respectively; $p=0.014$). IBD was observed in neither group. Histological confirmation of diagnosis was obtained in 20 of 30 of seropositive group, and all had LPSP. Histological diagnosis was available in 5 of 6 in seronegative group. One had LPSP and 4 had chronic pancreatitis without specific findings of LPSP or IDCP.

Conclusions: The incidence of OOI was lower in seronegative group. Histologically, all patients in seropositive group had LPSP, while most in seronegative group had chronic pancreatitis without specific findings of AIP. Our data suggest that seronegative AIP might be a unique form of chronic pancreatitis distinctive from LPSP and IDCP.

F-082

Characteristics of Autoimmune Pancreatitis Based on the Serum IgG4 Levels and EUS-FNA Specimens

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Objectives: To investigate the differences in characteristics of autoimmune pancreatitis (AIP) based on the serum IgG4 levels and EUS-FNA specimens.

Methods: We retrospectively reviewed 48 patients who were diagnosed with AIP at our institute since July 2003. Serum IgG4 levels were tested in 38 patients and they were classified into two groups, high value group (group H, $n=28$) and normal group (group N, $n=10$) with cutoff value 135 mg/dl. Thirty-three patients underwent EUS-FNA and pathological findings were examined.

Results: Mean age was younger in group N (52.0 vs 68.4, $P<0.0001$). The ratio of female to male was higher in group N (30% vs 7.1%, $P=0.066$). No significance was seen in the prevalence of extrapancreatic lesions, but the number of them was significantly fewer in group N (0.70 vs 1.57, $P=0.015$), and all extrapancreatic lesions in group N were cholangitis. Twenty-nine patients (H 22 and N 7) were treated with steroid, and all of them showed improvement in radiological findings. Recurrence rate was lower in group N (10% vs 25%). Adequate material was obtained in 30 of 33 patients who underwent EUS-FNA, and differentiation from pancreatic cancer was possible. Although 9 cases (H 7 and N 2) showed specific pathological findings of lymphoplasmacytic sclerosing pancreatitis (LPSP) and IgG4 immunostaining was positive in 6 out of 19 cases, the others showed nonspecific inflammation. Neutorophils were detected in 6 cases (H 4 and N 2) and 2 of them were clinically suspected to be idiopathic duct-centric chronic pancreatitis (IDCP).

Conclusions: There were differences in gender, age, extrapancreatic lesions and reccurence rate between two groups. EUS-FNA is useful to differentiate AIP from pancreatic cancer, and it also makes possible to evaluate pathological finding such as LPSP and IDCP, although needing further investigation.

F-083

Metachronous Extrapancreatic Lesions in Autoimmune Pancreatitis

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Objective: Autoimmune pancreatitis (AIP) is frequently associated with various extrapancreatic lesions. The distribution and frequency of extrapancreatic lesions preceding or subsequent to AIP are unknown. The aim of this study was to investigate metachronous extrapancreatic lesions of AIP.

Methods: Extrapancreatic lesions were examined clinically, radiologically, and histologically in 56 AIP patients.

Result: Extrapancreatic lesions were associated in 25 (45%) of 56 AIP patients. Twenty-nine extrapancreatic lesions were detected synchronously with AIP in 18 patients, and 18 lesions were detected metachronously in 11 AIP patients. Fourteen patients had more than 2 extrapancreatic lesions. There was no significant difference in serum IgG4 levels between AIP patients with preceding extrapancreatic lesions and synchronous extrapancreatic lesions. Extrapancreatic lesions preceding AIP were sclerosing sialadenitis (n=8), cervical lymphadenopathy (n=4), swelling of the lacrimal glands (n=2), retroperitoneal fibrosis (n=1), and hilar lymphadenopathy (n=1). Retrospective histopathological examination confirmed that these lesions were compatible with IgG4-related sclerosing disease. Steroid therapy was not given for these initial lesions, and AIP occurred 3 to 48 months after these initial lesions. Swelling of the preceding extrapancreatic lesions persisted when AIP occurred. Extrapancreatic lesions subsequent to AIP were retroperitoneal fibrosis (n=1) and systemic lymphadenopathy (n=1), both of which occurred during follow-up of AIP without steroid therapy. All extrapancreatic lesions improved after steroid therapy.

Conclusion: Swelling of salivary or lacrimal glands, lymphadenopathy, and retroperitoneal fibrosis can precede AIP. Lymphadenopathy and retroperitoneal fibrosis can occur subsequent to AIP. Recognition of these findings will aid in the correct diagnosis of AIP.

F-084

Gastric Emptying in Autoimmune Pancreatitis Patients

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Background/Aim: We proposed that autoimmune pancreatitis (AIP) may be a pancreatic lesion of IgG4-related systemic disease. Various extrapancreatic lesions are present in AIP patients, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis. We previously reported that abundant IgG4-positive plasma cells infiltrated the gastric mucosa, and these cells almost disappeared after steroid therapy in AIP patients. However, it is unknown whether the stomach is a target organ of IgG4-related systemic disease. We investigated gastric function in AIP patients.

Methods: In 6 AIP patients (3 men and 3 women, aged 56–73 years), gastric emptying was assessed by ^{13}C-acetate breath test following ingestion of a 300kcal-liquid meal before and after steroid therapy. Based on 4h breath samples, the half $^{13}CO_2$ excretion time ($T_{1/2}$) and the time of maximal excretion (T_{max}) were calculated as gastric emptying parameters. ^{13}C-acetate breath test data of 13 healthy volunteers were used as controls. Number of IgG4-positive plasma cells in the gastrofiberscopic biopsy specimens was counted before and after steroid therapy.

Results: All patients achieved remission after steroid therapy. Both $T_{1/2}$ and T_{max} of AIP patients in active stage significantly decreased after steroid therapy ($T_{1/2}$: 1.89±0.21 vs. 1.69±0.15, p=0.046; and T_{max}: 1.1±0.2 vs. 0.96±0.2, p=0.027). Both $T_{1/2}$ and T_{max} of AIP patients in remission were similar to those of controls ($T_{1/2}$: 1.66±0.17 and T_{max}: 0.98±0.15). Number of IgG4-positive plasma cells infiltrating the gastric mucosa decreased after steroid therapy.

Conclusion: Since gastric emptying in AIP patients improved to normal range after steroid therapy, activity of AIP appears to affect the gastric function. Stomach may be a target organ of IgG4-related systemic disease.

F-085

Autoimmune Markers in Children with Chronic Pancreatitis

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Background: In the last decade we can observe gradual increase of autoimmune diseases. The reported paediatric experience with chronic pancreatitis (CP) is small and little is known about the role of autoimmune chronic pancreatitis (AICP).

Aim: The aim of the study was to assess the frequency of autoimmune markers in children with CP.

Patients and Methods: During 2000 to 2009, we hospitalized 62 children with CP (33 boys and 29 girls; age 2.8–18 years, mean age: 11.9 years). Clinical data were recorded and analyzed. Gammaglobulins, IgG4, autoantibodies (ANA, ASMA, AMA, APCA, LKM and AHA) were measured in all children.

Results: Autoimmune disease was present in 5 patients (8%): CU in 2 patients, PSC, dermatomiositis and panniculitis in 1 patient each. Hypergammaglobulinemia (>16g/l) was present in 10 cases. An increase of IgG4 level was present in 4 children. Autoantibodies were present in 34 children (54.8%). ANAs (>1/80e) were present in 16 patients with CP (in 6 pts >1/640e). ASMAs (>1/80e) were present in 16 children. APCAs, AMAs, AHAs and LKM were absent in all patients. Combining clinical and biochemical autoimmune parameters, 37 patients (59.7%) had at least 1 autoimmune marker of the disease. In 17 patients (27.4%) with CP and autoimmune stigmata other known causative factors of CP were present. In 14 patients we found gene mutations predisposing to CP. There was no difference in the severity of the disease and clinical course between children with autoimmune stigmata and patients without autoimmune markers.

Conclusions: In children with CP, similarly to adults, there is a high frequency of clinical and biochemical markers of autoimmunity. Number of CP with autoimmune origin in children is greatly underreported.

F-086

Prophylactic Pancreatic Duct Stent to Prevent Post-ERCP Pancreatitis In Patients with Difficult Biliary Cannulation

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Background & Aims: Difficult biliary cannulation can be one of risk factors of post-ERCP pancreatitis. Recent studies have reported that prophylactic pancreatic stent reduce the frequency of post-ERCP pancreatitis. The aim of this study was to evaluate the efficacy of 3 Fr pancreatic stent to prevent post-ERCP pancreatitis in patients with difficult biliary cannulation.

Methods: A total of 65 patients with difficult cannulation were randomly divided into the stent group (S group, n=30) or the non-stent group (nS group, n=35). The stents used was 3 Fr ZimmonR pancreatic stents. Difficult biliary cannulation was defined as the failure to achieve biliary access with more than 5 times or 10 min of cannulation attempts. The incidence of post-ERCP pancreatitis was compared between S group and nS group.

Results: Pancreatic duct stenting was successful in all patients of S group. Spontaneous stent dislodgment within 7 days was recognized in 96.6% (29/30). The incidence rate of post-ERCP pancreatitis in S and nS group was 10% (3/30) and 31.4% (11/35), respectively (p=0.036). The severity of pancreatitis was 1 moderate and 2 mild in in S group, whereas 8 moderate and 3 mild in nS group. Mean serum amylase level after ERCP in S and nS group was 197.13 U/L and 420.77 U/L, respectively (p=0.005). No procedure-related complication occurred.

Conclusions: Prophylactic pancreatic duct stent placement in patient with difficult cannulation during ERCP seems a safe and effective procedure to prevent for post-ERCP pancreatitis.

Forum 14 Pancreatic Cancer Basic 1

F-087

Nestin Modulates the Migration and Invasion of Pancreatic Cancer Cells by Regulating Actin and E-cadherin Expression

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Background: Nestin, a class VI intermediate filament (IF), was originally described as a neuronal stem cell marker. We have reported that Nestin was expressed in approximately 30% of human pancreatic ductal adenocarcinoma (PDAC) cases, and Nestin expression in PDAC correlated with nerve involvement and invasion of peripancreatic tissue margin. A recent study showed that activation of oncogenic K-ras in the Nestin cell lineage is sufficient for the initiation of pre-malignant pancreatic intraepithelial neoplasia lesions in mice. We used a silencing strategy to clarify the role of Nestin in human pancreatic cancer cells.

Methods: An expression vector carrying a short hairpin RNA (shRNA) targeting Nestin was stably transfected into PANC-1 and PK-45H human pancreatic cancer cells. Alterations in morphology and alignment of actin filaments, effects on cell growth, migration in scratch and Boyden chamber assays, invasion, and cell adhesion on extracellular matrices were examined. Transient Nestin transfection was then carried out in Nestin-shRNA transfected clones, and the consequences of restored Nestin expression were assessed. Differences in mRNA levels of selected signaling molecules were examined by PCR arrays.

Results: By comparison with sham-transfected cells, Nestin shRNA-transfected cells exhibited a sheet-like appearance with tight cell-cell adhesion, increased expression of filamentous (F)-actin, and increased E-cadherin expression as determined by PCR array. By contrast, cell growth and adhesion were similar in Nestin shRNA and sham-transfected cells, whereas cell migration and invasion were attenuated in the Nestin shRNA -transfected cells. Restoring Nestin expression in Nestin-shRNA transfected PANC-1 and PK-45H cells reversed the inhibitory effects on cell migration and invasion.

Conclusion: Nestin plays important roles in migration and invasion in pancreatic cancer cells by affecting the expression levels of actin and E-cadherin. Nestin may serve as a novel candidate for molecular targeting to suppress invasion and metastasis in pancreatic cancer.

F-088

Differences in Migration between Primary and Metastatic PDAC Cells

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Background: The intrinsic ability of cancer cells to migrate is the key mechanism of metastasis. The aim of this study was to understand the different characteristics of primary vs. metastatic PDAC cells. We therefore employed a series of microfluidic devices which would allow us to investigate these cells' dynamic movement.

Methods: Thirteen pancreatic cancer cell lines (6 primary and 7 metastatic PDACs) were spiked by 3uL in 106 cells/mL and put into the series of microfluidic devices. The motility assay was performed over 72–96 hrs and movement constantly monitored with pictures taken every 15 minutes. The data was analyzed by following parameters: velocity, time of delay to mobilization, number of cells mobilized, and pattern of movement in each cell line.

Results: All PDAC cells were capable of spontaneous migratory movement. Surprisingly, primary PDAC cells had statistically significant higher velocities than metastatic PDAC cells: their range was 30~57 and 12~38 um/hr, respectively (median velocity 45 vs. 20 u/hr, $p = 0.038$). All primary PDAC cells moved within 7.5 hrs; none of the metastatic cell lines had moved by that time. However, the percentages of cell population making successful migration were similar between the two groups (primary vs. metastatic PDAC cells: 25 vs. 23%).

Conclusion: We could observe persistent and spontaneous movement in 100% of PDAC cells. Primary PDAC cells had significantly higher velocities and shorter times to inception of movement than metastatic cell lines. This phenomenon implies that there may be intrinsic mechanisms driving cancer cell motility. Further examination of the mobility characteristics of these cell lines may provide useful insights into the biology of cancer cell dissemination.

F-089

Detection of Circulating Tumor Cells (CTCs) in Pancreatic Ductal Adenocarcinoma (PDAC)

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Background: Measurement of CTCs using a microfluidic platform (CTC chip) coated with EpCAM has been clinically useful for certain solid tumors such as breast and prostate. Accurate detection of CTCs requires cancer-specific capture and detection antibodies. Our aims were to evaluate EpCAM expression as a capture antibody on CTC chip and the use of Plectin-1 as a pancreatic cancer-specific identification antibody, and to determine purity of captured cells for genome analysis.

Methods: Quantitation of EpCAM antigens on the surface of PDAC cells was performed by FACS analysis. PDAC cells (5,000/ml) were spiked into 5 ml of blood and passed through the CTC chip. Captured cells were characterized by IF staining. Total cells were determined by DAPI (nucleated cell marker), cancer cells by CK (epithelial marker) vs. plectin-1 (PDAC-specific marker), and WBCs by CD45 (WBC marker). DNA was extracted from the CTC chip.

Results: EpCAM expression was evaluated qualitatively and quantitatively in 12 human PDAC and 6 xenograft PDAC cell lines. Surprisingly, 100% of PDAC cells expressed EpCAM, most at very high levels (25,000~215,274 EpCAM antigens/cell). EpCAM was uniformly expressed throughout the population. The capture yield of pancreatic cancer cells varied among cell lines (23–49%), correlating positively with EpCAM expression. Captured cells had sufficient quality and quantity. Examining the epithelial marker population, a total of 9,890 DAPI+ cells were captured; 3,901 cells were DAPI+Plectin-1+, resulting in a 38% capture yield, whereas 2,472 cells were DAPI+CK+, giving a 25% yield. The purity of captured cells (Plectin-1+DAPI+/DAPI+) was 71%.

Conclusion: EpCAM appears to be an ideal capture antibody; identification of CTCs using Plectin-1 appears to be a promising pancreatic cancer-specific marker. The purity this method affords will make it possible to extract sufficient amounts of CTC DNA for genome analysis and give us insights into the genetics and biology of tumor cell dissemination.

F-090

Interaction Between Pancreatic Cancer Cells and Alpha-SMA Positive Myofibroblast-like Cells Activation in Rat Orthotopic Pancreatic Cancer Model

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Aim: Pancreatic ductal carcinoma cells induce fibrotic change in pancreatic parenchyma by stimulating pancreatic stellate cells (PSCs) to proliferate and synthesize matrix. Quiescent PSCs are activated and transformed to myofibroblast-like cells, which express alpha-smooth muscle actin (alpha-SMA). To investigate the relationship between activated PSCs and cancer cells on pancreatic fibrosis in vivo, we histopathologically examined the distribution of alpha-SMA positive myofibroblast-like cells in pancreatic cancer tissue using orthotopic rat pancreatic cancer model.

Method: Lewis rat orthotopic pancreatic cancer model was prepared with DSL-6A/C1 derived from Lewis rat ductal pancreatic adenocarcinoma cell line. The animals were treated with GEM (100mg/kg/weekly) to inhibit pancreatic cancer growth. At the end of treatment, alpha-SMA positive myofibroblast-like cells and fibrosis were histopathologically evaluated using alpha-SMA protein analysis and Picro Sirius-red staining.

Results: Alpha-SMA positive myofibroblast-like cells and Sirius-red positive extracellular matrix were significantly increased in rat pancreas cancer tissue compared with normal pancreas

(p=0.005). DSL-6A/C1 cell proliferation was significantly reduced by co-cultured with GEM (p=0.004), and mean animal survival time of rat pancreatic cancer model (59.6+13.4 days) was significantly improved by treatment with GEM (89.6+21.8 days; p=0.0005). The histopathological and Western blot analyses showed that alpha-SMA expression in pancreatic cancer tissue were significantly reduced after treatment with GEM (p=0.03).

Conclusion: Our in vivo study suggested that pancreatic cancer cells had a pivotal role in PSCs activation leading to desmoplastic reaction that characterizes pancreatic adenocarcinoma.

F-091

Jagged1 Contributes to the Epithelial-mesenchymal Transition as a Target Gene of TGF Beta and BMP Signals in Pancreatic Cancer Cell Line

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Background: Recent researches have clarified the contribution of multiple signaling pathways to the cancer invasion and metastasis. Among them, the epithelial-mesenchymal transition (EMT) plays important role during cancer progression. Wide variety of growth factors and cytokines are reported to induce EMT in cancer cells. We also found that bone morphogenetic protein (BMP) causes EMT in pancreatic cancer cell line, as well as transforming growth factor (TGF) beta. In this study, we identified Jagged1, a known ligand of Notch pathway as a common target gene of TGF beta and BMP signals.

Methods: The human pancreatic cancer cell line Panc-1 was stimulated by recombinant human BMP4 and TGF beta. The induction of Jagged1 was confirmed by RT-PCR, fluorescent immunohistochemistry and Western blotting. The induction of Notch target gene HES1 was confirmed by RT-PCR and Western blotting. The cellular migration of Panc-1 cells after TGF beta or BMP treatment was measured by two-chamber assay.

Results: In Panc-1 cells, both TGF beta and BMP treatment induced Jagged1 expression. HES1 induction was also confirmed in these experiments, indicating TGF beta and BMP signals activated Notch signaling pathway in Panc-1 cells. The TGF beta and BMP treatment facilitated the cellular migration in Panc-1 cells, and the gamma-secretase inhibitor DAPT (N-[N-(3,5-difluorophenacetyl)-l-alanyl]-S-phenylglycine t-butyl ester) attenuated these effects.

Discussion: The TGF beta and BMP signals activate Notch signaling pathway via the Jagged1 induction. This pathway could be a novel therapeutic target against the cancer invasion and metastasis.

F-092

Characterizations of Pancreatic Cancer Cells: KMP-3, KMP-4, KMP-5, KMP-6. and Growth Inhibition Effect of Selective Prostaglandin Receptor Antagonist on COX-2 expressing cell Pancreatic cancer cell

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Backgrounds: Pancreatic cancer (PaCa) cell lines (KMP-3, -4, -5 and -6) have been maintained in our department. Recently, n-3 polyunsaturated fatty acid (PUFA): eicosapentaenoic acid (EPA) and n-6 PUFA: arachidonic acid (AA) show opposite growth effect on PaCa cell lines. This effect is associated with cyclooxygenase (COX)-2 expressions and prostaglandin E2 (PGE2) synthesis. PGE2 shows growth stimulation effect via EP receptor. The n-6 PUFA stimulated growth of COX-2 positive cancer cells, which is mediated by COX-2 generated PGE2. The aim of this study is to characterize KMP cell lines regarding COX-2 expression and PGE2 production. Moreover, we demonstrate the growth inhibitory effect of EP4 antagonist to establish new therapeutic approach.

Methods: Eight PaCa Cell were used: COX-2 positive BxPC-3(B), HPAF-II(H), COX-2 negative MIA PaCa-2(M), Panc-1(P) and KMP-3(K3), KMP-4(K4), KMP-5(K5) and KMP-6(K6). The expression of COX-1, COX-2, cytosolic phospholipase A2 (cPLA2), Microsomal PGE2 synthesis (mPGES)-1and EP4 receptors were detected by western blot analysis (W/B). After exposure to AA or EPA, cell growths were determined by cell count and a proliferation assay. cAMP formation, which is generated by binding of PGE2 to EP4, was analyzed by ELISA.

Results: W/B shows high expression of COX-2, cPLA2 and EP2/4 only in B, H, K4 and K6. AA stimulate cell growth and cAMP formation in COX-2 positive cells. EP4 receptor antagonist completely suppresses the cell growth and cAMP formation in COX-2 positive PaCa.

Conclusion: Our results show PGE2 production in COX-2 positive PaCa was correlated with the expression of cPLA2, mPGES-1 and EP4 expression. The growth of K4 and K6 cells was stimulated by AA, which correlated with cAMP formation. Therefore, these data suggest the significance of the COX-2 metabolism in PaCa growth. Our data further suggest that inhibition of PGE2 activation by EP4 antagonist may become a new therapeutic approach for the treatment of PaCa.

F-093

IL-32 Is a Factor Contributing to Anti-apoptotic Activity of Pancreatic Cancer Cells

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Background: Interleukin (IL)-32 is a recently-described proinflammatory cytokine characterized by the induction of nuclear factor (NF)-κB activation. We studied IL-32 expression in human pancreatic tissue and pancreatic cancer cell lines.

Methods: Tissue samples were obtained surgically. IL-32 expression was evaluated by standard immunohistochemical procedures. IL-32 mRNA expression was analyzed by Northern blotting and real-time PCR analyses.

Results: IL-32 was weakly immunoexpressed by pancreatic duct cells. In the inflamed lesions of chronic pancreas, the ductal expression of IL-32 was markedly increased. A strong expression of IL-32α was detected in the pancreatic cancer cells. In pancreatic cancer cell lines (PANC-1, MIA PaCa-2, and BxPC-3 cells), the expression of IL-32 mRNA and protein was enhanced by IL-1β, interferon (IFN)-γ and tumor necrosis factor (TNF)-α. An inhibitor of phosphatidylinositol 3-kinase (LY294002) significantly suppressed the IL-1β-, IFN-γ- and TNF-α-induced IL-32α mRNA expression. The blockade of NF-κB and AP-1 activation markedly suppressed the IL-1β-, IFN-γ- and/or TNF-α-induced IL-32 mRNA expression. Furthermore, IL-32-specific siRNA significantly decreased the uptake of [3H]thymidine and increased annexin V-positive population (apoptotic cells) in PANC-1 cells. IL-32-knockdown also suppressed the mRNA expression of anti-apoptotic proteins (Bcl-2, Bcl-xL, and Mcl-1).

Conclusions: Pancreatic duct cells are the local source of IL-32, and IL-32 may play an important role in inflammatory responses and pancreatic cancer growth.

Forum 15 Pancreatic Cancer Chemotherapy

F-094

Low Level of Circulating IL-6 Is Associated with Neutropenia of Gemcitabine in Advanced Pancreatic Cancer

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Background: Neutropenia is an important dose limited toxicity of gemcitabine (GEM) in advanced pancreatic cancer (PC). Haptoglobin, regulated by pro-inflammatory cytokines including IL-6, is a predictive marker for neutropenia of GEM in PC. We aimed to identify the association between circulating IL-6 and neutropenia of GEM in advanced PC.

Methods: Serum levels of IL-6 were measured by electrochemiluminescence assay (detection limit 0.23 pg/mL) in 55 patients with unresectable PC. All patients (male/female: 26/29, performance status: 0/1/2: 31/21/2, median age: 67 years) received GEM monotherapy as the initial treatment for PC. The severity of neutropenia within the first 90 days of the GEM treatment was graded according to NCI Common Terminology Criteria for Adverse Events version 3.0. Categorical or non-categorical data was compared using Fisher's exact test or Student t test. The correlation was examined using Spearman's rank correlation test.

Results: A mean value of serum IL-6 was 4.21 pg/mL in 55 patients. Mild neutropenia (grade 1–2) occurred in 12 patients (21.8%) and severe neutropenia (grade 3–4) occurred in 23 patients (41.8%). The other 20 patients (36.4%) did not experience neutropenia. Mean IL-6 level of severe neutropenia group (1.13 pg/mL) was significantly lower than that of no neutropenia group (8.08 pg/mL, $P=0.001$) or mild neutropenia group (3.69 pg/mL, $P<0.001$). The IL-6 level was negatively correlated with the grade of neutropenia ($r=-0.627$, $P<0.001$). Low cytokine level was defined as being less than 4.00 pg/mL, all patients were assigned to low IL-6 group ($n=39$, mean IL-6 1.38 pg/mL) and high IL-6 group ($n=16$, mean IL-6 11.1 pg/mL). Severe neutropenia in low IL-6 group (56.4%) was more frequent than that in high IL-6 group (6.3%, $P=0.025$).

Conclusions: Low IL-6 level was associated with severe neutropenia. The circulating IL-6 level may be the predictive marker for neutropenia of GEM in advanced PC.

F-095

Radiation Therapy as Adjuvant Therapy for Surgery in Pancreatic Cancer

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Aim: The primary objective of this trial was to evaluate the efficacy of radiation therapy as the adjuvant therapy of surgery for pancreatic cancer.

Methods: Intra-operative radiotherapy (IORT) was directed at the pancreatic tumor bed and regional lymphatics to a dose of 20–25 Gy. EBRT was directed at the same area with IORT to a total dose of 30–50 Gy by 2 Gy in fraction 5 days per week after surgery. Patients received weekly Gem (200mg/m^2) on the first days of the weak with concurrent external-beam radiotherapy (EBRT).

Results: Since Aug 2001 to Dec 2007 55 patients were entered onto this trial. Patients characteristics: 31 male / 24 female; mean age 67.1 years (47–80); Stage II 1, III 18, IVa 20, IVb 16. The median overall survival of these 55 patients was 21.6 months, and 1, 3 and 5 years survival rate were 66.0, 38.4 and 34.0%, respectively, and the survival rate was significantly higher than that of 86 non-radiation control group. The MST of 39 stage II~IVa cases was 39.8 months and it indicated significant longer survival compared with non-radiation group. While 16 stage IVb cases did not indicate significant difference with non-radiation group. The MST of 37 R0 or R1 case was 27.9 months and it indicated significant longer survival compared with 48 non-radiation cases. The recurrence rate and DFS of these 37 R0-1 cases was 62.2% and 7.8 Mo and these were significantly different from 93.8% and 3.7 Mo of non-radiation cases. The local recurrence rate of R0-1 cases was 21.7% and it was much lesser than 51.3% of non-radiation group.

Conclusion: This preliminary data would suggest that combination radiation therapy is efficient as adjuvant therapy for surgery in pancreatic cancer with local recurrence control.

F-096

Multidisciplinary Treatment with Neoadjuvant Chemoradiation Combining with Portal Infusion Chemotherapy for Potentially Curative Pancreatic Cancer

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We have performed neoadjuvant chemoradiation (NCRT) for potentially curative pancreatic cancer at T3 or T4 according to the JPS Classification and the portal infusion chemotherapy (PIC) after surgery to minimize local tumor recurrence and liver metastasis. The patients received radiation at a total dose of 40Gy and concurrent 5-FU, heparin, MMC, and CDDP, followed by surgical resection. In addition, 5-FU- and heparin-based PIC via the recanalized umbilical vein combined with systemic administration of MMC and CDDP was performed for four weeks right after surgery. Between 2003 and 2009, NCRT was performed in 22 patients with potentially curative pancreatic cancer. After a restaging workup, 15 of 22 patients underwent the resection of the primary tumor (a resection rate: 68.2%). Furthermore, 13 of 15 patients received PIC after surgery. The 13 patients were composed of 8 men and 5 women. There were 7 in radiographic Stage III, 5 in Stage IVa, and 1 in Stage IVb before NCRT. After surgery, pathological Stage 0 was present in one patient, Stage III in 9, Stage IVa in 2, and Stage IVb in one. 84.6% of the patients had negative surgical margins and 69.2% had negative lymph node status. 4 patients developed recurrent diseases during 13 months of median follow-up periods as follows: locoregional in 2, liver in one, and lung in one The disease-free survival rates at 1, 3, and 5 years of the patients who received both NCRT and PIC were 90, 90, and 67.5%, and the overall survival rates at 1, 3, and 5 years were 100, 100, and 80%, respectively. The intent-to-treat analysis including all 22 patents given NCRT showed that the 1-, 3-, and 5-year survival rates were 73.6, 60.2, and 50.2%, respectively. NCRT followed by PIC for the patients with potentially curative pancreatic cancer could improve surgical outcome.

F-097

The Strategy of the Adjuvant Chemotherapy After Radical Resection for Pancreatic Cancer, Which Is Better Gemcitabine or S-1?

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Background: Gemcitabine as adjuvant therapy brings about a longer survival rate compared to surgery alone by two RCTs. Gemcitabine was approved for clinical use in Japan in 2001. S-1 was also approved for clinical use in 2006. The aim of this retrospective study is to clarify which agent is effective as adjuvant therapy for the resectable pancreatic cancer.

Patients: Patients who underwent pancreatic resection at Nagoya University Hospital were given gemcitabine at 1000mg/m^2 weekly for 2 weeks followed by a week rest and for at least 3 cycles or S-1 at 80mg/m^2/day for 2 weeks every 3 weeks for 6 months. Overall survival rates were calculated using the Kaplan-Meier method. Stage of pancreatic cancer is according to JCS. Ninety four stage III, 161 stage IVa and 160 stage IVb patients with the resectable pancreatic cancer are enrolled in this study. There are 26 patients in the gem group and 6 in the S-1 group in stage III, 43 in the gem group and 14 in the S-1group in stage IVa, 35 in the gem group and 10 in the S-1 group in stage IVb.

Results: In stage III, the median OS is 24 months in the gem group, however we could not decide the median OS in the S-1 group. In stage IVa, the median OS is 23.4 months in the gem compared with 25.5 months in the S-1. In stage IVb, the median OS is 10.1 months in the gem compared with 16.8 months in the S-1, respectively.

Conclusions: This result suggests that adjuvant therapy with S-1 has a survival benefit in stage IVb resectable pancreatic cancer, however a similar outcome with gem compared with S-1 is shown in stage IVa. We are looking forward to the results of RCTs for adjuvant therapy.

F-098

Feasibility and Efficacy of a Tailored S-1 Chemotherapy in Elderly Patients with Advanced Unresectable Pancreatic Cancer

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Background: The extension of the average life span results in an increase in elderly patients with various cancers. The aim of this study was to evaluate the feasibility and efficacy of a tailored S-1 chemotherapy in elderly patients with advanced unresectable pancreatic cancer.

Patients and Methods: Elderly (> or=75 years) patients with advanced, unresectable pancreatic cancer diagnosed using the contrast-enhanced PET/CT imaging and serum tumor marker levels were eligible if they met the following inclusion criteria: no previous chemotherapy and radiotherapy, ECOG performance status 0 or 1, creatinine clearance (Cockcroft-Gault) > or=50 ml/min. The regimen was 50 mg/m^2 (level 0) or 60 mg/m^2 (level 1) of oral S-1 daily for two weeks followed by one week of rest in the first cycle. The dose level was adjusted in the range between 30 mg/m^2 (level -2) and 80 mg/m^2 (level 2) according to the onset of adverse events in the following cycles. The cycles were continued until the occurrence of disease progression, unacceptable toxicities or patient refusal to continue.

Results: Nine Japanese elderly patients (male:2, female:7) were enrolled. The median age was 81 years (range 78–86), the PS was 0 in all patients, the disease stage was III (two patients), IVa (three patients) and IVb (four patients). Eighty-one cycles were administered in total. The dosing delay rate was 7.4% and the dosing skip rate was 3.7%. Grade 3 toxicities of fatigue, diarrhea, ALT, AST, GGT and hyperglycemia were observed in three patients. One patient withdrew the chemotherapy due to an unacceptable toxicity (diarrhea). Overall response rate was 22.2% and the response rate including stable disease was 66.7%. Median progression-free survival was 147 days.

Conclusion: The tailored S-1 chemotherapy used in this study was tolerable and effective even for the elderly patients with advanced unrececetable pancreatic cancer.

F-099

Chemoradiotherapy vs. Gemcitabine-based Chemotherapy in Patients with Unresectable, Locally Advanced Pancreatic Cancer: a Retrospective Analysis

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Background: The aim of this retrospective analysis was to compare the long-term outcome of patients (pts) with unresectable, locally advanced pancreatic cancer (LAPC) treated with chemoradiotherapy (CRT) or gemcitabine (GEM)-based chemotherapy (CT).

Methods: The subjects were 267 pts with histopathologically confirmed LAPC, who had been treated with CRT (199 pts) or GEM-based CT (68 pts) as first-line therapy between April 2001 and March 2008.

Results: CRT group showed similar progression-free survival (PFS) compared with that in the CT group (median PFS, 8.0 months vs. 6.2 months (P=0.73). Also, overall survival in the CRT group was similar compared with that in the CT group (median overall survival, 12.4 months vs. 12.6 months (P=0.36). The estimated overall survival rates at 12 and 24 months were 50.3% and 13.6% in the CRT group and 55.9% and 13.2% in the CT group, respectively. As to the pattern of disease progression, local progression rate in the CT group was significantly higher than that in the CRT group (54.4% vs. 15.1%, P<0.001). A multivariate analysis using the Cox proportional hazards model demonstrated that opioid use (hazard Ratio [HR] 1.764, P<0.001), initiation of therapy before September 2004 (HR 1.573, P=0.001), leukocyte count<5500 (HR 1.441, P=0.006), AST level ≥ 21 (HR 1.439, P=0.008), CRP level ≥ 0.1 (HR 1.696, P=0.001), CEA level ≥ 4.0 (HR 1.406, P=0.012), and CA19-9 level ≥ 503 (HR 1.591, P=0.001) were independent poor prognostic factors, but therapy (CRT vs. CT) was not.

Conclusions: The results of this study showed no differences in long-term outcome between CRT and GEM-based CT as first-line therapy for LAPC.

F-100

Phase II Study of S-1 with Concurrent Radiotherapy for Locally Advanced Unresectable Pancreatic Cancer

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Background: S-1 is a new oral fluoropyrimidine anticancer agent and has shown a good efficacy for pancreatic cancer. In the phase I trial, we evaluated the safety of S-1 combined with external-beam radiotherapy (EBRT) to determine the maximum tolerated dose

(MTD) and dose-limiting toxicity (DLT) in unresectable pancreatic cancer patients. This phase I trial determined the recommended of S-1 for the phase II chemoradiotherapy trial to be 80 mg /m2/day given on days 1–21. This phase II study was conducted to evaluate the efficacy and toxicity of EBRT combined with S-1 for locally advanced and unresectable pancreatic cancer.

Methods: Eligible patients had locally advanced and unresectable pancreatic cancer without distant metastases, ECOG PS 0-1, adequate organ and marrow function, and no prior anticancer therapy. S-1 was given orally at a dose of 80 mg/m2/day twice a day on days 1-21. EBRT was delivered in fractions of 1.25 GyX2 per day, totaling 50 Gy per 40 fractions for 4 weeks. After completion of chemoradiotherapy, S-1 was administered for 14 days followed by a 14-day rest period and continued until disease progression or unacceptable toxicity as maintenance.

Results: Fifty patients were enrolled in this phase II study. Median follow-up period is 14 months (5–51 months). Of the 50 patients, 48 (96%) completed the scheduled course of chemoradiotherapy. The objective tumor responses by RECIST criteria included 13 PR (26%), 26 SD (52%) and 11 PD (22%). The median survival time was 14 months. 1-year and 2-year survival rate was 62% and 27%, respectively. No grade 4 toxicities were observed.

Conclusions: Combination therapy of S-1 and radiation in patients with locally advanced and unresectable pancreatic cancer appears to be a promising and well-tolerated approach with consideration of application to outpatients.

Forum 16 Pancreatic Cancer Case Report

F-101

Invasive Ductal Adenocarcinoma Developing in the Remnant Pancreas 14 years after Distal Pancreatectomy for IPMN Concomitant with Carcinoma in situ of the Pancreas: A Case Report

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We report a case of invasive ductal adenocarcinoma which developed in the remnant pancreas 14 years after distal pancreatectomy for IPMN concomitant with carcinoma in situ (CIS) of the pancreas. A 59-year-old man was referred to our hospital for the treatment of early gastric cancer in 1996. CT incidentally revealed a cystic lesion, measuring 1cm, in the pancreatic tail. Endoscopic retrograde pancreatography showed the cystic lesion communicating with the main pancreatic duct (MPD) in the pancreatic body and a filling defect due to mucin in MPD. Cytology of the pancreatic juice from distal MPD was positive for adenocarcinoma. EUS showed a 1.4x1.2cm branch duct IPMN with no mural nodules. We performed distal pancreatectomy and total gastrectomy. Histological examination showed intraductal papillary mucinous adenoma with mild dysplasia and, apart from it, CIS in a branch duct of the pancreatic body. The cut margin was free from malignant cells. Early gastric carcinoma was also evident. The patient was monitored with serum test and CT or MRI at a 6-months interval after the operation. CT in December 2008 showed no evidence of recurrence in the remnant pancreas. However, in January 2010, he was referred to our hospital for back pain. His serum CA19-9 level was elevated to 1,552 U/ml. Radiologic imaging revealed a solid mass, measuring 4cm, in the remnant pancreatic head and multiple liver metastases. We diagnosed that advanced IDC metachronously occurred in the remnant pancreas and started gemcitabine chemotherapy. Previously we reported 22 patients with IPMN concomitant synhronously or metachronously with independent ductal adenocarcinoma of the pancreas. And we proposed that clinicians should pay attention to the possible presence of ductal adenocarcinoma of the pancreas in patients with IPMN. This case supports our proposition and emphasizes the need for everlasting follow-up of patients at regular intervals after the treatment of IPMNs.

F-102

Analysis of Prognostic Factor in Long-term Survivors with Unresectable Advanced Pancreatic Cancer

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The aim of this study is to investigate the characteristics of long-term survivors with unresectable advanced pancreatic cancer. The subject of this study was six patients who were treated for unresectable pancreatic cancer, which was histopathologically proven, at our hospital from March 1998 to December 2009 and survived for more than 4 years. Six patients consisted of 4 men and 2 women, mean age was 65.5 years (range, 51–73 years) and mean survival time was 69.3 months (range, 52–87 months). Tumors were located in head (n=4) and body (n=2) of the pancreas and mean tumor size was 34.2 mm (range, 18–60 mm). Performance status (PS) and clinical stage of the patients at start of the treatment were PS 0 (n=3), 1 (n=3), stage IVa (n=2), and IVb (n=4).The option for treatment was chemoradiotherapy (n=3), chemotherapy alone (n=2), and chemotherapy+surgical resection (n=1). Among them, 4 patients showed CR and all the patients showed PR by the 3rd course and CR after 7–12 course of the chemotherapy. No recurrence was detected in all the patients who showed CR. On the other hand, in two patients who did not show CR, one patient showed PR after 1 course of chemotherapy, while the other showed PR after 9 course of chemotherapy. The latter showed the shortest survival among all six patients due to liver and lung metastasis. From these analyses, early response to the therapy might be a prognostic factor in patients with unresectable advanced pancreatic cancer.

F-103

A Case of Pancreatic Adenosquamous Carcinoma Directly Invading Stomach

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Background: Pancreatic adenosquamous carcinoma is an uncommon type of pancreatic cancer. We reported a case of this cancer invading stomach associated with tarry stool.

Case Report: A 73-year-old female with diabetes was admitted to our hospital complaining of tarry stool and anemia (Hb 7.4 g/dL). Emergent endoscopy showed hemorrhagic gastric tumor with a deep ulceration and a bump like submucosal tumor in posterior wall of the upper body of stomach. Dynamic computed tomography (CT) revealed a 4 cm mass in the body-tail of pancreas, directly invading stomach and splenic hilum. CT was also showing low density area within the mass, which might suggest necrotic change, resulting from expansive tumor growth. This CT finding could be characteristic of an uncommon pancreatic cancer. Additionally multiple liver metastases, and cancerous occlusion and encasement of splenic artery and vein were observed. Endoscopic biopsy specimen indicated that the tumor was pathologically diagnosed as squamous cell carcinoma (SCC). This tumor was regarded as pancreatic adenosquamous carcinoma. Though no varix was observed previously, gastric varies developed due to compression of the portal vein system by rapid growing tumor without variceal hemorrhage. Considering a clinical stage, we chose chemotherapy consisting of systemic gemcitabine (1000mg/m2) administration on day 1st, 8th, 15th, every 4 weeks. Following two courses, the primary lesion and liver metastatic tumors were apparently reduced in size without side effect.

Conclusion: Prognosis of patients with pancreatic adenosquamous carcinoma is generally quite poor because of its rapid progression, invasion and metastasis. Therefore treatment should be started immediately when the tumor is suspected to be adenosquamous carcinoma. In this case, we could confirm pathological diagnosis using endoscopic biopsied specimen from invading tumor in the stomach. We experienced a rare case of pancreatic cancer invading stomach, pathologically diagnosed as an uncommon histological type.

F-104

Gemcitabine-induced Pericardial Effusion and Right Ventricular Failure in a Patient with Pancreatic Cancer

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Background: Gemcitabine monotherapy or gem-containing chemotherapy is the standard first-line therapy for advanced pancreatic cancer.

We report a case of gemcitabine-induced pericardial effusion and right ventricular failure in a patient with pancreatic cancer.

Case: The patient was a 56-year-old woman.

She had received pancreaticoduodenectomy for pancreatic cancer and four years later, had a local recurrence and lymph node metastasis. A 1000mg/dose of gemcitabine was administered on Days 1 and 8 of a 15-day cycle. After receiving six courses of gemcitabine,she noticed edema of both legs and was found pericardial and bilateral pleural effusion on echocardiography and computerized tomography.

She also had proteinuria (2+) and hematuria (3+).

Pericardiocentesis was performed for pericardial effusion and right ventricular failure.

After that, her symptoms resolved. Discontinuation of gemcitabine and diuretics stabilized her symptoms. There were no metastases in the thorax or mediastinum.

A cytological study of the pericardial and pleural effusions revealed no malignant cells. Cultures for bacteria mycobacteria and fungi were negative. Autoantibodies indicating autoimmune disease were also negative and hormones associated with endocrine disease were normal. Thus, pericardial effusion and right ventricular failure may have been caused by gemcitabine.

Conclusion: Physicians should be aware of the potential for developing a gemcitabine-induced pericardial effusion and right ventricular failure.

F-105

Aggressive Surgical Resection After Gemcitabine and S-1 Combination Chemotherapy for Patients with Initially Unresectable Pancreatic Cancer

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Although the surgical resection is the only hope for cure against pancreatic cancer, majority of the patients are diagnosed to be unresectable due to the locally advanced disease or existence of metastatic lesions. Recently several new chemo-reagents are introduced clinically and showed the efficacy against these advanced pancreatic cancer. We experienced three cases of patients with initially unresectable pancreatic cancer who underwent surgical resection after treatment with gemcitabine and S-1 combination chemotherapy (GEM/S-1).

At the diagnosis, one patient had small liver metastasis and two patients had extended arterial invasion (SMA, CHA) of the cancer. In two cases, internal biliary drainage with metallic stent was performed for the obstructive jaundice. Patients were treated with GEM/S-1 therapy and evaluated with CT scan at least every three months. In patient with liver metastasis, metastatic lesion could not be recognized by CT after 8 months of chemotherapy and kept vanished for 17 months. Then pancreaticoduodenectomy were performed. In patients with arterial invasion, after 10 and 3 months of chemotherapy, the reduction of arterial invasion was recognized and then pancreaticoduodenectomy was performed. The arterial resection was not required in both cases. Within these three patients, pathological marginal

involvement was found in one. Pathological responses to the chemotherapy were Grade 1a in two cases and 1b in one case. Two patients with lymph node involvement were treated with adjuvant chemotherapy after the operation. All three patients were survived without recurrences for 3 to 27 months.

GEM/S-1 combination chemotherapy followed by aggressive surgical resection may extend the indication of surgical resection and contribute the survival benefit of pancreatic cancer. Further analysis of this therapy is needed to estimate the indication and the most appropriate timing of operation.

F-106

Modified FOLFOX-6 Chemotherapy for Gemcitabine and S-1-refractory Advanced Pancreatic Cancer

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Background: Recurrent pancreatic cancer is lethal and difficult to treat. Gemcitabine (GEM) has only a modest activity on survival and treatment with GEM and/or S-1 is the most common approach in Japan. We report 2 cases of the recurrent pancreatic cancer with a favorable course treated by modified FOLFOX-6 (mFOLFOX6) after failure of both GEM and S-1.

Case Reports

CASE-1: A 64-year-old woman with cancer of the pancreatic body underwent distal pancreatectomy after neoadjuvant chemotherapy using GEM with evaluable response and marked reduction of tumor markers. The tumor was R0-resected and histologically proven as Stage IIB (TNM) pancreatic cancer. Despite administration of adjuvant chemotherapy with GEM, liver metastases were detected 8 months after the surgery. Single-agent S-1 was administered after GEM, which resulted in failure after 3 courses. We introduced mFOLFOX6 as the third line setting. The size of liver metastases had remarkably decreased after 6 courses of the treatment, which was well tolerated.

CASE-2: A 49-year-old man with cancer of the pancreatic head underwent pancreaticoduodenectomy after neoadjuvant chemoradiation using GEM with marginal response. The histological findings revealed Stage III pancreatic cancer with no cancer cells at the margin. Although the adjuvant chemotherapy with GEM was administered, liver metastases were detected 4 months after the surgery. Either single-agent S-1 or combination of GEM and S-1 could not stop the progression. Paclitaxel was administered as forth-line therapy, which temporally reduced tumor marker and the tumor size. After 22 courses, paclitaxel regimen resulted in failure. As the fifth line therapy, mFOLFOX6 was administered. It contributed to the stabilization of the tumors for additional 5 months.

Conclusion: For patients with GEM and S-1-refractory advanced pancreatic cancer, mFOLFOX6 was well tolerated and effective in selected patients. Further studies are warranted.

F-107

Distal Pancreatectomy with En Bloc Celiac Axis Resection (DP-CAR) Monitoring Heapatic Arterial Flow with Electromagnetic Flowmetry During Operation for Safely

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Pancreatic body cancer often involves the common hepatic artery and/or the celiac axis and is regarded as an unresectable disease.

The matters that require attention are hepatic blood flow when it enforces distal pancreatectomy with en bloc celiac axis resection (DP-CAR) for the progress pancreas body cancer. We reported it as the blood flow confirmation safely before by monitoring hepatic venous oxygen saturation (ShvO2) to prevent hepatic ischemia caused by occlusion of common hepatic artery.

However, there were difficult to insertion technically and it takes a long time to insert a catheter. This time we use a heapatic arterial flow with electromagnetic flowmetry hepatic artery during operation. It is simpler and easier and, in addition, it is effect for safely for the operation.

Case report: A 78 year-old man was admitted for evaluation of back pain. Enhanced computed tomography showed no main trunk of the portal vein but a developed collateral circulation. MRCP, ERCP in the part and recognized the stoppage of the pancreatic duct. MD-CT revealed encasement of the common hepatic, splenic and celiac artery and obstruction of the portal and splenic veins with cavernous transformation surrounding these veins. Pre-operative diagnosis was TS4(3.8X3.4), node type, T4, CH(-), DU(-), S(+), N1(+), Ho, Po, M0, StageIVa.

DP-CAR could be performed cause of pancreas head arcade was able to confirm by MD-CT angiography.

When it measured a CHA, a PHA,GDA using a hepatic artery monitaring hepatic arterial flow with electromagnetic flowmetry during operation. It was 2.0ml/sec, 1.2ml/sec, 1.6ml/sec. When CHA was exposed to clamped it, PHA became 1.8ml/sec, GDA accepted 2.0ml /sec to rise afterwards.

Hepatic blood flow confirms that it is supplied stability in this.

We performed distal pancreatectomy with en bloc celiac axis resection in safely. Operation time is 357min. Blood loss was 552ml during operation. The post-operative course was uneventful and now chemotherapy was started.

Forum 17 Endocrine, Exocrine, Others

F-108

EUS-guided Broad Plexus-neurolysis Over the Superior Mesenteric Artery Using a 25 Gauge Needle

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Objective: Endoscopic ultrasound (EUS)-guided celiac plexus neurolysis (EUS-CPN) is safe and effective but not beneficial for some patients with extended abdominal cancer. We compared the effectiveness of standard EUS-CPN and EUS-guided broad plexus-neurolysis that extends over the superior mesenteric artery (EUS-BPN) and is administered using a 25-gaude needle.

Methods: Consecutive patients referred to our quaternary EUS center were eligible for inclusion. To evaluate the neurolytic spread, contrast was mixed with the neurolytic agent and post-procedure CT scanning was performed. The regions containing the celiac, superior, and inferior mesenteric arteries were divided on the frontal plane into six areas: upper right and left, middle right and left, and lower right and left. The number of contrast-bearing areas after EUS-CPN and EUS-BPN were related to the degree of pain relief achieved.

Results: Sixty-seven patients with advanced abdominal cancer were included (34 EUS-CPN, 33 EUS-BPN). The qualitative variable of the two groups did not differ significantly. The EUS-BPN group had more patients with six contrast-bearing areas (42%) than the EUS-CPN group (0%). Such patients had significantly better short-term and long-lasting pain relief than patients with less than five contrast-bearing areas. EUS-BPN patients exhibited significantly greater reductions in day 7 and 30 visual analog pain scale (VAS) scores than EUS-CPN patients.

Conclusion: Our preliminary data suggested that EUS-BPN using a 25-gauge needle provides patients with advanced abdominal cancer with better pain relief than standard EUS-CPN, and without incurring serious complications. Moreover, broad neurolysis over the superior mesenteric artery may superior analgesia.

F-109

EUS-guided Fiducial Marker Plascement of Pancreas Cancer for Cyberknife Radiotherapy

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Background: The CyberKnife frameless image-guided radiosurgery system enables to deliver radiation doses to tumors with precision by the use of real-time image guidance. Interventional EUS have multiple applications in the multidisciplinary approach to malignant tumors.

Objective: The aim of this study is to evaluate the safety and feasibility of placing fiducial markers for CyberKnife radiotherapy under EUS guidance.

Design: Patients were evaluated success rate and complication rate after EUS-guided fiducial marker placement to pancreas cancer. Standard linear ultrasound scope (UC240P, Olympus, USA) was used to evaluate the tumor. Fiducial marker was placed to the tip of the 19-gauge needle, then the needle was traversed into the pancreas cancer and 3 fiducial markers were placed separately in the pancreas tumor under EUS-FNI technique under fluoroscopy guidance.

Setting: UC Irvine medical center, between January 2007 and June 2009.

Patients: 8 patients with locally advanced pancreas cancer scheduled to underwent CyberKnife radiotherapy.

Results: EUS-guided fiducial marker placement into the pancreas cancer was successful in a total of 8 patients (100%). No complication (0%) was noted. Subsequently, all patients were treated with CyberKnife radiotherapy.

Conclusion: EUS-guided fiducial marker placement to locally advanced pancreas cancer for CyberKnife radiotherapy is a safe and feasible technique to mark the tumor site and guide radiation. Further experiences are needed for this new application of interventional EUS in Japan.

F-110

Patterns of Pathologic Lymph Nodal Involvement in the Resected Pancreatic Head and Body Cancer – Implications for Radiotherapy Clinical Target Volume Delineation

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Purpose: To maximize the treatment tolerability and efficacy in the chemoradiotherapy of pancreatic cancer, we examined pathologic nodal involvement in the resected cases.

Methods and Materials: One hundred and one cases with pancreatic head cancer and 31 cases with pancreatic body cancer, who underwent primary tumor resection at our hospital were analyzed.

Results: In pancreatic head cancer, 85 cases (84%) had positive lymph nodes. In pancreatic body cancer, 27 cases (87%) had positive lymph nodes. For cases with pancreatic head cancer, most common site of involvement was posterior pancreaticoduodenal lymph node (52%), followed by superior mesenteric artery lymph node (32%), anterior pancreatico- duodenal lymph node (30%), hepatoduodenal ligament lymph node (25%), paraaortic lymph node (11%), common hepatic artery lymph node (6%), celiac trunk lymph node (1%), whereas no splenic hilus lymph node was involved. For cases with pancreatic body cancer, most common site of involvement was splenic artery lymph node (52%), followed by infrapancreatic body lymph node (26%), common hepatic artery lymph node (13%), superior mesenteric artery lymph node (7%), celiac trunk lymph node (3%), splenic hilus lymph node (3%), whereas no hepatoduodenal ligament nor paraaortic lymph node was involved.

Conclusions: The distribution of pathologic nodal involvement was quite different between pancreatic head and body cancer. Lymph node regions close to the primary tumor was frequently involved. High rate of hepatoduodenal ligament lymph node involvement in the pancreatic head cancer might suggest the high frequency of liver metastasis via this drainage pathway and the inclusion of this region in the clinical target volume might be justified. Our data combined with other reported series might become a guideline for delineating the clinical target volumes in the radiotherapy for pancreatic head and body cancer.

F-111

Impact of Resecting Pylorus Ring in Pancreaticoduodenectomy to Reduce Delayed Gastric Emptying: A Prospective Randomized Controlled Trial of Pylorus-resecting Versus Pylorus-preserving Pancreaticoduodenectomy

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Objective: Several prospective randomized controlled trials (RCTs) have compared Pylorus-preserving pancreatoduodenectomy (PpPD) and conventional pancreatoduodenectomy (PD) with antrectomy. However, no study has reported the difference between pylorus-resecting pancreatoduodenectomy (PrPD) and PpPD. We conducted this RCT to confirm the hypothesis that PrPD reduces the incidence of delayed gastric emptying (DGE) compared to conventional PpPD.

Methods: Between October 2005 and March 2009, at Wakayama Medical University Hospital (WMUH), 130 patients with pancreatic or periampullary lesions were randomized to preservation of the pylorus ring (PpPD) or to resection of the pylorus ring (PrPD). In PpPD, the proximal duodenum was divided 3–4cm distal to the pylorus ring. In PrPD, the stomach was divided just adjacent the pylorus ring and the nearly total stomach more than 95% was preserved. This RCT was registered at Clinical Trials.Gov NCT00639314.

Results: The incidence of DGE was 4.5% in PrPD and 17.2% in PpPD, a significant difference. DGE was classified into three categories proposed by the International Study Group of Pancreatic Surgery. The proposed clinical grading classified 11 cases of DGE in PpPD into grades A (n=6), B (n=5), and C (n=0), and one case in PrPD into each of the three grades. The time to peak $^{13}CO_2$ content in the ^{13}C-acetate breath test at 1, 3, and 6 months postoperatively was significantly delayed in PpPD compared with PrPD (34.3±24.6 min vs. 18.7±11.8 min, 26.5±21.1 min vs. 17.3±11.7 min, 26.7±18.8 min vs. 17.4±13.2 min, respectively). PrPD and PpPD had comparable outcomes for quality of life, postoperative weight loss, and nutritional status during a 6-month follow-up period.

Conclusion: This study clarified that PrPD can lead to a significant reduction in the incidence of DGE compared with conventional PpPD, and therefore, PrPD is recommended for patients with periampullary tumors.

F-112

Risk Factors for Post-ERCP Pancreatitis: Evaluation in a Prospective Randomized Trial Comparing the Guidewire Cannulation Technique with the Conventional Cannulation Technique

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Objective: To investigate the potential risk factors for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in a prospective randomized trial comparing the performance of the guidewire cannulation (GWC) technique and the conventional cannulation (CC) technique in selective bile duct cannulation.

Design: Multicenter randomized, controlled trial.

Setting: Nine tertiary referral centers.

Patients: A total of 322 patients with indications for ERCP requiring selective biliary cannulation were enrolled from April 2008 to March 2009.

Interventions: Bile duct cannulation with the GWC technique or CC technique.

Outcome Measurements: The primary endpoint was the incidence of post-ERCP pancreatitis.

Results: One hundred sixty-three patients were assigned to the GWC group (Group I) and 159 to the CC group (Group II). The two groups were comparable with regard to baseline patient characteristics, endoscopic findings and additional procedures. The incidence of post-ERCP pancreatitis was the same between the groups (6.13% vs. 6.29%, n.s.). However, there was a slight tendency for the severity of pancreatitis to be higher in Group I (mild 3, moderate 6, severe 1) than in Group II (mild 8, moderate 2, severe 0). In the multivariate analysis, accidental pancreatic duct injection/wire cannulation (adjusted odds ratios (ORs): 8.02, 95% confidence interval (CI): 2.30–27.97, P=0.001) was the only risk factor for post -ERCP pancreatitis.

Conclusions: GWC technique does not reduce the risk of post-ERCP pancreatitis. Accidental pancreatic duct injection/wire cannulation is a risk factor for post-ERCP pancreatitis.

F-113

Interferon Regulatory Factor-2 Plays a Pivotal Role in Exocytosis in Pancreatic Acinar Cells

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Background: Interferon regulatory factors (IRFs) are a family of DNA binding proteins that regulate gene expressions induced by interferons (IFNs). We found that *Irf2*$^{-/-}$ mice revealed major and consistent abnormalities in pancreas and this study was aimed to clarify the molecular abnormalities in *Irf2*$^{-/-}$ pancreatic acinar cells.

Methods: Pancreas tissues from *Irf2*$^{+/-}$ and *Irf2*$^{-/-}$ mice were compared. Serum levels of digestive enzymes were measured and pancreatic amylase secretion was examined using dispersed acini. Alterations of SNARE proteins were examined using Western blotting and immunohistochemistry. To assess the contribution of elevated type I IFN signals, acini from *Irf2*$^{-/-}$ *Ifnar1*$^{-/-}$mice were also studied. The effect of IRF-2 expression level on exocytosis was studied using AR42J cells and the retroviral system.

Results: In *Irf2*$^{-/-}$ pancreas, which was white and opaque, zymogen granules (ZGs) were markedly increased in number, distributed throughout the cytoplasm, and their accumulation near the apical pole was not observed. Fused ZGs to the apical membranes and secreted contents into the apical lumen could not be found. Acini of salivary glands in *Irf2*$^{-/-}$ mice showed no abnormalities. Serum levels of amylase and elastase-1 were low and dispersed *Irf2*$^{-/-}$ acini did not secrete amylase in response to CCK8. The expressions of SNARE proteins, localized to the apical membrane and ZG membrane, were decreased and increased, respectively. Acini from *Irf2*$^{-/-}$ *Ifnar1*$^{-/-}$ pancreas were not rescued from the abnormalities. Down-regulation and Up-regulation of IRF2 expression in AR42J cells decreased and increased the secretion of amylase in response to CCK8, respectively.

Conclusion: The accumulation of ZGs throughout the cytoplasm in *Irf2*$^{-/-}$ pancreatic acini was due to the alterations of SNARE proteins and the lack of regulatory exocytosis. This abnormality was specifically observed in pancreatic acini and was independent of type I IFN signaling. Thus, IRF-2 plays a pivotal role in regulatory exocytosis in pancreatic acinar cells.

F-114

Glycated Albumin Inhibits Insulin Secretion from Islets

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Purpose: Glycated albumin (GA) is a non-enzymatic, reversible glycation of albumin and GA has been used as a marker for the severity of diabetes. Previously it was shown that GA, itself had biological effects, such as insulin resistance in muscle cells. In this study, we evaluated the effects of GA on insulin secretion from islets.

Methods: Islets of Wister rat, 9–11 weeks after birth were isolated by collagenase digestion method, and were cultured for 16 hrs in RPMI, containing 10% fetal bovine serum. Then, islets were transferred to RPMI, containing 0.1mg/ml Human albumin (HA), or 0.1mg/ml GA. HA and GA were purchased from Sigma (St. Louis, MO). After 16 hrs of culture, 3 islets were picked-up and were incubated for 60 min at 37C, in the presence of 3 mM (G3), 7 mM (G7), 15mM (G15) glucose. Also, islets were incubated in the presence of GLP-1(10nM), Forskolin (10μM), or 30 mEq/L of potassium (K30) in 7mM glucose. Insulin secretion was measured by RIA and was expressed as means ±SEM 3 islets/ 60 min.

Results: Insulin secretions of HA and GA were 19.2±8.5 and 20.9±13.1 in G3 (P=0.77), 59.9±26.5 and 40.3±15.6 in G7 (P=0.039), and 116.0±28.4 and 40.3±15.6 in G15 (P=0.003). GLP-1 and Forskolin did not abrogate the inhibition of insulin secretion by GA. However, insulin secretion recovered when islets were incubated in K30.

Conclusions: GA inhibited insulin secretion from islets in rat model. The mechanism of the inhibition is partly due to the insufficient opening of KATP-channel.

Forum 18 Others

F-115

Stage 0 and Stage IA with Tumor Less Than 1 cm in Diameter Is Suitable for an Early Pancreatic Cancer

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Background: According to the pancreatic cancer registration report of Japan Pancreas Society, the 5-year survival rate of the pancreatic cancer after surgery is around 60% even if the tumor size is less than 2 cm. Therefore, a small pancreatic cancer cannot be defined as an early pancreatic cancer. The aim of this study is to evaluate a definition of the early pancreatic cancer from point of view of the surgical results, retrospectively.

Methods: Twenty-one patients who underwent pancreatectomy for a small pancreatic cancer within 2 cm in diameter between 1981 and 2006 were chosen in this study. Four patients were Stage 0 and 17 patients were Stage1A according to the 6th edition UICC classification.

Results: In Stage 0 pancreatic cancer, duodenum and spleen preserving total pancreatectomy was performed in one patient, middle pancreatectomy in two patients and distal pancreatectomy in one patient. No patient died of pancreatic cancer. A total resection of the remnant pancreas was required in two patients (1 year later, 4 years later) for a remnant pancreatic cancer. In Stage IA pancreatic cancer, pylorus-preserving pancreatoduodenectomy was performed in 7 patients, conventional pancreatoduodenectomy in 3 patients and distal pancreatectomy in 7 patients. The 5-year survival rate was 61.9%. Nine patients have been surviving without tumor recurrence. However, six patients died of tumor recurrence within 5 years after surgery and two patients died of remnant pancreatic cancer (8 years later, 10.6 years later). None of three patients with tumor less than 1 cm in diameter had tumor recurrence.

Conclusions: It is desirable for a definition of the early pancreatic cancer to be Stage 0 and Stage IA with tumor less than 1 cm in diameter. The regular check of the remnant pancreas after surgery is important to acquire more favorite prognosis in the early pancreatic cancer.

F-116

Clinical Features of Elderly Patients with Pancreatic Cancer

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The numbers of elderly patients with cancer have been increasing in Japanese aged peoples. In the treatment of these patients, the comprehension of the clinical features of them would be getting more important. We reviewed the clinical features of 18 cases of pancreatic cancer aged more than 80 years who visited our hospital from 2001 to 2009 as compared with 97 cases randomly sampled in patients aged less than 80 who contemporarily visited our hospital. Each of gender gap, BMI at diagnosis, the initial symptoms, the proportion of smoking, drinking and multiplicities of other cancers history, the existence of DM or cardiovascular complications, the difference of cancer localization or extent, patterns of care, and the overall survival rate was evaluated between the two groups.

Results: The presence of male gender was lower in the elderly group ($p=0.04$) but there were no significant differences in the BMI, the initial symptoms, and the proportion of smoking, drinking, history of multiplicities of other cancers, and DM. However cardiovascular complications were encountered more frequently in the elderly ($p=0.02$). The cancer localization and extent showed no significant correlation with aging. As to the patterns of care, the proportion of surgery was similar in the two groups (elderly 11% vs. younger 10%). However the proportions of cases with radiotherapy and any chemotherapy were less frequent in the elderly (radiotherapy: elderly 0% vs. younger 19%, $p=0.07$, chemotherapy: 33% vs. 91%, $p=0.0008$). The proportion of cases with best supportive care was significantly higher in the elderly (56% vs. 9%, $p=0.01$). There was no significant difference in the overall survival rate between the two groups (elderly 211 days vs. younger 240 days)

Conclusion: This study suggested that the careful selection of appropriate treatment for elderly patients with pancreatic cancer taking into consideration the quality of life should be necessary.

F-117

Radiographic Classification and Pathological Grade of Portal Vein Wall Invasion in Pancreatic Head Cancer: Single Institution Experience

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Backgrounds/Objectives: In many cases of pancreatic cancer, PV resection is indispensable to obtain cancer free margins, but there has been no accumulated data for analysis. A retrospective study was

performed to clarify the correlation between radiographic type of portal vein (PV) invasion and pathological grade of PV wall invasion and their correlation with postoperative prognosis.

Methods: Six hundred thirty-three patients who had undergone surgery for invasive adenocarcinoma of the pancreas at Nagoya University Hospital between July 1981 and September 2009 were analyzed. Radiographic types of PV invasion of the pancreatic head cancer were classified into Type A (normal), B (unilateral narrowing), C (bilateral narrowing) or D (complete obstruction with collateral veins). In addition, pathological grades of PV wall invasion were classified into Grade 0 (no invasion), 1 (tunica adventitia), 2 (tunica media) or 3 (tunica intima).

Results: Four hundred thirty of 633 patients underwent resection, and PV resection was performed in 278 cases (64.7%). Combined arterial vessel resection was performed in 16 cases. No significant difference in operative mortality was observed between PV preservation (0.6%) and PV only resection (2.3%), and no operative death occurred after 1999. The radiographic classification of PV invasion was able to better stratify patients into subgroups with different prognoses, whereas in the pathological classification, invasion-positive groups had similar prognoses.

Conclusions: Pancreatectomy with PV resection can be performed safely. Radiographic classification of PV invasion reflected postoperative survival better than pathological degree of PV wall invasion.

F-118

Surgical Outcomes of Invasive Pancreatic Cancer in Shikoku Cancer Center

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Invasive pancreatic cancer has a poor prognosis and is one of the 10 causes of death from cancer in Japan. Surgical resection has only curative potential but poor prognosis,too. Recently, it was reported that adjuvant chemotherapy using gemcitabine improve the outcome after pancreatectomy for invasive pancreatic cancer. We studied surgical outcomes of invasive pancreatic cancer patients in our institute. 60 patients with invasive pancreatic cancer were performed pancreatectomy from 2004 to 2009. There were 31 men and 29 women. Mean age was 68±8.2 years old and ranged from 53 to 80. Pancreaticoduodenectomy were performed in 27cases and distal pancreatectomy in 33cases. One operative mortality from deterioration of interstitial pneumonia was recognized during this period. The postoperative complications were recognized in 16 cases (26.7%), with the most common complications being pancreatic fistula (n=3), early delayed gastric emptying (n=3), and bowel obstruction (n=3). Pathological stage showed 3 Stage I, 1 Stage II, 32 Stage III, 19 Stage IVa and 4 Stage IVb. Residual degree showed 27 R0, 25 R1, and 5 R2. Adjuvant chemotherapy was administrated in 27 patients, which consisted of 23 gemcitabine and 4 S-1. Median observation period was 9.3 months (ranged 0.4- 50.3). Recurrences were occurred in 31 patients, with most common sights of recurrence being liver (n=13), local (n=12) and peritoneum (n=8). 50% Disease-free survival was 8.8 months. Disease related death was occurred in 23 patient. Mean survival time was 21.6 months. Adjuvant therapy made no difference in 50% disease free survival and mean survival time. Thus, if resected, invasive pancreatic cancer had a poor prognosis in our institute. We need aggressive multidisciplinary strategy including surgery, radiation and chemotherapy to improve outcome for invasive pancreatic cancer.

F-119

Impact of Preoperative Nutritional Factors on the Prognosis and Postoperative Complications of Invasive Adenocarcinoma of the Pancreas

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Background: Nutritional status plays an important role in the incidence of postoperative complications and the prognosis of various tumors. However, there has never been a large study of preoperative nutritional factors in pancreatic cancer.

Objectives: A retrospective study was performed to determine the implications of nutritional status on the prognosis and incidence of postoperative complications of pancreatic cancer.

Methods: This study included 319 resected cases of invasive adenocarcinoma of the pancreas. We surveyed the correlations between prognosis, postoperative complications, especially pancreatic fistula, and clinico-pathological parameters with the primary objective of investigating the contribution of nutritional factors including three constitutional indexes, 10 blood tests and the Prognostic Nutrition Index (PNI; 10 x serum albumin (ALB g/dl) + 0.005 x total lymphocyte count (TLC /mm3), normal level>50).

Results: Preoperative% ideal body weight (%IBW)<90%, low TLC and low ALB were significantly associated with adverse prognosis (P=0.0485, P=0.0302 and P=0.0226, respectively). Patients with low PNI had remarkably poor prognosis, even classifying by pathological staging. Additionally, low preoperative ALB significantly correlated with the incidence of postoperative complications (P=0.0055), especially pancreatic fistula (P=0.0016). Multivariate analysis with a stepwise regression model identified low PNI as an independent prognostic factor for survival (Hazard ratio 1.561, P=0.0231).

Conclusions: In this study, it was indicated that preoperative hypoabuminemia is a predictive factor of prognosis and postoperative complications, especially pancreatic fistula, in pancreatic cancer. Additionally, PNI had an even stronger association with prognosis. Our results offered valuable insight for a method for evaluation of nutritional status and the importance of nutritional management in pancreatic cancer.

F-120

Portal Vein Stenting for Gastrointestinal Hemorrhage Caused by Portal Vein Stenosis After Pancreaticoduodenectomy; A Case Report

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We present a case treated by the placement of expandable metallic stent in the portal vein (PV) for repeated gastrointestinal bleeding associated with jejunal varices.

The patient was a 52-year-old man who underwent pancreaticoduodenectomy (PD) for the ampullary carcinoma. Although curative resection had been performed, pancreatic fistula with bacterial infection was prolonged postoperatively. Melena was first noted 32 months after surgery, and the patient was admitted by hemorrhage shock. Abdominal CT revealed severe PV stenosis and dilated collaterals through the jejunal vein of the Roux-en-Y loop. There was no recurrent disease of cancer, and the cause of PV stenosis was suspected by proliferation of scar tissue due to perioperative pancreatic fistula. Rupture of jejunal varices were suspected as the cause of melena. Although endoscopic hemostasis was temporarily effective, melena was occurred repeatedly. Recanalization of PV flow was necessary to prevent melena by jejunal varices. The patient underwent placement of expandable metallic stent in the portal vein, and there was no intestinal bleeding and complication 20 months after the stent placement.

PV stenosis after PD is not rare, and it is one of the critical late complications. Portal stent placement for PV stenosis after PD was one of the useful treatments, to decrease the portal hypertension and to prevent gastrointestinal hemorrhage.

F-121

Preliminary Results of the Quantitative Analysis in Diagnosing Fibrous Change of Bright Pancreas Using Real-time Tissue Elastography®

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Recently fatty pancreas with pancreatic fibrosis has been considered as counterpart of steatohepatitis. Fatty pancreas is usually depicted as bright pancreas and can be divided into two subtypes. One is characterized as having uniform parenchyma, and the other as not-uniform parenchyma. The aim of this study is to detect quantitative parameters of pancreatic heterogeneity by comparing bright pancreas and normal pancreas.

Methods: Thirty patients without chronic pancreatitis were enrolled. We defined bright pancreas as high echogenic pancreas compared with liver, 17 patients were classified into bright pancreas group and the other control group. The ultrasound systems used were the EUB-8500 and HV-900 (Hitachi, Japan). In these systems, pancreatic body was observed with B-mode and elastography (EG)-mode images. Prototype analysis software (Hitachi) was used for quantitative analysis of EG-mode images of pancreatic body. Evaluated points were as follows: 1) To extract quantitative parameters of pancreatic heterogeneity with reproducibility. 2) To compare pancreatic echogenicity and clinical findings (age, gender, BMI, alcohol consumption, fatty liver, diabetes mellitus, serum albumin level, quantitative parameters of pancreatic heterogeneity). 3) To compare diabetes mellitus and clinical findings.

Results: 1) Contrast (Indicator of existence of high difference values among adjacent points on strain images) and Correlation (Indicator of existence of same values in one direction on strain images) were selected. Strain image is the image that the red-green-blue value of the elastography image was converted into relative strain value (256 levels). 2) Contrast showed comparatively higher values, on the other hand, Correlation indicated lower values in bright pancreas group. 3) Contrast showed higher values, serum albumin level and Correlation presented lower values in the cases of diabetes mellitus.

Conclusions: EG-mode images revealed the pancreatic parenchyma of bright pancreas as heterogeneous. Contrast and Correlation can be quantitative parameters of pancreatic heterogeneity.

Forum 19 Chronic Pancreatitis Diagnosis

F-122

Clinical Significance of B Cell-Activating Factor (BAFF) in Autoimmune Pancreatitis

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Objective: Autoimmune pancreatitis (AIP) is presumed to have an autoimmune etiology, but little is known about its precise pathogenesis or pathophysiology. Overexpression of B cell-activating factor (BAFF) has been involved in murine and human autoimmunity. The aim of this study was to determine whether BAFF is involved in the pathogenesis of AIP.

Methods: Patients with AIP (n=17) were compared with two disease control groups [chronic pancreatitis (n=16) and pancreatic cancer (n=16)] and a healthy subject group (n=17). Serum BAFF levels were assessed using an enzyme-linked immunosorbent assay. The expressions of BAFF and BAFF receptor (BAFF-R) in the pancreatic tissue of patients with AIP were estimated using immunohistochemistry.

Results: Mean serum BAFF levels were higher in AIP patients (1930±653 pg/ml) than in chronic pancreatitis patients (1148±306 pg/ml), patients with pancreatic cancer without distant metastases (1013±155 pg/ml), and healthy subjects (931±225 pg/ml) ($P < 0.001$ for all groups). Using the cutoff value of 1386 pg/ml for the serum BAFF level determined by receiver operating characteristic curve data, the sensitivity and specificity to distinguish AIP from other groups except pancreatic cancer with distant metastases were 88.8% and 92.9%, respectively. In AIP patients, elevated serum BAFF levels were associated with increased serum levels of IgG ($r=0.72$; $P=0.0011$) and IgG4 ($r=0.62$; $P=0.0078$). Immunohistochemical analysis revealed that BAFF and BAFF-R were expressed on cells infiltrating the pancreas of AIP patients.

Conclusion: These results support the view that BAFF contributes to the pathogenesis of AIP and may be a marker for diagnosis.

F-123

Serum IgG4 levels and IgG4-related Sclerosing Disease

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Background and Aim: Recently a new clinicopathological entity, IgG4-related systemic disease, is proposed. Autoimmune pancreatitis (AIP) and Mikulicz's disease are thought to be IgG4-related systemic diseases. This study aimed to clarify clinical utility of serum IgG4 levels in differentiating AIP from other pancreatobiliary diseases, in differentiating Mikulicz's disease from other salivary gland disorders, and in identifying other IgG4-related diseases.

Method: Serum IgG4 levels were measured in 468 patients who were suspected of having pancreatobiliary, allergic, or immunological diseases in Tokyo Metropolitan Komagome Hospital from July 2002 to February 2009. We noted their final diagnoses from the medical records retrospectively.

Results: In 468 patients, we extracted 6 types of pancreatobiliary diseases: AIP (n=39), chronic pancreatitis (n=18), idiopathic pancreatitis (n=8), pancreatic cancer (n=116), bile duct cancer (n=34), and sclerosing cholangitis (n=4). The median serum IgG4 level was significantly greater in AIP (301.5 mg/dl) than in other five pancreatobiliary diseases ($p<0.01$). We also extracted 3 types of salivary gland diseases: Mikulicz's disease (n=18), Sjogren's syndrome (n=32), and sialolithiasis (n=10). The median serum IgG4 level was significantly greater in Mikulicz's disease (357.0 mg/dl) than in other two salivary gland diseases ($p<0.01$). In 468 patients, other 189 patients finally had diseases other than upper 9 diseases. Of 189 patients there were 15 patients with elevated serum IgG4 levels who had diseases other than pancreatobiliary and salivary gland diseases.

Conclusion: Serum IgG4 levels were useful for diagnosing AIP and Mikulicz's disease. Some diseases with serum IgG4 level elevations may be lesions of IgG4-related systemic disease without manifestations of AIP and Mikulicz's disease.

F-124

Positive Response to Steroid Therapy for Autoimmune Pancreatitis Evaluated with FDG-PET

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We report a case of autoimmune pancreatitis (AIP) in whom positive response to steroid therapy was evaluated with fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan and diagnosis of AIP was confirmed.

A-45-year-old man with a history of excessive alcohol consumption visited a general practitioner due to sudden severe abdominal and back pain. Moderately elevated serum amylase indicated acute pancreatitis. Although the symptoms were relieved by conservative medical management within a few days, he was referred to our hospital because a CT scan revealed a mass in the pancreatic tail. A detailed CT scan showed an enlarged pancreas with encasement of the splenic artery, obstruction of the splenic vein, a growth that had invaded the retroperitoneum, a hepatic mass of 2 cm and parabronchial lymphadenopathy. The main pancreatic duct was not detected in the pancreatic tail on MRCP and ERCP failed. The pancreatic and hepatic lesions appeared as high-intensity areas on diffusion weight MRI. PET scans also revealed intense FDG uptake in the pancreatic and hepatic lesions, as well as in the parabronchial and mediastinal lymph nodes. The imaging findings indicated advanced pancreatic cancer with hepatic and extensive lymph node metastases, but laboratory findings, including tumor markers such as CA19-9 and CEA, and serum IgG4 levels were normal. However, since the enhancement was delayed in the enlarged pancreas, we performed EUS-guided fine-needle aspiration before administrating chemotherapy. Histological examination of the obtained pancreatic tissue revealed dense fibrosis with abundant infiltration of lymphocytes and IgG4-positive cells, but no cancer cells.

Steroid therapy with oral prednisolone (30mg/day) was started considering a diagnosis of AIP with extensive extrapancreatic lesions. Pancreatic enlargement improved 1 month later, and FDG uptake in various lesions had vanished on FDG-PET 2 months later. Based on these findings, diagnosis of AIP was confirmed.

F-125

Autoimmune Pancreatitis with Inflammatory Bowel Diseases

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Background: In the international classification of autoimmune pancreatitis (AIP), far less is known about the clinical spectrum of type 2 AIP who was complicated inflammatory bowel disease (IBD) than is known about type 1 AIP who was not. The study is to clarify about clinical aspect of people with autoimmune pancreatitis (AIP) plus inflammatory bowel disease (IBD).

Methods: The study included eight patients with IBD whose AIP was diagnosed in my hospital according to the Diagnostic Criteria of the Japan Pancreatic Society and 2 patients with IBD whose AIP was suspected. The clinicopathological findings of them were examined.

Results: Four (0.5%) of 801 patients with Crohn's disease and 4 (0.5%) of 759 patients with ulcerative colitis complicated AIP. There mean age was 36 years. None of them had jaundice. One patient had diabetes mellitus. Autoantibody was positive in seven patients. Mean serum IgG and IgG4 were 1674 mg/dl and 30 mg/dl, respectively. Two patients had extrapancreatic lesions. There was no correlation between the activity of CD and AIP, but UC with AIP were active. Two of 5 patients whose percutaneous pancreas biopsy was carried out showed granulocyte epithelial lesion and had UC. None of 5 biopsy specimens had few IgG4-positive cells. In 5 of 7 patients who showed symptoms of acute pancreatitis, pancreatitis was ameliorated only by intravenous infusion of protease inhibitor for a short period without steroid treatment, and in 2 of them, steroid treatment was given for about 6 months. In one patient who developed acute cholangitis, cholangitis was ameliolated only by implantation of plastic stent to bile duct for a short period without steroid treatment. There mean observation period was 71 months, and none of the patients have had any recurrence.

Conclusion: AIP with IBD should be distinguished from AIP without IBD.

F-126

Comparative Discussion of Country-specific Diagnostic Criteria of Autoimmune Pancreatitis on Our Hospital's 14 patients

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Background and Aims: Today, International consensus for autoimmune pancreatitis (AIP) is a hot topic. The aim of this study is to compare investigation of each country-specific diagnostic criteria on our AIP cases.

Methods: 14 patients were enrolled in this study[Follow-up period; 2002–2010, Age; 68±11 years, M/F=11/3, IgG4; 713±516 mg/dl, Imaging test; pancreatic parenchymal enlargement. All patients suspected with AIP by clinical course, imaging test and IgG4, and with negative work-up for pancreatobiliary cancer and other pancreatic disease.

Results:

Japanese Criteria: 9 patients (64%) fulfilled the definite diagnosis. 11 patients were performed endoscopic retrograde cholangiopancreatography (ERCP), of which 9 patients (81%) had narrowing of the main pancreatic duct (MPD). 2 patients were a failure to cannulate MPD, or had occlusion of the tail of MPD and lymphoplasmacytic sclerosing pancreatitis (LPSP) with open biopsy.

Korean Criteria: 13 patients (93%) fulfilled the definite diagnosis. 2 patients were performed only ERCP and had the MPD narrowing. 12 patients were performed magnetic resonance cholangiopancreatography (MRCP), of which 9 patients (75%) had the MPD narrowing and 2 patients' MPD were not visualized. As noted before, of which 1 patient had occlusion and the LPSP, but not pancreatic resection specimen, so not fulfilled the diagnosis.

Asian Criteria: Definite rates were 64%. ERCP was most affected the rates similar to Japanese criteria.

Mayo Criteria: Total definite rates were 79%. Group A (7%), Group B (29%). Group C (64%); 9 patients had steroid therapy and all were relieved with it.

Summary: (i) In this study, we could find out information of the AIP's MPD image by MRCP. Steroid response rates were 100%. (ii) In the presence or absence of biopsy, we could diagnose AIP.

Conclusion: So, we need a new international criteria for AIP.

F-127

Autoimmune Pancreatitis in Hungary. A Multicenter Nationwide Study

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Background: Most cases of autoimmune pancreatitis (AIP) have been reported from Japan. The aim of the present study was to assess the clinical features and management of AIP cases in Hungary.

Methods: The demographics, clinical presentation, laboratory and imaging findings, extrapancreatic involvement, treatment response and recurrence were assessed in the firs 10 patients diagnosed with AIP in Hungary.

Results: The median age at presentation was 44 years (range: 19–74); 50% were men. New-onset mild abdominal pain (90%), weight loss (50%) and jaundice (30%) were the most common symptoms, with biliary strictures and ulcerative colitis as the most frequent

(30%) extrapancreatic manifestations. Diffuse pancreatic swelling was seen in 7 patients (70%), and a focal mass in 3 (30%). Pancreatic duct strictures were present in all 10 patients. The serum immunoglobulin-4 level was elevated in 66% at presentation. All the percutaneous core biopsies (3 patients), a biopsy of the papilla of Vater (1 patient) (nem, 4böl 2 lett pozitív) and surgical specimens (2 patients) revealed the typical characteristic findings of AIP: diffuse lymphoplasmacytic infiltration, marked interstitial fibrosis, and obliterative phlebitis. A complete response to steroid treatment was achieved in all 10 patients. Because of the suspicion of pancreatic tumor, 2 patients with focal AIP underwent partial pancreatectomy, Recurrences were not observed. The Japanese Pancreas Society diagnostic criteria for AIP were fulfilled in 80% of these cases.

Conclusions: In this first Hungarian series, we have confirmed several findings previously reported in AIP. The occurrence in young patients and the lack of a male preponderance were interesting features of AIP in this series. The response to immunosuppressive therapy was excellent. The performance of percutaneous biopsy is highly recommended.

F-128

Chronic Pancreatitis Induced Massive Dilatation of Pancreatic Duct with Terminal Bile Duct Stricture – An Interesting Image

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Background: Chronic pancreatitis presenting with severe obstructive jaundice and massively dilated pancreatic duct leading to near total replacement of pancreatic tissue is uncommon.

Clinical History: A 25 years old non alcoholic diabetic female presented with pain and jaundice since 2 months. Serum total bilirubin was 25.7mg/dl, direct bilirubin 14.6 mg/dl and alkaline phosphatase 400 IU/L. Amylase, lipase and C-reactive protein were normal. USG and CT scan showed, a massively dilated PD (6cm) with multiple stones along with dilated CBD of 2.6 cms with terminal bile duct stricture. CEA and CA 19-9 were normal.

At ERCP, a dilated CBD with terminal smooth stricture for which a 10 Fr stent was inserted, PD could not be cannulated due to the presence of impacted stone.

4 weeks later on she underwent an exploratory laparotomy. Intraoperatively a massively dilated PD (7 cm) filled with stones, completely replacing the pancreatic tissue was seen. CBD was 1.2 cm and normal with the presence of stent. Lateral Pancreatico jejunostomy with stone removal and a choledochoduodenostomy was preformed. Pancreatic tissue biopsy from head and peripancreatic lymphnode was negative for malignancy. She had an uneventful postoperative course and 18 months post surgery patient is doing well.

Discussion: In such patients the difficulty in making the differential diagnosis between benign and malignant disease is discussed. Various treatment options like ERCP with ESWL and surgery and the probable cause of massive dilation of PD are discussed.

Conclusion: Terminal CBD traverses the pancreas leading to obstructive jaundice associated with chronic pancreatitis. Idiopathic tropical pancreatitis is associated with large stone load in the PD and the pancreatic parenchyma. Complete replacement of the pancreatic tissue could be the result of longstanding impacted stone in the ampullary region. In cases of ERCP failure the surgical approach will be dictated by the intra operative findings.

F-129

Chronic Pancreatitis Associated with Abdominal Trauma in Children

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Objectives: Chronic pancreatitis (CP) is a rare disease in childhood. The etiology of CP in children includes anatomic anomalies, gene mutations, metabolic disorders and others. The aim of our study was to evaluate the role of abdominal trauma as a cause of chronic pancreatitis in children.

Methods: 148 children with CP, hospitalized since 1995 to 2009, were enrolled into the study. The medical records of these patients were reviewed for data on the presentation, diagnostic findings and endoscopic treatment.

Results: History of abdominal trauma (AT) was present in 10 cases (6,8%) (2 girls and 8 boys; mean age 11.5 years, range: 6.6–16 years). In 5 patient we found gene mutation predisposing to CP (SPINK1- N34S/- in 3 patients, CFTR- delF/- in 2 patients). In 3 cases we detected pancreas divisum. Family history was positive in five cases. There was no difference in age of the disease onset between children with CP after AT and patients without history of AT (10.5 years vs. 8.7 years, NS). There was no difference in the severity of the disease between children with CP after AT and patients without history of AT (according to the Cambridge Classification System) (1.75 vs. 1.87, NS). Pancreatic dust stenting was done in 4 patients after AT (40%).

Conclusions:

1. CP associated with abdominal trauma is rather common in children and has similar clinical course as CP in patients without history of abdominal trauma.
2. In our opinion, abdominal trauma often starts pancreatitis in patients with other known causative factor of CP, as gene mutation or anatomic anomaly of pancreatic duct.

F-130

Comparison of the Mannheim Diagnostic Criteria of Autoimmune Pancreatitis with Other Diagnostic Criteria Systems

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Background: Different diagnostic criteria for autoimmune pancreatitis (AiP) have been developed in various centers from Europe,

the USA and Asia. Based on previously introduced diagnostic criteria systems, we developed the Mannheim AiP Diagnostic Criteria. A consensus about the diagnosis of AiP and the different diagnostic systems has not been reached, and a comparison of the Mannheim AiP Diagnostic Criteria with other diagnostic systems has not been performed.

Aims: To compare the Mannheim AiP Diagnostic Criteria with other diagnostic systems from throughout the world.

Methods: The Mannheim AiP Diagnostic Criteria define "definite", "probable" and "possible" AiP. "Mannheim Definite AiP" was diagnosed in patients fullfilling Mayo HISORt or Asian AiP Criteria, or in patients simultaneously presenting with pancreatic disease, other autoimmune disease and/or elevated autoantibodies, and response of pancreatic disease to steroids. "Mannheim Probable AiP" was diagnosed in patients with pancreatic disease, elevated IgG4 and/or other autoantibodies, and other autoimmune disease. "Mannheim Possible AiP" was diagnosed in patients with pancreatic disease and either elevated IgG4 and/or other autoantibodies, or other autoimmune disease. Patients (n=228) with non-alcoholic pancreatitis from our clinic (1997–2008) were studied. In patients with "Mannheim Definite AiP", we compared the Mannheim Diagnostic Criteria with Japan Criteria, Korean Criteria, Asian Criteria, Mayo HISORt Criteria, Revised Mayo HISORt Criteria and Italian Criteria.

Results: We detected "Mannheim Definite AiP" in n=19 patients. In n=3/19 patients, pancreatic histology was obtained by surgery. In only these patients, diagnosis of AiP could be established by any diagnostic system. In n=8/19 patients, the diagnosis of AiP was only achieved with the Mannheim AiP Diagnostic Criteria. In this cohort of patients, all individuals responded to steroid medication.

Conclusions: The Mannheim AiP Diagnostic Criteria are superior to other criteria systems and allow the diagnosis of AiP in atypical forms of the disease.

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F-131

Insig2 Was Overexpressed in Pancreatic Cancer and Its Expression Was Induced by Hypoxia

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Backgrounds/Aims: Hypoxic microenvironment is characteristic in pancreatic cancer. Hypoxia induces various genes involved in malignant features such as invasion and metastasis in pancreatic cancer. Insulin-induced gene-2 (Insig2) has recently been found to be related with cellar invasion in colon cancer. However, there have been no reports regarding its expression and its relation with hypoxia in pancreatic cancer.

Materials and Methods: We evaluated Insig2 mRNA expression in cultured pancreatic cancer cells and investigated the effect of hypoxia in its expression. We also analyzed tissue samples from invasive ductal carcinoma (IDC) (n=29), normal pancreatic epithelial cells (n=32) and pancreatic intraepithelial neoplasia (PanIN) cells (n=9) using laser-microdissection.

Results: All 15 pancreatic cancer cell lines expressed Insig2 mRNA. In analyses of microdissected tissues, all samples from IDC tissues expressed higher levels of Insig2 mRNA than those from normal pancreatic ($p<0.001$) and PanIN ($p=0.082$) cells. IDC cells expressed significantly higher levels of, Insig2 mRNA in cases with stage IIB-IV (n=20) compared with those in cases with stage I-IIA (n=9)($p<0.032$). In the analysis of tissues from cases, in which local recurrence or distant metastasis were observed after resection, the levels of Insig2 expression were significantly higher in cases with in distant metastasis (n=9) compared with in cases with local recurrences (n=3)($p<0.013$). Under hypoxic condition (1% O_2), pancreatic cancer cells showed over two-fold higher levels of Insig2 mRNA compared with normal condition (21% O_2).

Conclusions: The present data suggest that an invasion-related gene, Insig2, may be associated with malignant potential of pancreatic cancer under hypoxia.

F-132

Circulating Myeloid Dendritic Cells as a Prognostic Factors in Patients with Pancreatic Cancer Who Have Undergone Surgical Resection

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Aim: Pancreatic cancer is one of malignant neoplasms with poor prognosis that might be associated with defective immune function. We aim to clarify a role of circulating myeloid dendritic cell (c-m-DC), circulating lymphoid DC (c-l-DC) and DC of the tumor tissue in patients with pancreatic cancer.

Patients and Methods: This study involved 110 patients with ductal adenocarcinoma of the pancreas who was consisted of 42 patients underwent pancreatectomy, and of 68 patients had unresectable pancreatic cancer between December 2001 and June 2006. We measured the number of c-m-DC, c-l-DC using the flow cytometry, and counted DCs in the tumor tissue using the immunohistochemical staining with Anti-fascin mAb.

Results: The percentage of c-m-DC subset in the pancreatic cancer patients was significantly higher than that in healthy volunteers, and the similar finding was observed between patients who underwent surgical resection and non-resection. The patients with high percentage of c-m-DC subset or with highly accumulated DC in the cancer tissue survived longer than patients with low percentage of c-m-DC or with low number of DC in the cancer tissue. Moreover, there was a closely positive correlation between c-m-DC subset in the peripheral blood mononuclear cell and DC number per field in the cancer tissue.

Conclusion: The pre-operative c-m-DC levels in patients with pancreatic cancer and DC counts in cancer tissue can be one of prognostic factors after surgical resection. The control of biological distribution of DC may be one of effective therapy in pancreatic cancer patients with the dismal prognosis.

F-133

The Comprehensive Analysis of Signaling Pathways Related to Annexin II in Gemcitabine-resistant Pancreatic Cancer: Clinical Value of Expression Analysis

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Background: We previously identified Annexin II as an up-regulated protein in gemcitabine-resistant pancreatic cancer cell line using the agarose two-dimensional gel electrophoresis. The aim of this study is to elucidate what cellular signaling pathways Annexin II deeply related in pancreatic cancer, and the goal of this study is the application of Annexin II to the development of new method for tailor-made treatment for this disease.

Method: We investigated the 12 targeted phosphorylated proteins involved in pancreatic cancer cells by using Bio-Plex™ Phosphorylation protein assay system in the comprehensive phosphoprotein analysis, compared protein profiling of gemcitabine-resistant pancreatic cancer cell line with its wild-type. Western blot analysis was used to evaluate the phosphorylation of the candidate proteins. The expression levels of Annexin II and the candidate phosphoproteins were analyzed by immunohistochemistry of pancreatic cancer tissues. In addition, the expression level of Annexin II at the primary pancreatic cancer was compared with the recurrent tissue after gemcitabine adjuvant therapy.

Results: Annexin II overexpression in cancer cells was significantly associated with rapid recurrence after gemcitabine adjuvant chemotherapy in postoperative patients ($P=0.0078$), and its staining was also an independent prognostic indicator of recurrence in pancreatic cancer patients who underwent adjuvant gemcitabine treatment after curative surgery on multivariate analysis ($P=0.0047$). After gemcitabine adjuvant therapy, the expression level of the Annexin II in the recurrent tissue was up-regulated. Of all targeted signal proteins, the components of two major signal transductions, Akt and ERK pathways, were identified for candidate signalproteins in pancreatic cancer cell lines.

Conclusion: These results indicated that Annexin II overexpression in pancreatic cancer was associated with the mechanism of the gemcitabine-resistance via the Akt and ERK signaling pathways. Near future, Annexin II will be applied to select a tailor-made therapy for pancreatic cancer patients.

F-134

Pancreatic Stellate Cells Promote Pancreatic Cancer Proliferation and Invasiveness Via Inducing Epithelial-to-mesenchymal Transition

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Objective: Pancreatic ductal adenocarcinoma is characterized by desmoplastic stroma that is mainly induced by activated pancreatic stellate cells.The aim of this study is to investigate the influence of pancreatic stellate cells on pancreatic cancer cell proliferation, invasion and migration, and to elucidate the role of epithelial-to-mesenchymal transition (EMT) in this process.

Methods: Puta8988 Pancreatic cancer cells were cocultured with conditioned medium of immortalized pancreatic stellate cells (IPSC). In vitro proliferation, apoptosis, adherence, invasion, migration, soft-agar colony formation were measured in Patu8988. Epithelial-to-mesenchymal transition of Patu8988 was detected by measuring EMT markers E-cadherin, snai1 and vimentin.

Results: Conditioned medium of IPSC promoted pancreatic cancer cell line Puta8988 growth, adherence, invasion, migration, and inhibited H_2O_2 induced apoptosis of pancreatic cancer cells. Up-regulation of snai1 and vimentin while down-regulation of E-cadherin in Puta8988 was found in both gene and protein levels, and this change was time-dependent.

Conclusion: These data indicate that pancreatic stellate cell can promote pancreatic cancer proliferation and invasiveness. Pancreatic stellate cell derived factors may induce epithelial-to-mesenchymal transition of pancreatic cancer cells, and then enhance the malignancy of pancreatic cancer cells.

F-135

Immunological Evaluation of Circulating T Cell and Antigen Presenting Cell in Patients with Pancreatic Cancer

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Aim: It has been reported in vitro and in vivo studies that regulatory T cells (T-reg) directory suppressed the expression of co-stimulatory molecules (CD80/86) on the cell membrane of antigen presenting cell (APC) via the process of CD28/CTLA4. There have been few reports concerning the dynamics of T-reg in patients with pancreatic cancer. To evaluate interaction between circulating T-reg and APC in patients with pancreatic cancer, we investigated the CD28 on circulating CD4+ helper T cell (Th) or CD8+ cytotoxic T cells (Tc), and CD86/CD40 on circulating APC.

Patients and Methods: This study involved healthy volunteers ($n=7$) and 25 patients with pancreatic adenocarcinoma who had con-

sulted with our department in 2009. The patients were classified as followed; Stage (UICC TMN) Ia (1): IIa (6): IIb (1): III (6): IV (11) and pancreas head (22): body & tail (3). Blood sample was taken before treatment, and analyzed the number of circulating CD28+/CD4+/CD3 cell (CD28+Th), CD28+/CD4+/CD3 cell (CD28+Tc), CD86+/ MHC classII+ cell (CD86+APC), CD40+/ MHC classII+ cell (CD40+APC), and CD4+/CD25+/CD3+ cell (T-reg) using flow cytometry.

Results: The ratio of CD28+Th to Th in pancreatic cancer was significantly lower than that in healthy volunteers ($p=0.0173$), and there was a similar finding on the ratio of CD86+APC and CD40+APC to APC ($p=0.0148$, $p=0.0026$). The number of T-reg in the pancreatic cancer patients was significantly higher than in healthy volunteers ($p=0.0103$). There was a significantly negative correlation between the ratio of T-reg and 86+APC or 40+APC ($R^2=0.30815$, $p=0.0049$ and $R^2=0.368136$, $p=0.0017$). Furthermore, there was a significantly negative correlation between the ratio of T-reg and mean fluorescence intensity of CD86 ($R^2=0.28152$, $p=0.0111$).

Conclusions: These data indicates that the decreased APC expressing CD86 may be associated with the increased T-reg, resulting in impairment of Th cell function in patients with pancreatic cancer.

F-136

The Role of Lumican in the Extracellular Space of Pancreatic Cancer

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Background: Lumican is a member of a small leucine-rich proteoglycan family and its overexpression has been reported in breast, colorectal, neuroendocrine cell, uterine cervical and pancreatic cancers. From the immunohistochemical evaluation of human pancreatic cancer patients, the lumican expression in stromal tissues adjacent to pancreatic cancer cells correlated with the advanced stage, retroperitoneal and duodenal invasion and tended to correlate with shorter survival time. However, the function of lumican in the extracellular space of pancreatic cancer is still not well understood. In this study, we clarified the function of lumican in pancreatic cancer.

Methods: Lumican mRNA and protein were examined in pancreatic cancer cell lines (i.e. PANC-1, MIA PaCa-2, KLM-1) by real-time PCR and western blot. Enzymatic digestion of lumican secreted into culture medium was performed. Lumican stably transfected PANC-1 cells were prepared. Then, the growth rates in vitro and in vivo were compared with mock cells. The lumican expression of PANC-1 cell was knocked down using siRNA. Then, the growth rate in vitro was compared with the control cell.

Results: lumican mRNA and the protein were detected in all pancreatic cancer cell lines and PANC-1 cells expressed median level of lumican in the cancer cell lines examined.70kDa specific type of lumican was only detected in the culture medium of pancreatic cancer cell lines and it was digested to its core protein. This type of lumican was highly secreted into culture medium in lumican-transfected PANC-1 cells. The growth rate of lumican-transfected PANC-1 cells was significantly higher than that of mock cells both in vitro and in vivo. Moreover, the growth rate of lumican-knocked down PANC-1 cell was significantly lower than that of the control cell.

Conclusion: Specific type of lumican might secrete into extracellular space and regulate pancreatic cancer cell growth.

F-137

Stimulating Actions of N-6 Polyunsaturated Fatty Acid on Pancreatic Cancer Cell Proliferation and Invasion

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Background and Aims: Epidemiologic studies suggest that polyunsaturated fatty acids (PUFAs) possess tumor activity. The aim of the present study was to evaluate the effects of AA, as well as of PGE2, on the proliferation of pancreatic cancer cells in vitro.

Methods and Results: AA dose-dependently increased the growth of pancreatic cancer cells as determined by the MTT assay and cell count and stimulated cell invasion as measured by the Matrigel invasion assay. This effect was restricted to pancreatic cancer cells, which expressed the COX-2 enzyme. AA dose-dependently increased PGE2 production of COX-2 positive pancreatic cancer cells. PGE2 dose-dependently enhanced proliferation and invasion of COX-2 positive pancreatic cancer cells. PGE2 signals by binding to EP receptors, of which 4 subtypes have been described. The effects of PGE2 were inhibited by a combined EP1/EP2 antagonist and a selective EP4 antagonist. In contrast, selective EP1 and EP3 antagonists had no inhibitory effect.

Conclusions: The n-6 PUFA AA and PGE2 stimulated pancreatic cancer cell growth and invasion in vitro. The effects of PGE2 were mediated by the EP2 and EP4 receptors.

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MicroRNA Expression in Pancreatic Cancer

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MicroRNAs (miRNA) may regulate up to 30% of all human genes and there is substantial evidence for their involvement in carcinogenesis. In this initial study we compared in cell line models and tumour

samples the expression of five miRNAs previously reported to be aberrantly expressed in pancreatic or colorectal carcinomas to determine (a) if our cohort of tissue samples is representative of previous findings (b) whether these cell lines appropriately model the situation seen in carcinomas for studies of the effects of aberrant miRNA expression.

We successfuly determined the expression level of five miRNAs (miR-21, 148a, 151, 181b and 375) in three pancreatic cancer cell lines (PSN-1. Hup T3 and Mia-Pa-Ca 2) and in fifteen resected pancreatic adenocarcinoma samples. All tumour samples were compared to matched normal tissue.

We found upregulation of miR-21 and downregulation of miR148a and miR-375 in all samples. MiR-181b was downregulated in the cell lines and in 3/15 tumours. miR-151 was upregulated in the cell lines and in 7/15 tumours.

Within our patient cohort we have shown inter-individual variation in expression of some miRNAs. These variations may be linked to differences in prognosis and patient outcome. The comparison of cell lines to tumour samples has demonstrated similarity in the trends of expression for 6 of the miRNAs tested. Further studies are now investigating the functional implication of these miRNAs, using the cell lines as models to determine changes to cellular homeostasis that could be involved in carcinogenesis.

F-139

Endoglin (CD105) Expression in Pancreatic Cancer

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Endoglin (CD105) is a homodimeric cell surface glycoprotein which is mainly expressed on immature B-lineage leukemia cells and endothelial cells. CD105 is a proliferation-associated cell membrane antigen on endothelial cells and leukemia cells, and is strongly expressed on tumor-associated angiogenic vascular endothelium. Recently, several studies indicated that CD105 represents a more specific and sensitive marker for tumor angiogenesis and/or tumor progression than the commonly used pan-endothelial markers such as CD34 and CD31 in various types of human malignancies. Therefore, CD105 is a useful candidate for the target of anti-angiogenic therapy. However, little is known about the CD105 expression in human pancreatic cancer. In this study, we examined the expression pattern of CD105 and CD34 in human pancreatic cancer tissues, and also investigated the relationship between CD105 expression and clinicopathological factors in pancreatic cancer patients. Pancreatic cancer tissues obtained from 66 patients were subjected to immunohistochemical staining using anti-CD105 antibody (SN6h) and anti-CD34 antibody. CD105 was specifically expressed in endothelial cells in pancreatic cancer tissues. On the other hand, CD34 expression was observed in both cancer tissues and adjacent normal tissues. The microvessel density (MVD) was evaluated based on the number of CD105-positive vessels. Patients with a higher MVD of CD105-positive vessels had a statistically significant shorter overall survival than those with a lower MVD ($P < 0.05$). The results of the current study suggest that CD105 might be a promising target for anti-angiogenic therapy and that the MVD of CD105-positive vessels might be a useful prognostic marker in pancreatic cancer patients.

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Cancelled

F-141

HP1γ Mediates Centrosome Separation in Pancreatic Cancer Cells via Aurora A Phosphorylation: Impact on Chromosomal Instability

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The centrosome possesses a significant and unique epigenetic role, whereby structural information is propagated onto somatic cell progeny via non-genetic pathways. Considering normal centrosome biology involves a pivotal role in balanced chromosomal segregation during mitosis, aberrant centrosome function results in catastrophic events, such as chromosomal instability. Notably, pancreatic ductal adenocarcinomas display an unusual degree of numerical and structural chromosomal instability, though the mechanism by which they are generated remains poorly understood. Human HP1 comprises a family of three non-histone chromosomal proteins (HP1α, β, and γ) involved in the establishment and maintenance of higher order chromatin structures mediating long term epigenetic gene silencing. In this study, we uncover a new mechanism for the involvement of HP1γ in chromosomal stability during mitosis in pancreatic cancer cells, entailing Aurora-mediated phosphorylation at Ser83 thus resulting in a significant increase of this modified protein upon entry into mitosis. P-Ser83-HP1γ colocalizes with Aurora A at the centrosomes and is phosphorylated by this kinase early in mitotic entry. Association of HP1γ to centrosomes colocalizes with the cdk1/cyclin B complex located at this organelle, and HP1γ knockdown results in increased cyclin B1, cyclin B2, and cdk1 levels along with G2/M arrest. Moreover, P-S83-HP1γ is found on the cyclin B1 and B2 promoters, implicating this protein in direct regulation of this complex. Intriguingly, knockdown of HP1γ not only results in chromosomal instability but impairs centrosome separation in pancreatic cancer cells. Although duplication of centrosomes appears intact, the separation of these organelles to their proper spindle pole alignment is significantly disrupted. Therefore, the novel involvement of HP1γ in centrosome biology and more specifically, centrosome separation places this protein as a central player in another epigenetic phenomenon, normal to development and altered in pancreatic cancer, in addition to epigenetic silencing of genes due to heterochromatin formation.

F-142

Discovery of Prognostic Factor using Proteomic Analysis with Formalin-Fixed Paraffin-Embedded Tissues of Pancreatic Cancer

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Background: Pancreatic cancer is one of the most lethal cancers. Identification of the new prognostic factor will help for decisions of the treatment and will play an important role in achieving personalized medicine. Recently, a method for extracting proteins from Formalin-fixed paraffin-embedded (FFPE)tissue in the form of tryptic peptides was developed. We try to prove the efficacy of a highly sensitive mass spectrometry (MS)-based proteomic analysis with FFPE to identify the novel biomarker.

Methods: We conducted a global proteomic analysis of patients whose postoperative survival years were under 2 years (early recurrent group, n=5) and approximately 5 years (long survival group, n=5). The two groups had same stage distribution (IIB), tumor differentiation and postoperative tumor marker. Laser microdissection was combined with recently developed techniques for protein extraction from FFPE tissues. The analysis system uses liquid chromatography (LC)-based high-resolution separation of peptides with an interface to tandem MS/MS, a technology which has been attracting great attention as the shotgun method of proteome analysis. Approximately 30,000 cancerous epithelium cells, collected from FFPE tissue sections by laser microdissection were processed for LC/MS and bioinformatic analysis.

Result: 1437 unique proteins were identified from two groups. The analysis system detected 120 proteins were differentially expressed between the two groups. It also could semi-quantify using spectral counts and evaluated the statistical difference using the generalized G test with a significant threshold of 0.05. Those 120 proteins are now verified by immunohistochemistry and multiple-reaction monitoring MS-based quantification.

Conclusion: The method for candidate proteomic analysis of FFPE tissue described here offers new opportunities to identify disease-specific biomarkers and therapeutic targets using widely available archival samples with corresponding detailed pathological and clinical records. Furthermore, we aim to identify the effective biomarker using this methodology with blood or biopsy specimen samples in near future.

F-143

Identification of Genes Related to Radioresistance in Pancreatic Cancer Cell Lines

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Objectives: Pancreatic cancer is a devastating disease characterized by marked resistance to radiotherapy. In this study, we identified genes involved in resistance to radiation therapy in pancreatic cancer cells.

Methods: To identify genes that contribute to radioresistance, two pancreatic cancer cell lines, CFPAC-1 and Capan-1, were subjected to repeated exposures to radiation, establishing two radioresistant cell lines. Subsequently, gene expression profiling using a cDNA microarray to identify genes responsible for radioresistance were performed.

Results: We identified 27 genes that showed differential expression between the radioresistant and parent pancreatic cancer cell lines. Microarray analysis identified 4 genes that were relatively overexpressed in two radioresistant cell lines compared with the parent cell lines, while 23 gene expressions are repressed. The 4 overexpressed genes included S100A4 that was reported to be related with radiation exposure. Meanwhile, 23 down-regulated genes, which have not been reported to have relevance with radioresistance, included 7 down-regulated genes that were potentially involved in apoptosis, cell attachment, inhibition of cell proliferation and tumor suppression. The pancreatic cancer cell lines with high levels of S100A4 mRNA expression, KP-2, Suit-2, MiaPaca-2, and Panc-1 were more radioresistant compared with those with low expression of S100A4, NOR-P1 and Capan-2. Radioresistant Capan-1 and CFPAC-1 cells acquired stronger invasion capacity compared with their parent cells. RNA interference-mediated S100A4 downregulation in radioresistant cells resulted in a decrease in the invasion capacity.

Conclusion: S100A4 genes may play an important role in the poor response to radiation therapy in patients with pancreatic cancer.

Forum 22 IPMN Diagnosis 2

F-144

Main Duct Intraductal Papillary Mucinous Carcinoma of the Pancreas Preoperatively Confirmed by Cytological Examination of Pancreatic Juice Collected at ERCP

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Preoperative discrimination between benign and malignant IPMNs are still difficult and cytological examination of the pancreatic juice at endoscopic retrograde cholangiopancreatography (ERCP) is a useful option in the definitive diagnosis of malignancy in IPMNs.

A 69-year-old female was referred to our hospital for the examination of IPMN of the pancreas. Cystic dilatation of branch duct (20mm) and main duct dilatation (5mm) without mural nodules were demonstrated in the pancreatic body by ultrasonography, computed tomography and magnetic resonance imaging, suggesting benign branch duct IPMN. Malignant cells were identified by cytological examination of pancreatic juice collected at ERCP. Segmental pancreatectomy of the pancreatic body was performed and histological examination of the resected specimen disclosed an intraductal papillary mucinous neoplasm (noninvasive carcinoma) predominantly located in the main duct (TisN0M0, stage0 (UICC classification)).

The international consensus guidelines recommended surgical resection for all main duct IPMNs and branch duct IPMNs with higher likelihood of malignancy (symptomatic cases, branch duct dilatations (>30mm), main pancreatic duct dilatations (>6mm), mural nodules and positive cytology). We discuss the efficacy and importance of cytological examination of pancreatic juice for IPMNs.

F-145

Pancreatic Juice Cytology in the Diagnosis of Intraductal Papillary Mucinous Neoplasm

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The differential diagnosis between malignant and benign Intraductal papillary mucinous neoplasm (IPMN) is often difficult only by imaging. Pancreatic juice cytology (PJC) is considered as one of the useful method for this purpose. In this study, we evaluated the diagnosability of PJC in patients with IPMN.

Methods: The subject were 19 patients (13 men and 6 women, mean age:70.8 years) with IPMN who underwent surgical resection between April 2004 and February 2009. Six patients were classified as main duct (MD)-type IPMN and 13 as branch duct (BD) -type IPMN. The patients with MD-type IPMN were histopathologically diagnosed as adenoma in 1 patients, carcinoma in situ in 2, and invasive carcinoma in 3. The patients with BD-type IPMN were diagnosed as adenoma in 8 patients, as borderline in 1, and carcinoma in situ in 4. Pancreatic juice was collected from a catheter during ERCP or from endoscopic naso-pancreatic drainage (ENPD) tube after ERCP for several days. Cytological results of class 3b, 4, and 5 were regarded as positive for malignancy.

Results: Of the 9 patients with malignancy, the cytological diagnosis was positive in 4. Of the 10 patients with nonmalignant or borderline IPMN, the cytological diagnosis was positive in 1. The sensitivity, specificity, and positive and negative predictive value of PJC were 44%, 90%, 80% and 64%, respectively.

Among 8 patients whose cytological examination were repeated more than once, the cytological diagnosis was positive in 4 of the 5 patients with malignancy, and positive (3b) in 1 of the 3 patients with nonmalignant or borderline IPMN. The cytological diagnosis was all negative of the 4 patients with malignancy who were examined PJC just one time.

Conclusion: It may be useful to examine PJC several times using ENPD tube in the diagnosis of malignant IPMN.

F-146

Utility of Contrast-enhanced Endoscopic Ultrasonography for the Diagnosis of Intraductal Papillary Mucinous Neoplasm

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Back ground and Aim: Intraductal papillary mucinous neoplasm (IPMN) is a unique clinicopathological entity characterized by

mucous production and cystic dilatation of the main or branch pancreatic duct. The differential diagnosis between malignant and benign IPMN is important to make management decisions. The size of mural nodules is established as one of the predictive factors of malignancy in IPMN. But the distinction between mucous clots and mural nodules is often difficult by B-mode EUS alone. The aim of this study was to reveal the usefulness of contrast-enhanced endoscopic ultrasonography (CE-EUS) for discriminating the mural nodules from the mucous clots.

Methods: From July 2004 to February 2008, a total of 25 IPMN patients with mural nodules, which were previously diagnosed by B-mode EUS, underwent CE-EUS at Chiba University Hospital or Chiba cancer center. Contrast enhancement in the mural nodules was assessed in comparison with that of adjacent pancreatic parenchyma. If the mural nodules were contrasted to the same degree as adjacent pancreatic parenchyma, it was evaluated as iso-enhanced. If the mural nodules were not contrasted, it was evaluated as non-enhanced. The iso-enhanced mural nodules were considered as real mural nodules and the non-enhanced mural nodules as mucous clots or inflammatory products.

Results: Ten patients (40%) had non-enhanced mural nodules. There was a significant difference in cyst size and MPD diameter between iso- enhanced and non- enhanced mural nodules ($p < 0.05$). Especially in small cyst, CE-EUS was more valuable in assessment of mural nodules than B-mode EUS. Six IPMN patients with mural nodules, which were confirmed by CE-EUS, were surgically treated and CE-EUS findings were compared with the pathological findings. Nodule size that was estimated by CE-EUS accurately predicted real nodule size.

Conclusions: CE-EUS is useful for the evaluation of mural nodules in IPMN.

F-147

Volumetry and Morphological Analysis of Intraductal Papillary Mucinous Neoplasm of the Pancreas (IPMN) with Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

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Background: It is difficult for us to predict the malignancy of intraductal papillary-mucinous neoplasm (IPMN). The aim of this study was to investigate the clinical facters for malignancy in intraductal papillary-mucinous neoplasms of pancreas, and to determine the findings which suggest malignancy.

Methods: Sixty-eight cases of intraductal papillary-mucinous neoplasm of pancreas that were treated between 1996 and 2008 were analyzed morphologically. IPMN type was classified as main-duct or branch-duct, and tumors were classified as either benign (adenoma) or malignant (carcinoma in situ or invasive cancer). Imaging findings were mainly analyzed as predictors of malignant. In this study, volumetry of IPMN was especially added as the new clinical facter .

Results: Among 68 IPMN cases, 55 cases were branch-duct type and 13 cases were main-duct type. 20(36%) of 55 branch-duct type and 9(69%) of 13 main-duct type were malignant. Multivariate analysis identified three independent factors (diameter, volume of tumor, and mural nodules) for malignancy in branch-duct type, but we can not have the independent factors in main-duct type.

Conclusions: The findings of there factors in branch-duct type IPMN are supported to be considered in the diagnosis of IPMN to facilitate the indication of operation.

F-148

New Preoperative Criteria for Diagnosing Malignant Branch-Type Intraductal Papillary-Mucinous Neoplasm of the Pancreas

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Purpose: It is generally difficult to diagnose IPMN with malignant potential preoperatively. This retrospective study aimed to establish preoperative diagnostic criteria for diagnosis of malignant branch-type IPMN.

Patients and Methods: Fifty-nine patients underwent surgical resections with a diagnosis of branch-type IPMN. These IPMNs were pathologically classified as benign group ($n = 46$), which were subclassified with hyperplasia, adenoma and borderline lesion, and malignant group ($n = 13$), which were subclassified with non-invasive adenocarcinoma and invasive adenocarcinoma. Tumor size, main pancreatic duct (MPD) diameter, and the presence of mural nodules were assessed and compared between 2 groups,.

Results: In the malignant group, we found larger tumor size (52.9 vs 27.1mm; $p < 0.01$) and larger MPD diameter (10.3 vs 5.3mm; $p < 0.01$) than those seen in the benign group. There were 30 patients with mural nodules, and all of them were included in the malignant group. Sensitivity/specificity was 100/43.4%. If mural nodules were not identified, all ($n = 24$) were benign. Negative predictive value was therefore 100%.

New diagnostic criteria that is 1; present mural nodules and 2; 30 mm or larger in tumor diameter or 10mm or larger in MPD diameter might indicate IPMN as malignancy and its sensitivity and specificity were 92.3, 84.8%, respectively.

Conclusion: Even in the case of 30mm or more in the tumor diameter, half of our series were diagnosed with benign. It seemed not to be suitable for malignant diagnosis. Our new criteria for diagnosing malignant IPMN have high sensitivity and specificity in our series, and might be useful.

F-149

Natural History of Branch Duct IPMN: A Multicenter Study in Japan

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Objective: The international consensus guidelines for management of IPMN/MCN was proposed in 2006. The guidelines recommended surgery for patients with all main duct IPMNs and branch duct IPMNs (BD-IPMNs) who have mural nodules, a dilated main pancreatic duct, or a cyst size >30mm. However, more extensive data based on follow-up observation of BD-IPMNs are needed to determine if these BD-IPMNs should be resected immediately. The aim of this study was to evaluate the clinical outcome of patients with BD-IPMNs on follow-up in 10 representative institutions in Japan.

Methods: We retrospectively analyzed BD-IPMN patients who underwent follow-up or surgical resection during the follow-up period of more than 1 year after the initial diagnosis.

Results: A total of 549 patients with BD-IPMNs were evaluated. The median follow-up period was 3.5 years. Among 147 patients who exhibited obvious progression, 85 underwent surgery were pathological diagnosis of carcinoma in 37 and adenoma in 48. The remaining 402 patients showed no changes during the follow-up periods, 21 cases underwent surgery were diagnosed as carcinoma in only 2 and adenoma in 19.

By univariate analysis, tumor location and appearance and/or enlargement of mural nodules were significantly associated with malignancy of BD-IPMNs, but the other factors failed to display significant correlation. A multivariate analysis showed that only the appearance or enlargement of mural nodules was a risk factor of malignancy.

Conclusions: Most BD-IPMNs can be followed up without surgery. The appearance or enlargement of mural nodules is the most important factor for predicting malignancy.

Poster 01 Acute Pancreatitis Basic, Diagnosis

P-001

Preventive Effects of TMMC in Cerulein Induced Acute Pancreatitis

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HO is the rate limiting enzyme in the catabolism of excess heme and generation of iron, carbon monoxide (CO) and biliverdine which has antioxidant, anti-inflammatory, and antiapoptotic actions. Recently, the upregulation of HO-1 was associated with prevention of pancreatitis in murine model of cerulein induced acute pancreatitis and pancreas transplantation. We were shown previously that 2',4',6'tris (methoxymethoxy) chalcone (TMMC), a synthetic chalcone derivative, displays potent anti-inflammatory and antiproliferative effects by the induction of HO-1 expression in murine macrophage, rat hepatic stellate, and TNBS induced colitis.In the present study, we have used a cerulein induced murine model of pancreatitis to ascertain the preventive role of TMMC.

Intraperitoneal injection of cerulein in mice resulted in severe, acute pancreatitis characterized by edema, neutrophil infiltration and necrosis and elevated serum levels of amylase and lipase. The TMMC significantly reduced the degree of pancreas injury, amylase, and lipase serum levels. Furthermore, TMMC pretreatment reduced MPO activity in lung and pancreas tissue, and production of tumor necrosis factor-α, interleukin-1, and interleukin-6. After cerulein administration, the HO-1 was induced. But, the TMMC significantly increased the induction of HO-1.

All of these findings confirm the view that TMMC exerts potent antiinflammatory effects. TMMC reduces the degree of cerulein induced acute pancreatitis by a heme oxygenase dependent pathway. TMMC might be a novel agent for preventing acute pancreatitis and its pulmonary complication via upregulation of HO-1.

P-002

Therapeutic Effect of Islet-like Cells Induced by Bone Marrow Mesenchymal Stem Cells BM-MSCs on Pancreatic Injury of Rat

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Background: The bone marrow-derived mesenchymal stem cells (MSCs) exist in the adult stem cells of the bone marrow. In the certain conditions, MSCs could be induced into 9 kinds of above tissue cells including nerve cells, blood vessels,muscle, lung and pan-

creas so on, which are from 3 kinds of embryonic layer. MSCs were easy to culture in vitro and had the advantages of low immunogenicity so that the allogeneic transplantation was widely applied to repair the damaged tissue or to treat the corresponding diseased tissue.

Aim: Allogeneic MSCs were injected into the rat pancreatic necrosis model by the rat tail vein and the repairment of pancreatic injury was investigated and the possible mechanism to repair pancreatic injury was explored.

Methods: BM-MSCs were segregated and purified by adherence method to in rats, then used to treat pancreatic injury of model rats after induced by basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), 2% B27, active A, ß-mercap to ethanol and nicotinamide 12–14days, identified by RT-PCR, marked by DAP I. One week later, the migrations and locations of islet-like cells were observed by Laser Scanning Confocal Microscope (LSCM), and the source of cells participating in reparation of pancreatic injury was identified by RT-PCR.

Results: After 12–14 days, BM-MSCs were induced into the islet-like cells expressing Ins1 and Ins2. The islet-like cells were used to treat pancreatic injury after marked DAPL. One week later, the cells were discovered in injured pancreatic tissues, where inflammatory cells infiltration obviously, cell structure confusion,and pancreatic islet disintegration, and the injured pancreatic tissues began to recover, pancreatic islet re-established. The result of RT-PCR further confirmed that there were infused islet-like cells in injured pancreatic tissues. Conclusion:BM-MSCs can be induced into islet-like cells, which participate in reparation of pancreatic injury.

P-003

Effect of Bone Marrow Mesenchymal Stem Cells on Serum Biochemical Indexes of Rats with Pancreas Tissue Injury

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Aim: To observe the effect of bone marrow mesenchymal stem cells (MSCs) on the serum biochemical indexes of rats with pancreas tissue injury.

Methods: The rat model of pancreas tissue injury was established by ligating pancreas. The MSCs of healthy rats were isolated, purified and cultured in vitro, then determined for cell cycle and surface markers by flow cytometry. The model rats were injected i.v. with MSCs and observed daily, and their serum samples were collected 24h, 48h, 7 day and 15 day after treatment for determination of amylase and lipase.

Results: The isolated and purified MSCs, 86.67% were at G0/G1 phase. The expression of surface marker CD44 was observed on the surface of MSCs, but no expression of hemopoietic stem cell surface marker CD34. Visible observation showed that the appearance of necrotic pancreas tissue of rats recovered to normal 15 day after treatment with MSCs. The serum amylase contents of rats 24h, 48h and 7 day after treatment with MSCs were significantly lower than those of model rats untreated, while showed no significant difference 15 day after treatment. The serum lipase content of rats 24h, 48h, 7 day and 15 day after treatment with MSCs were significantly lower than those of model rats untreated. However, both the serum amylase and lipase contents of rats at any time points after treatment with MSCs were significantly higher than those of healthy rats.

Conclusion: MSCs showed curative effect on pancreas tissue injury in rats.

P-004

Usefulness of the New Japanese Severity Scoring System for Acute Pancreatitis

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Background and Aims: The Japanese severity scoring system (JSS) for acute pancreatitis (AP) was revised in 2008. In the present study we investigated the usefulness of the new JSS in comparison with the original JSS system and several other conventional scoring systems.

Methods: We prospectively analyzed the results of evaluation by AP scoring system in 50 consecutive AP patients (M:F=31:19) admitted to our hospital between 2008 and 2009. The usefulness of the new JSS for predicting mortality was compared with that of the other scoring systems by a receiver-operator characteristic curve analysis.

Results: According to the original JSS the AP was assessed as mild in 23 patients, as moderate in 12 patients, and as severe (SAP) in 15 patients, whereas according to the new JSS the AP was assessed as mild in 37 patients and SAP in 13 patients. Assessment by the new JSS in 15 patients with SAP according to the original JSS showed 4 (27%) had mild, and their mortality rate was 0%, while the other 11 patients (73%) had SAP, and their mortality rate was 18%. Regression analysis showed a good correlation. The formula used to make the calculation was (score on the new JSS)=0.1943 + 0.4919 x (score on the original JSS). The correlation coefficient (r square value) was 0.78. The areas under the curve for prediction of the mortality based on new JSS, the original JSS, Glasgow score, and Ranson score were 0.995, 0.974, 0.979, and 0.964, respectively. The optimal cut-off values of the new JSS, the original JSS, Glasgow score, and Ranson score were 5, 6, 5, and 5, respectively.

Conclusions: Despite the small number of cases, the results of this study show that the new JSS is useful and easier to use to make a prognosis than the conventional scoring systems.

P-005

Clinical Characteristics of Patients with Severe Acute Pancreatitis Classified by the New Japanese Diagnostic Criteria Revised in 2008

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The diagnostic criteria for acute pancreatitis established by the Japanese Ministry of Health, Labour, and Welfare in 2008 does not require CT imaging findings. We retrospectively evaluated the clinical characteristics of patients with severe acute pancreatitis classified with this new diagnostic criteria among 430 patients with acute pancreatitis experienced between 1990 and 2010 in our institution, comparing with the characteristics of patients with severe acute pancreatitis classified by the previous diagnostic criteria. New diagnostic criteria classified 69 patients (16.0%) into severe pancreatitis with the mortality of 24.6% (17 patients), whereas previous diagnostic criteria classified 106 patients (24.7%) into severe pancreatitis with the mortality of 17.6% (18 patients). Patients with severe pancreartitis classified by new diagnostic criteria showed higher prevalence of elderly patients and lower prevalence of alcoholic pancreatitis, presumably because the diagnostic criteria includes patient age as a factor for classification. Twenty-nine patients with severe pancreatitis by new diagnostic criteria showed grade 2 or more severity on CT imaging findings, and all 18 patients with one or more point of poor-enhancement of pancreas classified into those with sever pancreatitis. The new diagnostic criteria for severe acute pancreatitis is based on the concept that a multiple organ failure, not a damage of pancreas itself, causes high mortality during the early phase of this disease, and it includes these factors for the determination of severe acute pancreatitis. Our results showed that the severity and the risk of mortality of acute pancreatitis can be predicted with these factors. The new g diagnostic criteria is useful for the detection of patients with acute pancreatitis with high likelihood of mortality.

P-006

BISAP Score for the Evaluation of Severity in Acute Pancreatitis

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Introduction: Acute pancreatitis (AP) has a variable etiology and natural history and some patients can have severe complications with a significant risk of death. The prediction of severe disease is very important to reduce the morbidity and mortality. However, there are no complete scoring index with high sensitivity and specificity till now. Recently, BISAP (Bedside index for severity in AP: BUN>25mg/dl, impaired mental status, systemic inflammatory response system, age>60, presence of pleural effusion) score was suggested (maximum score: 5) and high score (>3) showed good correlation with developing organ failure and pancreatic necrosis. However, this is not evaluated by another center. We evaluated the clinical utility of BISAP score for the prediction of severity among severe AP in our center.

Method: The BISAP score was retrospectively evaluated among 343 cases of AP admitted to our institution between Jan 2005 and July 2009. AP was classified as mild and severe with Atlanta classification. BISAP scores, duration of admission days, organ failure and mortality were also calculated on all cases.

Results: Among 56 severe AP, 3 patients (5.3%) were expired and BISAP score was not less than 3 in all cases. Among 287 mild AP, there was no mortality and BISAP score was less than 3 in all cases except 1 patient. Mean duration of admission day was 24 days among high BISAP score (>3) which was significantly longer than 15 days among low BISAP score (<3) ($p<0.001$). A high BISAP score was associated with an increased risk of developing organ failure (odds ratio = 8.3).

Conclusion: The BISAP score can predict the development of organ failure and duration of admission day in patients with AP. So the BISAP score may be useful for the evaluation of severity in AP.

P-007

Relationship of Visceral Adiposity to Severity in Acute Pancreatitis: A Population-Based Study

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Background &Aim: Relation of obesity and severity of acute pancreatitis (AP) has been recognized. However, limited information about the potential association of visceral adiposity and severity of AP has been obtained so far. Thus, the aim of our study was to determine whether visceral adiposity was associated with severity of AP.

Methods: A total of 153 patients from Olmsted County with AP were enrolled in this study (Mean age (+/- SD): 59.1+/-19.8, 54% male). Forty four subjects who presented with abdominal pain but diagnosed as not having AP served as control group (Mean age (+/-SD) 56.1+/-23.8, 50% male). All patients had CT at presentation or within one year of onset of AP. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) areas at L2-3, L3-4, and L4-5 levels were measured by CT. Body mass index (BMI) was also calculated. We examined the following parameters as outcome variables; APACHE II, SIRS, and hospital stay. We set cut-off value (CO) of BMI as 30. The mean value of VAT and SAT among controls was taken as the CO and used to divide AP patients into two subgroups; those above the CO and those below.

Results: Comparison was made between the two patients groups described above with regard to APACHE II, SIRS, and hospital stay. BMI or SAT had no significant relation to any of the outcome variables. Patients with VAT (L2-3, L3-4, and L4-5) above CO value had significantly greater APACHE II score ($P<0.001$, $P<0.001$, $p<0.001$, respectively), and SIRS ($P=0.01$, $P=0.009$, $P=0.003$, respectively). VAT did not have significant relation with hospital stay.

Conclusions: Acute pancreatitis patients with visceral adiposity above mean were associated with higher APACHE II or SIRS scores. However, correlation between BMI and severity of acute pancreatitis was not proven in our series.

Poster 02 Chronic Pancreatitis Basic, Diagnosis

P-008

Haplotype Analysis of CFTR Gene In Japanese Patients With Chronic Pancreatitis

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Background: Cystic fibrosis transmembrane conductance regulator (CFTR) anion channel plays a key role in HCO_3^- secretion in pancreatic duct cells. Over 1,400 mutations and polymorphisms have been identified in the *CFTR*. Loss of its function due to severe mutations in the *CFTR* gene causes cystic fibrosis. Mild dysfunction due to less severe mutations or polymorphisms is thought to be related to a certain cases of chronic pancreatitis. For example TG dinucleotide repeats, $(TG)_{12}$, at the junction of intron8 and exon9 tend to induce exon9 skipping and M470V reduces the function of the CFTR by 60%. To define the significance of those mild mutations/polymorphisms in the pathogenesis of chronic pancreatitis, in the present study, we analyzed haplotype of *CFTR*.

Materials and Methods: Sixty five patients with alcoholic chronic pancreatitis (ACP), 21 patients with idiopathic chronic pancreatitis (ICP), and 180 normal subjects (NS) participated in this study. DNA was extracted from blood leukocytes. -895 t/g, -790δt, (GATT)n, (TG)n, M470V, and 2694 t/g were identified by direct sequences or RFLP. The haplotype was defined by linkage of these mutation/polymorphisms.

Results: Three -790δt alleles were identified in ACP but not in ICP and NS. The -790δt was linked to $(TG)_{12}$-V470, although the dominant haplotypes in Japanese (over 89%) were $(TG)_{11}$-V470 or $(TG)_{12}$-M470.

Conclusion: -790δt-$(TG)_{12}$-V470 of *CFTR* is a candidate haplotype of alcoholic chronic pancreatitis in Japanese. The position of -790 in the promoter region of *CFTR* is a putative binding site for a transcription factor, Foxd3. -790δt mutation may alter the expression of *CFTR*. The combination of -790δt mutation with $(TG)_{12}$ and M470V polymorphisms may further reduce CFTR function and cause a certain cases of alcoholic chronic pancreatitis.

P-009

Chymotrypsin C Gene Variations in Japanese Patients with Chronic Pancreatitis

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Background/Aim: Genetic studies of chronic pancreatitis (CP) have highlighted the importance of a tightly regulated balance between activation and inactivation of trypsin within the pancreas to disease susceptibility and resistance. Recently, chymotrypsin C (CTRC) has been shown to be highly specific in degrading all human trypsin/trypsinogen isoforms. CTRC variations such as p.R254W and p.K247 R254del have been reported to be associated with idiopathic or hereditary CP. Functional analyses of these variations showed impaired activity and/or reduced secretion. These findings indicated that CTRC is a new pancreatitis-associated gene. The aim of this study was to investigate whether CTRC variations are present in Japanese patients with CP.

Methods: All individuals enrolled gave their informed consent according to the ethical guidelines of the Declaration of Helsinki. This study was approved by the Ethical Committee of Tohoku University School of Medicine. Genomic DNA was isolated from a cohort of 251 Japanese patients with CP. Their origins were as follows, hereditary (n=11), idiopathic (n=103), alcoholic (n=109), and autoimmune (n=28). In addition, genomic DNA was obtained from 95 healthy Japanese subjects. We analyzed all eight exons of the CTRC gene by direct sequencing.

Results: None of 259 Japanese patients with CP had common variations including p.R254W and p.K247 R254del. A total of 9 intronic variations were found, but the frequencies of these variations were not significantly different from those in the controls. We found novel polymorphism p.R29Q in one patient with alcoholic CP. He had previously diagnosed with acute pancreatitis at the age of 22 and undergone the Frey operation at the age of 28.

Conclusion: The common CTRC variations in western population might be rare in Japanese patients with CP. Functional analysis is necessary to clarify the role of novel polymorphism p.R29Q as a modifier of CP.

P-010

Effects of Splenectomy on Spontaneously Chronic Pancreatitis in aly/aly Mice

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Background and Aim: Mice with alymphoplasia (aly/aly) mutation characterized by a lack of lymph nodes, Peyer's patches and well-defined lymphoid follicles in the spleen were found, and the role of secondary lymphoid organs in immune responses was evaluated, which are considered to be completely lacking in secondary lymphoid organs. In this study, we used splenectomized aly/aly mice to elucidate the effects of secondary lymphoid organs in the development of aly/aly autoimmune pancreatitis.

Methods: Forty-eight 10-week-old aly/aly mice were divided into two groups for splenectomy and sham operation. Histological and immunohistochemical analyses of the pancreas were performed at 20-, 30-, and 40-week-old after operation, respectively.

Results: Our results showed that mononuclear cell infiltration was restricted to the interlobular connective tissues of splenectomized aly/aly mice at the age of 20 weeks, and the infiltrated cells did not increase obviously at the age of 30 and 40 weeks in splenectomized aly/aly mice. Furthermore, an apparent decrease in the expressions of CD4+ T, CD8+ T and B cells was detected in the pancreatic tissues of splenectomized aly/aly mice compared with sham aly/aly mice; however, no significant difference in macrophage expression was detected in pancreatic tissues between mice with and without a splenectomy.

Conclusions: Inflammation infiltration and development of the pancreatitis in aly/aly mice were suppressed effectively after splenectomy, which was, at least partly, correlated to inhibition of the infiltration of T and B cells in pancreatic tissues but not to macrophages.

P-011

MCP-1 Inhibits DNA Synthesis in Rat Pancreatic Stellate Cells

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Background: Activated pancreatic stellate cells (PSCs) synthesize various kinds of cytokines and chemokines including monocyte chemoattractant protein-1 (MCP-1) and play major roles in promoting inflammation and fibrogenesis in the pancreas. MCP-1 is a potent chemotactic factor for leukocytes and it has recently been shown that the target is not restricted. This study investigated whether MCP-1 exerts a biological effect on PSCs.

Methods: The expression and secretion of MCP-1 was evaluated by RT-PCR and ELISA. The expression of receptor components was examined by RT-PCR. PSCs activation and proliferation was measured by Western blotting and BudU incorporation assay, respectively. The effect of MCP-1 on intracellular signaling cascade was evaluated by Western blotting.

Results: Cultured rat PSCs secreted MCP-1 independent of the concentration of TGF-β_1 in the culture media. Although PSCs lack the typical receptor system (CCR2), MCP-1 inhibited DNA synthesis in PSCs without activation, this suggesting that the presence of CCR2-independent MCP-1 signaling pathway. Further, MCP-1 inhibited the proliferation of PSCs in which TGF-β_1/Smad pathway was blocked by the dominant-negative Smad2/3 over-expression. MCP-1 did not affect the phosphorylation state of MAPK, Akt, nor EGFR.

Conclusions: MCP-1 inhibited DNA synthesis of cultured rat PSCs in an autocrine or paracrine manner without activation. This effect was exerted through CCR2-independent and TGF-β_1/Smad-independent pathway.

P-012

Psychosomatic Abnormalities in Patients with Chronic Pancreatitis

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Introduction: Psychosomatic changes in patients with chronic pancreatitis (CP) are often evident and deteriorate clinical course. They should be taken into account for improvement of therapy results. But in practice doctors often do not consider psychosomatic abnormalities in patients.

Aim: to study psychosomatic status in CP.

Methods: 108 patients suffering from CP and 30 healthy persons were examined. Patients' psychosomatic status was assessed with the help of the psychogeometric and Lusher's tests.

Results: In the control group distribution on types according to psychogeometric tests was as follow: circle type - 46,7%, triangle type - 23,3%, square type - 13,3%, rectangle type - 6,7% and zigzag type - 10,0%.

57 patients (52,8%) corresponded to psychic status of rectangle type. They had following characteristic signs: inextricably in problems, indeterminate relation to himself, variability of mood and decisions. 24 patients (22,2%) corresponded to psychic status of square type: it were characteristic tendency to detailing, delay of decision making. 15 patients (13,9%) corresponded to psychic status of triangle type. Such people don't tend to find themselves wrong, pragmatically oriented, don't tolerant to other people. 8 patients (7,4%) corresponded to psychic status of circle type with follow characteristic signs: high sensitivity, advanced empathy, indecision, orientation on subjective factors of a problem. 4 patients (3,7%) corresponded to psychic status of zigzag type - creativity, synthetic mentality, ability to generate new ideas.

62 patients (57,4%) with CP according to results of Lusher's test had low activity and motivation for achievements, passive life attitude, low self-rating, sensation of dependence from external circumstances, introversion.

Conclusion: Patients with CP corresponded to evident psychosomatic changes that should be taken into account in institute therapy.

Poster 03 Chronic Pancreatitis Treatment 1

P-013

Antihomotoxic Therapy of Chronic Pancreatitis (CP) in Patients After Cholecystectomy

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Introduction: Annually in the world about 2,5 million cholecystectomies are performed, more than half of these patients have cholecystectomy syndrome. One of the most frequent manifestations of this syndrome is CP. Pathogenesis of pancreatitis is multicomponent, so treatment quite often is insufficiently effective.

Aim: To improve efficacy of CP treatment that developed after cholecystectomy by inclusion of complex antihomotoxic preparations in therapy.

Methods: 116 patients and 30 healthy persons were examined. Patients were divided into two groups depending on applied treatment. Patients of the main group (58 patients) received traditional CP treatment in combination with antihomotoxic preparations (Momordica compositum and Hepeel). Patients of the comparison group (58 patients) received only traditional CP treatment. Treatment in hospital continued 18–20 days, and then patients were observed in out-patient department during the year. Courses of antihomotoxic preparations treatment replicated every three months, so every patient of the main group received 4 courses of such treatment during the year.

Results: In patients of the main group abdominal pain decreased or disappeared in 1,25 times more frequently, than in the comparison group. Mean indices of fecal elastase at the time of discharge from the hospital in the main group were in 1,39 times higher. In the same group indices of pancreatic isoamylase and immunoreactive tripsin of blood significantly decreased. As a result of treatment sonographic data were much better in the main group. During the year CP exacerbation after treatment of antihomotoxic preparations developed in 1,69 times more rarely, than after traditional therapy.

Conclusion: It is reasonable to include antihomotoxic preparations Momordica compositum and Hepeel into CP therapy in patients after cholecystectomy.

P-014

New Therapeutic Approaches in Treatment of Chronic Pancreatitis (CP) on the Background of Obesity

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Introduction: CP on the background of obesity develops more severe, complications arise more often. At the same time, treatment of such CP that usually accompanied with hyperlipidemia, biliary sludge or cholelithiasis, fatty degeneration of pancreas, is a difficult task. We decided to use in treatment of patients a Grinization method that is based on the original principle of multistage processing of natural products.

Aim: to study efficacy of polynutrient complexes Green Mix and Green Pro in CP treatment on the background of obesity.

Methods: There were examined 44 patients with CP in association with obesity. Patients of the main group (20 patients) received basic treatment, and also products Green Mix and Green Pro. Patients of the comparison group (24 patients) received only basic treatment.

Results: Treatment with using Grinization products had considerable advantages concerning reduction of dyspepsia and asthenic syndromes. Full disappearance of dyspepsia was observed in 2,4 times more often, and asthenia - in 2,6 times more often in patients of the main group. Index L of ultrasonic histography of pancreas in that patients who received Grinization products significantly decreased. This indicated reduction of intensity of fatty degeneration of pancreas. Patients of the comparison group didn't have any significant dynamics of index L.

Conclusion: Inclusion of Grinization products in treatment of patients with biliary CP on the background of obesity promotes reduction of pancreatitis clinical manifestations and degree of fatty degeneration of pancreas.

P-015

Glucocorticoids Improve Pancreatic ß Functions in Autoimmune Pancreatitis

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Background: Autoimmune pancreatitis (AIP) is a rare type of chronic pancreatitis caused by an autoimmune abnormality. In AIP patients, it is well known that glucocorticoids improve glucose intolerance, however it is unclear whether they improve not only glucose intolerance but also ß cell function in maintenance treatment.

Methods: We evaluated the glucose metabolism and pancreatic ß cell function in AIP patients (N = 20) before and during maintenance glucocorticoids treatment, using 75g oral glucose tolerance test (75g OGTT) and glucagon test.

Results: We diagnosed diabetes in 55% of AIP patients before glucocorticoid treatment. In those of patients, mean values of HbA1c and fasting plasma glucose (FPG) were 6.54% and 131 mg/dl, respec-

tively. Their pancreatic ß cell function before glucocorticoid treatment were following: fasting C-peptide immunoreactivity (CPR) 0.8±0.6 ng/ml (mean ±SD), ΔCPR6 1.7±1.6 ng/ml, urinary CPR 71±94 µg/day, HOMA-R 1.6±0.9, HOMA-ß 38±32%, insulinogenic Index 0.2±0.2. In patients with AIP, 65% required insulin therapy during induction treatment, but 22% of those patients in maintenance treatment. There were no significant differences in HbA1c (6.54% vs 6.37%) and FPG (131 mg/dl vs 118 mg/dl) between before and in maintenance treatment. ß cell function of AIP patients in maintenance treatment, evaluated by ΔCPR6 and HOMA-ß, was significantly improved than those in patients before treatment.

Conclusions: Glucocorticoids may improve pancreatic ß cell functions in patients with AIP.

P-016

Assessment of Endoscopic Ultrasound-guided Pancreatic Pseudocyst Drainage

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Background: Endoscopic ultrasound (EUS)-guided transmural drainage is increasingly performed for the treatment in patients with pancreatic pesudocysts (PPCs). We investigated the utility and complication of EUS-guided pancreatic pseudocyst drainage.

Methods: Between September 1999 and October 2009, EUS-guided drainage was performed for 45 PPCs of 40 patients. The criteria of EUS-guided drainage in our hospital is presence of, 1) PPC>60 mm which did not shrink in 6 weeks, 2) PPC with any symptom, or 3) PPC with infection. Drainage was performed with nasocystic catheter, stent, or a combination of both. PPCs were punctured by 19-gauge EUS needle and drainaged by nasocystic catheter, stent, or a combination of both.

Results: The cause of PPCs was chronic pancreatitis (n=21), acute pancreatitis (n=19), trauma (n=4) and pancreatic cancer (n=1). The mean size of PPCs was 93 mm, and they were predominantly located in the pancreatic tail (n=28). Thirty-eight PPCs caused symptoms and 11 were infected. Insertion of stent and/or nasocystic catheter was successfully achieved in 44 (98%) of 45 PPCs. Twenty PPCs were drainaged with stent, 4 with nasocystic catheter and 20 with a combination of both. The reduction of PPCs was achieved in 40 (90%) of 45 and the improvement of symptoms occurred in 30 (81%) of 37. Procedure-related complications occurred in 4 (9%) of 45 procedures and stent-related complications in 3 (7%) of 45. There was no serious complication in this study.

Conclusions: EUS-guided drainage is useful treatment for PPCs. The incidence of complication is low and regarded as tolerable level.

P-017

Perioperative Challenge Associated with Total Gastrectomy for Gastric Cancer in Patient with Autoimmune-pancreatitis Relapsed After Choledocho-jejunostomy

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A 60- year-old asymptomatic male patient was admitted due to the presence of gastric tumor identified during routine upper gastrointestinal series and gastrointestinal fiver. Investigations revealed cancer of stomach (gastric cancer). Past history included obstructive jaundice due to auto-immune pancreatitis (AIP). The patient underwent a choledocho-jejunostomy in another hospital 3 years ago. Computed tomography revealed enlargement of the pancreas head with dilatation of the main pancreatic duct. Serum IgG4 concentration was very high level and he had sialoadenitis, we diagnosed gastric cancer with relapsed AIP. We administered steroid before operation, total gastrectomy was performed. Intraoperative ultrasonography revealed showed pancreas head mass and dilatation of main pancreatic duct. After surgical treatment of gastric cancer, oral administration of predonisolone was initiated. The serum IgG4 concentration was decreased and sialoadenitis was cured. Major complication did not occurred. This communication reports a total gastrectomy for gastric cancer in patient with Autoimmune-pancreatitis relapsed after choledocho-jejunostomy showing an interesting clinical course. The steroid therapy of the perioperative period is useful for gastric cancer operation with AIP.

P-018

Intracystic Haemorrhage in Pancreatic Pseudocyst Treated by Interventional Radiology in the Management of Bleeding Followed by Elective Distal Pancreatectomy with Splenectomy

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Pancreatic psuedocyst is often associated with pancreatitis. Following cyst formation, complications including infection, rapture and haemorrhage may occur. Particularly, as intracystic haemorrhage in pancreatic pseudocyst is a critical condition, which may have a fatal course, early diagnosis and immediate intervention are required.

In this study, we report a case of intracystic haemorrhage in pancreatic pseudocyst, which was aggressively treated by interventional radiology (IVR) for hemostasis followed by elective distal pancreatectomy with splenectomy. We report this case with some bibliographic considerations.

A 32-year-old man with diagnosis of alcohol-induced chronic pancreatitis and pancreatic pseudocyst had been followed up by nearby doctor. When a sudden dorsal pain occurred and the patient consulted with the doctor, the pancreatic pseudocyst was pointed out

to be enlarging. He was transferred to our hospital under suspicion of infection or haemorrhage of pancreatic pseudocyst. Detail examination after the hospitalization diagnosed as intracystic haemorrhage in pancreatic cyst of pseudo aneurysm. Emergency IVR was performed and the haemorrhage was successfully controlled. After the patient's condition improved, distal pancreatectomy with splenectomy was electively applied.

P-019

Splenic Pseudoaneurysm in Concomitant with Chronic Pancreatitis Treated by Interventional Radiology

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A 62-year-old woman, who had a history of excessive alcohol consumption, presented with left upper abdominal pain. Abdominal ultrasound and computed tomography showed a 5 centimeters cystic lesion in the tail of pancreas. Since the pain was relieved spontaneously, we take a wait-and-see approach. She had abdominal pain again 10 months later and the ultrasound showed larger size of the cystic lesion. She was admitted into our hospital for close examinations. Routine laboratory test results revealed slight anemia (hemoglobin of 10.1g/dl). Multi-detector computed tomography showed a enhanced tumor-like mass lesion within a cystic lesion. Ultrasound Doppler examination revealed high-blood flow in the tumor-like lesion. It suggested that the cystic lesion was pancreatic pseudocyst, and the tumor-like mass lesion was splenic pseudoaneurysm, based on the chronic pancreatitis. She was planned to perform distal pancreatectomy and splenectomy. However, since the size of pseudoaneurysm was increasing gradually, arterial embolization using coils performed ahead of the operation to avoid the rupture of the aneurysm. Furthermore, temporally pancreatic stent was inserted to prevent post-operative pancreatic fistula. After the embolization and stenting, the operation was performed successfully, and the patient was doing well without any complication.

Poster 04 Pancreatic Cancer Basic 1

P-020

Differential Methylation of Promoters in Ductal Adenocarcinoma and Cancers of the Ampulla Vateri of the Pancreas

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Background: Prognosis for patients with pancreatic carcinoma (PDAC) remains poor. Despite of increasing knowledge about the molecular basis of PDAC neither a specific marker for early diagnosis nor a target protein for a new therapeutic approach have been identified so far. Determination of DNA methylation events is a promising technology for the early detection and classification of cancer. We were therefore interested to elucidate the significance of DNA methylation to distinct between ductal adenocarcinoma and cancers of the ampulla vateri (AVT) of the pancreas.

Methods: DNA isolation using the Qiamp mini kit and modification using the Zymo EZ DNA Methylation-Gold system was performed. Primers for methylation specific PCR (MSP) for RELN, ADAMTS8, SFRP1, BNIP3, ID4 and TFPI2 were selected from the literature and tested for their performance on bisulfite modified fully methylated human DNA. After successfully establishing the assays, DNA samples isolated from formalin fixed and paraffin embedded tissue from patients with diagnosed ductal adenocarcinoma (n=14) and tumors of the ampulla vateri (n=7) were investigated. MSP was performed and the amount of produced fragment was scored semiquantitatively using agarose gelelectrophoresis.

Results: MSP analysis of the bisulfite modified DNA showed methylation differences in RELN (PDAC: 63%, AVT: 37%), ADAMTS8 (PDAC: 37%, AVT: 14%), BNIP3 (PDAC: 85%, AVT: 50%), SFRP1 (PDAC: 84%, AVT: 100%) and ID4 (PDAC: 93%, AVT: 62,5). Interestingly, for TFPI2 both tumors types showed nearly the same incidence of methylation events (PDAC: 86%; AVT: 87%).

Conclusion: Detection of DNA methylation is able to indentify differences between tumors of the pancreas. This might resemble crucial changes during tumor development, which are also reflected in gene expression and histopathologic appearance. For the establishment of a methylation-based discrimination of tumors further samples and promoters have to be tested.

P-021

Significance of Lymphangiogenesis in Primary Tumor and Draining Lymph Nodes During Lymphatic Metastasis of Pancreatic Head Cancer

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Purpose: The aim of this study was to investigate lymphangiogenesis in primary pancreatic tumors and in draining lymph nodes during lymphatic metastasis of human pancreatic head cancers.

Methods: Specimens of primary tumors and resected lymph nodes were obtained from 70 patients with pancreatic head cancer. To evaluate lymphangiogenesis, we measured lymphatic vessel density (LVD) using D2-40 antibody. AE1/AE3 antibody was used to detect tiny, histologically-negative metastases in lymph nodes, and the exact size of each metastasis was measured.

Results: LVD at the invasive front of primary tumors was significantly greater in cases with lymph node metastasis relative to cases without lymph node metastasis. In addition, the postoperative survival rate of patients with low LVD was significantly higher than that of high LVD patients ($P=0.0066$). The LVDs of non-metastatic lymph nodes in cases with lymph node metastasis were also significantly higher than non-metastatic nodes in cases without lymph node metastasis ($P<0.0001$). In metastatic lymph nodes, intranodal LVDs increased with increasing size of tumors. LVDs of metastatic peripancreatic nodes were significantly higher in cases with paraaortic lymph node metastases relative to those cases without paraarotic metastases ($P=0.0296$).

Conclusions: Lymphangiogenesis in the invasive front of a primary tumor and in draining lymph nodes is essential for efficient spread of tumor cells through the lymphatic system. Thus, inhibition of lymphangiogenesis could limit lymphatic dissemination of tumor cells

P-022

Pancreatic Stellate Cells Induce Epithelial-mesenchymal Transition and Proliferation of Pancreatic Cancer Cells

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Background & Aim: Pancreatic ductal adenocarcinoma is often characterized by an abundant desmoplastic stroma that is partially induced by pancreatic stellate cells (PSCs). Interactions between pancreatic cancer cells and PSCs remain unknown. This study aimed to investigate the effects of secretion products from PSCs on pancreatic cancer cells.

Methods: PSCs were isolated from resected pancreas tissue of patients undergoing operation for pancreatic cancer with approval from the Ethics Committee of Tohoku University Graduate School of Medicine. PSCs (passages between three and nine) were cultured in Ham's F-12/Dulbecco's modified essential medium supplemented with 0.1% fetal bovine serum for 48h and the conditioned medium (CM) was collected. Pancreatic cancer cell line, Panc-1 cells were treated by CM. Morphology, expression of E-cadherin and vimentin, and proliferation of Panc-1 cells were examined. In addition, cell migration was assessed by scratch assay.

Results: CM-treated Panc-1 cells showed loose cell contacts and scattered, fibroblast-like appearance along with downregulation of E-cadherin, a marker of epithelial cells. CM-treated Panc-1 cells increased expression of vimentin, a marker of mesenchymal cells. CM treatment enhanced cell migration and cell proliferation of Panc-1 cells.

Conclusion: These findings indicate that some secretion products from PSCs may be involved in pancreatic ductal adenocarcinoma development through the promotion of epithelial-mesenchymal transition and proliferation of pancreatic cancer cells.

P-023

Identification of MAPK-associated MiRNAs and Their Potential Targets in Pancreatic Cancer

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Background & Aim: Recently, it is hypothesized that aberrant expressions of miRNAs in various cancers including pancreatic cancer play important roles in malignant phenotypes. However, mechanism of the aberrant expressions and their pathobiological significances in cancer cells were poorly understood. Purpose of this study was to identify miRNAs associated with MAPK activity that plays crucial roles in pancreatic cancer and their pathobiological significances.

Methods and Results: By extensive quantification of miRNAs in MAPK-attenuated pancreatic cancer cells, we found that miR-7, -34a, -181b and -193b were specifically associated with MAPK activity. By exogenous overexpression of theses miRNAs, we found that miR-193b induced strong suppression of proliferation of pancreatric cancer cells. We explored target genes of miR-193b by transcriptome and proteome analyses and found that several transcripts and proteins were significantly down-regulated by its exogenous overexpression. To validate these results, we conducted real-time quantitative PCR analysis and immune-blot analysis.

Conclusions: We identified miRNAs associated with MAPK activity and their potential targets in pancreatic cancer cells.

P-024

MicroRNA-21 (miR-21) Modulates Biologic Functions of Pancreatic Cancer Cells Including Their Proliferation, Invasion and Chemoresistance

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Purpose: Due to the poor prognosis of pancreatic cancer, novel diagnostic modalities for early diagnosis and new therapeutic strategy are urgently needed. Recently, microRNA-21 (miR-21) was reported to be strongly overexpressed in pancreatic cancer as well as in other solid cancers. We investigated the functional roles of miR-21, which have not been fully elucidated in pancreatic cancer. Experimental Design: miR-21 expression was assessed in pancreatic cancer cell lines (14 cancer cell lines, primary cultures of normal pancreatic epithelial cells and fibroblasts, and a human normal pancreatic ductal epithelial cell line (HPDE)) and pancreatic tissue samples (25 cancer tissues and 25 normal tissues) by quantitative real-time reverse transcription-polymerase chain reaction amplification. Moreover, we investigated the proliferation, invasion and chemoresistance of pancreatic cancer cells transfected with miR-21 precursor or inhibitor.

Results: miR-21 was markedly overexpressed in pancreatic cancer cells compared with non-malignant cells, and miR-21 in cancer tissues was much higher than in non-malignant tissues. The cancer cells transfected with the miR-21 precursor showed significantly increased proliferation, matrigel-invasion and chemoresistance for gemcitabine compared to the control cells. In contrast, inhibition of miR-21 decreased proliferation, matrigel-invasion and chemoresistance for gemcitabine. Moreover, miR-21 positively correlated with the mRNA expression of invasion-related genes, matrix metalloproteinase-2 (MMP-2), MMP-9 and vascular endothelial growth factor (VEGF).

Conclusions: These data suggest that miR-21 expression is increased in pancreatic cancer cells, and that miR-21 contributes to the cell proliferation, invasion and chemoresistance of pancreatic cancer.

P-025

Significance of Combination Therapy by Zoledronic Acid and Gemcitabine on Pancreatic Cancer Cell Lines in vitro and in vivo

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Background: In clinical, zoledronic acid (ZOL) exhibited a potent anti-invasive effect against osteocarcinoma and breast cancer. There are a few reports of ZOL treatment for pancreatic cancer cell lines. Gemcitabine (GEM) has been established as the first-line chemotherapy for pancreatic cancer and shown efficient anti-proliferation activity in research and clinical.

Aim & Methods: To examine the effect of combination therapy of ZOL and GEM on pancreatic cancer. 4 human pancreatic cancer cell lines were used. Cells were treated with low dose ZOL, GEM or the combination of them. We evaluated effect on cell proliferation and invasion by PI assay and invasion assay, respectively. In addition, intrasplenic and orthotopic implanted nude mice models were used to evaluate effects of those therapies in vivo.

Results: The effect of low dose ZOL on cell proliferation was small, however it can inhibit cell invasiveness efficiently. Short-time treatment of GEM revealed no anti-invasive effect. The effects of ZOL on cell invasion and GEM on cell proliferation were proved in pancreatic cancer cell lines in vitro. In vivo, combination therapy exhibited dramatic prohibitive effects on both proliferation and metastasis.

Conclusions: Combination treatment with ZOL plus GEM effectively inhibits tumor proliferation and metastasis in in vitro and in vivo, and may provide a promising improved therapy for controlling pancreatic cancer.

P-026

MicroRNA-10b Is a Useful Prognostic Marker in Pancreatic Cancer and Promotes Its Invasiveness

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Backgrounds: Micro RNAs (miRNAs) have been gaining attention as new key molecules which contribute to carcinogenesis. In pancreatic cancer, previous miRNA expression profiling analyses have shown that several miRNAs were differently expressed in normal and cancerous tissues. However, several pancreatic cancer specific miRNAs were different in each analysis.

Materials and Methods: We investigated the miRNA expression profiles with high-throughput TaqMan qRT-PCR array analysis using pancreatic cancer cell lines, CAPAN-1, CFPAC1 and an immortalized human normal pancreatic ductal epithelial cell line (HPDE). The expression level of specific miRNA identified in the present array analysis was examined in a panel of 13 pancreatic cancer cells lines. We also analyzed the expression of miRNA using microdissected ($n=10$) and formalin-fixed paraffin-embedded (FFPE) ($n=115$) samples from pancreatic cancers by quantitative RT-PCR. We also investigated the effect of miRNA expression on the invasiveness of pancreatic cancer using in vitro.

Results: Based on microarray analysis, miR-372, miR-146a, miR-204, miR-10a and miR-10b showed particularly large differences (over 10 fold changes) in both CFPAC-1 and Capan-1 cell lines compared with HPDE cells. All 13 pancreatic cancer cell lines showed 2.1- to 36.4-fold (median, 15.3) higher levels of miR-10b than HPDE cells. Microdissection analysis revealed that miR-10b showed significantly higher expression level in pancreatic cancer cells ($n=5$) than in normal pancreatic ductal cells ($n=5$)($p<0.05$). Analysis of FFPE

samples revealed that high miR-10b expression was significantly associated with a shorter overall survival ($P<0.01$). Furthermore, miR-10b promoted the invasiveness of pancreatic cancer cells ($P<0.01$).

Conclusions: miR-10b overexpressed in a subset of pancreatic cancer may be involved in its invasiveness and related with poor prognosis.

Poster 05 Pancreatic Cancer Basic 2

P-027

MicroRNA-373 Is Downregulated in Pancreatic Cancer and Represses Its Invasiveness via Induction of Mesenchymal-epithelial Transition

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Backgrounds: Epithelial-mesenchymal transition (EMT) is characterized by loss of E-cadherin and is related with invasive behavior of pancreatic tumors. Micro RNAs (miRNAs) have been gaining attention as new key molecules related with carcinogenesis and some miRNAs have been also identified as key regulators of EMT. miR-373 has been recently reported to directly induce E-cadherin. However, there is no report regarding the effect of E-cadherin induction by miR-373. We focused on, in this study, the potential role of miR-373 in the invasiveness of pancreatic cancer and its relationship with EMT.

Materials and Methods: We investigated the effect of miR-373 reexpression on the invasiveness of pancreatic cancer and its relationship with EMT and dissemination using in vitro and in vivo models. We also analyzed the expression of miR-373 using formalin-fixed paraffin-embedded (FFPE) ($n=152$) and microdissected frozen ($n=57$) samples from pancreatic cancers by quantitative RT-PCR.

Results: The levels of miR-373 expression were low in pancreatic cancer cell lines. In the analysis of FFPE and microdissected samples, miR-373 expression was significantly downregulated in pancreatic cancer than those in normal pancreas ($P=0.001$, $P=0.005$, respectively). Reexpression of miR-373 induced mesenchymal epithelial transition (MET) and also repressed TGF-beta-induced EMT, leading to inhibition of invasiveness of cancer cells. Furthermore, reexpression of miR-373 significantly inhibited peritoneal dissemination in vivo ($P<0.001$).

Conclusion: miR-373 may be downregulated in pancreatic cancer and its reexpression may repress the invasiveness of pancreatic cancer cells via induction of MET.

P-028

MicroRNA-203 Expression as a New Prognostic Marker of Pancreatic Cancer

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Background: The detection of aberrant microRNA (miR) expression may contribute to the diagnosis and prognosis of various cancers. The aim of this study was to evaluate the correlation between miR-203 expression and the prognosis of patients with pancreatic cancer after curative resection.

Materials and Methods: A total of 113 formalin-fixed paraffin embedded tissue samples of pancreatic cancer, 20 samples of chronic pancreatitis, and 8 samples of normal pancreas were obtained. We investigated the association of miR-203 expression measured by quantitative reverse transcription-polymerase chain reaction assays with clinicopathological parameters and the survival times.

Results: MiR-203 was overexpressed in pancreatic cancer samples compared with chronic pancreatitis ($P<0.001$) and normal pancreas ($P=0.001$) samples. An association between miR-203 expression and clinicopathological factors of pancreatic cancers was not observed. In univariate analysis, the high miR-203 group and the 20% of cases with the highest overexpression of miR-203 had a significantly shorter survival time ($P=0.048$ and $P=0.024$, respectively). Multivariate analysis revealed that miR-203 expression was an independent predictor of a poor prognosis in cases with no residual tumor and 2.298 of relative risk ($P=0.027$).

Conclusions: MiR-203 expression is a new prognostic marker in pancreatic cancer patients.

P-029

SH3BGRL Expression Was Downregulated in Pancreatic Cancer

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Backgrounds & Aims: SH3 binding glutamic acid rich-like protein (SH3BGRL) was reported to be located at chromosome 21. Recently, it has been reported that the expression of SH3BGL was downregulated in v-Rel oncogene-expressing fibroblasts, lymphoid cells and splenic tumor cells. However, there was no report regarding the expression of SH3BGL in pancreatic cancer. The aim of the present study was to investigate the involvement of SH3BGRL expression in pancreatic cancer.

Methods: To evaluate the SH3BGR gene expression in normal pancreas and pancreatic cancer, quantitative RT-PCR was performed in 2 cultures of normal pancreatic epithelial cells, 3 cultures of pancreatic fibroblasts, and 15 cultures of pancreatic cancer cell lines. We also performed lazar-microdissection to obtain normal pancreatic ductal cells from 37 normal pancreas and invasive ductal carcinoma cells from 38 pancreatic cancer tissues and investigated the levels of

SH3BGRL mRNA expression in these cells using quantitative RT-PCR.

Results: The analyses of cultured cells revealed that the level of SH3BGRL mRNA expression was significantly lower in pancreatic cancer cells than that in normal pancreatic epithelial cells (P=0.002) and fibroblasts (P<0.001). The analyses of microdissection samples revealed that the level of SH3BGRL mRNA expression is significantly lower in invasive ductal carcinoma cells than that in normal pancreatic ductal cells (P=0.005).

Conclusion: The present data suggest that the decrease in SH3BGRL mRNA expression is involved in pancreatic tumorigenesis or cancer progression.

P-030

Inhibition of p600 Suppresses Invasiveness and Anoikis Resistance of Pancreatic Cancer Cells

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Purpose: Pancreatic cancer is one of the most aggressive malignancies and has a poor prognosis, because of a high incidence of metastasis and a lack of effective drug. Therefore, new therapeutic strategies are urgently needed. Recently, p600 was identified from a cervical cancer cell line, and reported to play an essential role in both the ability of resistance to anchorage-independent cell death (anoikis) and cell migration. In this study, we examined whether p600 was involved in metastasis of pancreatic cancer.

Experimental Design: We inhibited p600 expression in a pancreatic cancer cell line (Suit-2) using short interference RNA (siRNA). We examined the effect of p600 inhibition on the invasiveness by invasion assay and the anoikis resistance by propidium iodide (PI) assay under anchorage-independent condition.

Results: The invasion assay revealed that invasiveness was significantly reduced in p600 siRNA-transfected cells compared with control siRNA-transfected cells ($p<0.05$). Under anchorage-independent condition, cell viability was significantly reduced in p600 siRNA-transfected cells compared with control siRNA-transfected cells ($p<0.05$).

Conclusions: Our results revealed that both invasiveness and anoikis resistance of pancreatic cancer cells was suppressed by inhibition of p600, suggesting that p600 is involved in the progression of pancreatic cancer. Therefore, p600 may have the potential to be a new molecular target for pancreatic cancer therapy.

P-031

Prediction of Gemcitabine Sensitivity by Quantification of *S100A4* mRNA In Patients with Pancreatic Carcinoma

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Background: *S100A4*, a member of the S100 family of calcium-binding proteins, is known to be overexpressed in many solid tumors, including pancreatic cancer. Recently, S100A4 has been reported to contribute to gemcitabine-resistance and the inhibition of apoptosis in pancreatic cancer cells. The aim of this study was to investigate *S100A4* expression in resected pancreatic ductal adenocarcinoma (PDAC) tissues and its correlation with treatment outcome.

Methods: We obtained formalin-fixed paraffin embedded (FFPE) tissue samples from 70 patients with PDAC who underwent pancreatectomy in our institution from 1992 to 2007. Forty of 70 patients received gemcitabine-based adjuvant chemotherapy (AC). We measured *S100A4* mRNA levels by quantitative real-time RT-PCR, and investigated the association of *S100A4* mRNA expression with clinicopathological parameters and survival time using univariate and multivariate analyses. Furthermore, we investigated feasibility of individualized chemotherapy based on expression levels of *S100A4* mRNA using 22 endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) cytological specimens.

Results: The high *S100A4* group had a significantly shorter survival (P=0.028). Gemcitabine-based AC significantly prolonged survival time in the low *S100A4* group (N=39, P=0.028), whereas this AC did not show evident prolongation of survival time in the high S100A4 group (N=31, P=0.28). *S100A4* expression levels were significantly higher in microdissected neoplastic cells from EUS-FNA cytological specimens than those in non-malignant cells, whereas there was no significant difference in S100A4 expression levels of whole cell pellets.

Conclusion: Quantitative analysis of *S100A4* mRNA expression using FFPE tissue samples may be useful to predict the gemcitabine-sensitivity and prognosis of patients with PDAC.

P-032

Adenoviral Therapy is More Effective for Gemcitabine Resistant Pancreatic Cancer Cells Than in Gemcitabine Sensitive Cells

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Objective: Although gemcitabine is the current standard of care for pancreatic cancer, pancreatic cancer rapidly grows or has intrinsic chemoresistance and thus the response rate is below 10%. Chemoresistance plays critical roles in tumor progression, invasion and migration. Nevertheless, the effect of adenoviral therapy on chemoresistant cancer cells has not been studied. In this study, we compared transduction efficiency of adenovirus-delivered genes in chemoresistant and chemosensitive pancreatic cancer cells.

Methods: We used adenoviruses expressing GFP (Ad-GFP) or NK4, hepatocyte growth factor antagonist, (Ad-NK4). To establish a gemcitabine resistant pancreatic cancer cell line, we exposed SUIT2 cells to increasing concentrations of gemcitabine. Chemoresistant and chemosensitive cancer cells infected with Ad-GFP or Ad-NK4. RT-PCR were used to detect virus DNA. To investigate the transduction efficacies, GFP positive cells were counted or NK4 concentration in the supernatant was measured.

Results: The viral DNA content of gemcitabine resistant cells was significantly higher than that of gemcitabine sensitive cells ($p<0.05$). GFP was significantly more expressed in gemcitabine resistant cells than in gemcitabine sensitive cells ($p<0.05$). The NK4 level in gemcitabine resistant cells was significantly higher than that in gemcitabine sensitive cells ($p<0.05$).

Conclusion: The data revealed that both the uptake of adenoviral gene and the efficiency of transduction were higher in gemcitabine resistant cells than in gemcitabine sensitive cells, suggesting that adenoviral gene therapy is more effective in patients with pancreatic cancer which has acquired gemcitabine resistance.

Poster 06 Pancreatic Cancer Diagnosis

P-033

Examination of Detection Opportunity in Pancreatic Cancer Patients

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Background: The pancreatic cancer is often unresectable when it was diagnosed. The aim of this study is to examine detection opportunity in pancreatic cancer patients, and to consider the chance of early detection.

Methods: Between April 2006 and December 2009, 92 pancreatic cancer patients who were treated at Shimane University Graduate School of Medicine.

Results: <sex and age> Male; 48 (67.4 y.o., 47–84), Female; 43 (70.4 y.o., 54–83) <the site of tumor> pancreas head; 57, pancreas body; 20, pancreas tail; 14, all; 1<resection> resectable; 34(37%), unresectable; 58(63%) <detection opportunity> symptom and jaundice; 65, medical examination; 3, follow of IPMN; 3, examination of other disease; 20 <symptom> symptom of upper body; 32 (include combination of jaundice 12), jaundice; 10, appetite loss; 4, back pain; 8, abdominal distension; 6, others; 5. There was no significant difference between tumor site and existence of symptoms. In resectable cases, 17 (50%) patients have symptoms, but unresectable cases 48 (83%) patients have that ($p=0.0017$). The average period from appearance of a symptom to detection of pancreas cancer is 2.2 weeks in resectable cases, and is 7.7 weeks in unresectable cases ($p<0.01$). And there were significant difference at diameter of tumor (resectable; 2.5cm, unresectable; 3.9cm $p<0.0001$), the level of CEA (resectable; 5.0 ng/ml, unresectable; 24.7 ng/ml $p=0.0036$), and the level of CA19-9 (resectable; 247.8 IU/ml, unresectable; 5320.3 IU/ml $p=0.0007$)

Conclusion: For detecting pancreatic cancer in resectable state, it is very important to examine the existence of pancreatic cancer when we see the patient who suffers with upper body symptoms.

P-034

Prevalence of Pancreatic Cancer in Diabetics and Clinical Characteristics of Diabetes Associated with Pancreatic Cancer in Korea

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Background: Diabetes mellitus (DM) has been postulated to be both a risk factor and a consequence of pancreatic cancer (PC). In Korea, the prevalence of PC in general population has been reported as 14.8 in 100,000. This study was designed to estimate the prevalence of PC among DM patients, to characterize the patients with PC with and without DM, and to compare the clinical characteristics of DM patients with and without PC at Korea.

Methods: 5,082 patients (4,890 DM patients without PC, 78 PC patients with DM, and 114 PC patients without DM) were enrolled from Korea University Guro Hospital during a period of 4 years between January 2004 and January 2008. Multivariate logistic regression and discriminant analysis were used to compare the clinical characteristics.

Results: The prevalence of PC in DM patients was 1.6% and that of DM in PC patients was 40.6%. No significant differences in the clinical characteristics were observed between PC patients with DM and without DM. Among 78 PC patients with DM, DM was diagnosed in 19 (29.4%) and 29 (37.1%) patients concomitantly or within 2 years prior to the diagnosis of PC, respectively. DM patients with PC were found to have significantly higher total bilirubin, ALP, and

ALT levels than in DM patients without PC (4.7 vs. 0.9 mg/dL, 235.6 vs. 86.1 IU/L, and 89.5 vs. 39.8 IU/L, $p<0.01$).

Conclusions: The prevalence of PC in DM patients was higher than in the general population. DM in PC patients was frequently of recent onset (less than 2 years' duration). Clinicians should keep a possibility of PC in their minds when DM patients show abnormal level of bilirubin, ALP, or ALT.

P-035

Does Chronic Pancreatitis Increase the Risk of Pancreatic Cancer?

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Background/Aims: Chronic pancreatitis is known to increase the risk of pancreatic cancer from 2.3 to 18.5. We aimed to study the association between chronic pancreatitis and pancreatic cancer.

Methods: We evaluated 71 patients diagnosed with chronic pancreatitis between Jan 2000 and Dec 2004 and identified the occurrence of pancreatic cancer during follow-up. We also analyzed medical records of 254 patients diagnosed with pancreatic cancer between Sep 2005 and Sep 2009 and examined whether or not chronic pancreatitis coexisted in these patients to determine the association between pancreatic cancer and chronic pancreatitis. The diagnosis of chronic pancreatitis was based on image findings that showed pancreatic calcification or irregular ductal dilatation. The diagnosis of pancreatic cancer was made by histological confirmation and/or combination of radiologic, biochemical, and clinical findings.

Results: Of the 71 patients with chronic pancreatitis, 51 patients were able to follow up. The age of 51 chronic pancreatitis patients was 57.6±12.4 years and male/female ratio was 5.4:1. The etiologies of chronic pancreatitis were alcohol (72.5%), idiopathic (25.5%) and trauma (2.0%). The diagnostic modalities of chronic pancreatitis were CT (60.6%), ERCP (7.0%) and CT+ERCP (29.6%). The duration of follow-up was 91.1±49.1 months. There were no cases of pancreatic cancer during follow-up in these patients. The age of 254 pancreatic cancer patients was 65.5±11.7 and male/female ratio was 1.2:1. Smokers were 35% and alcohol drinkers were 25.2%. Diabetes coexisted in 57 patients (22.4%) and among them, 35 patients (61.4%) were diagnosed with diabetes within 2 years before the diagnosis of pancreatic cancer. No one showed the history of chronic pancreatitis and no cases revealed the evidence of chronic pancreatitis on imaging studies.

Conclusions: Chronic pancreatitis may not increase the risk of pancreatic cancer. Further studies with larger number of patients and longer duration of follow up are necessary.

P-036

Upper Gastrointestinal Lesions in the Patients with Pancreatic Cancer

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Purpose: Pancreatic cancer (PCa) is often complicated with upper gastrointestinal lesions. However, the incidence of them has seldom reported. We retrospectively investigated upper gastrointestinal lesions in the patients with PCa.

Methods: Upper gastrointestinal endoscopy was performed in 71 patients with PCa from 2003 to 2009. The age ranged from 32 to 86 (average, 65.4) years, with 50 males and 21 females. The tumors were located in the pancreatic head in 37 and in the body and/or tail in 33 cases. One patient had two tumors in the head and in the body to tail. The staging was judged as stage 3 in 2, as stage 4a in 29, and as stage 4b in 40 cases according to the TNM classification.

Results: Of 71 patients with PCa, 43 (61%) had upper gastrointestinal lesions. A total of 54 abnormal findings were observed. The details were as follows: gastroduodenal invasions in 18, ulcers in 15, esophagogastric varices in 13, radiation-induced gastritis in 3, and portal hypertensive gastropathy in 3 cases. In addition, duodenal metastasis and upper gastrointestinal bleeding of unknown primary site were recognized in each 1 case, respectively. Gastroduodenal invasions and ulcers were significantly dominant in the patients with PCa located in pancreatic head than in body and tail, respectively ($P=0.003$ and 0.04) and inversely esophagogastric varices occurred significantly in pancreatic body and tail than in head of the PCa patients ($P=0.03$). In 13 cases (25%), new upper gastrointestinal lesions developed according to progression of PCa.

Conclusions: The incidence of upper gastrointestinal lesions in the patients with PCa was relatively high. In particular, the complication of gastroduodenal invasions, ulcers, esophagogastric varices were common. The incidence was increasing as the progression of PCa. These results suggest that upper gastrointestinal endoscopy should be periodically performed in the patients with PCa.

P-037

EUS Elastography for the Differentiation of Solid Pancreatic Masses

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Background and Study Aims: Recently, the usefulness of endoscopic ultrasound (EUS) elastgraphy has been reported for differentiation of pancreatic lesions. We assessed EUS elastography as a diagnostic tool in patients with pancreatic masses by tissue elastic distribution and elasticity semiquantitatification using a strain ratio of tissue elasticity.

Patients and Methods: Patients who underwent EUS elastgraphy from September 2006 and May 2009 were prospectively evaluated. The calculation of tissue elasticity distribution was performed in real time and the results are represented in color over the radial B-mode image. In addition, we performed the quantification by using strain ratio (non mass area/mass area: SR).

Results: 109 patients (70M, 39F, mean age 65 years, range 31–85) with pancreatic lesions and control group underwent EUS elastgraphy. The final diagnosis was 13 with chronic pancreatitis (CP) including 7 with mass forming pancreatitis (MFP), 6 with autoimmune pancreatitis (AIP), 72 with pancreatic cancer (PC), 9 with pancreatic neuroendocrine carcinoma (PNET), 8 with normal control. Elastography for all PCs showed intense blue coloration, which indicated that the mass lesions had malignant aspects. While MFP presented the coloration pattern of mixed green, yellow and low intensity of blue. Normal control was an even application of green to red. The mean SR of MFP and PC were each 23.66 and 39.08, respectively ($p<0.05$).

Conclusions: EUS elastography is promising diagnostic tool to define the tissue characteristics of pancreatic masses. In addition, semiquantitative analysis of the elasticity using SR may allow the differentiation between MFP from PC.

P-038

A Study of the Usefulness of Pancreatic Juice Cytology by Placing ENPD Tube for Three Days

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Purpose: We perform pancreatic juice cytology by placing ENPD tube for three days to diagnose pancreatic cancer. We studied on its usefulness.

Subjects and Method: The subjects are 160 cases (78 men, 72 women, ages:66.8±10.1) in whom diagnoses were established after performing pancreatic juice cytology by placing ENPD tube from May 2005 to February 2009. We performed cytology three times and studied sensitivity/specificity of cytological diagnoses frequency/tumor size classifying, etc.

Result: ENPD tube was placed 179 times. There were 53 cases of pancreatic cancer, 12 cases of IPMC, 4 other malignant cases and 91 benign cases. Sensitivity of 69 malignant cases (43 positive, 20 suspicious and 6 negative cases) was 0.88. Sensitivity by frequency was 0.50 for the first time only, 0.72 for the second time and 0.85 for the third time, and a significant difference of $p<0.0001$ was recognized. Specificity was 1. Sensitivity by disease was 0.90 for pancreatic cancer and 0.86 for IPMC. Sensitivity by tumor size of pancreatic cancer was 1 for Tis (3 cases) and TS1(9 cases), 0.97 for TS2 (28 cases), 0.71 for TS3 (9 cases) and 0 for TS4 (4 cases), and a significant difference of $p=0.004$ was recognized. There were 4 cases of main duct type, 2 cases of branch type IPMC of positive cytological diagnosis. In the branch type, cystic lesion was under 30 mm diameter and mural nodule was not recognized.

Conclusion: The pancreatic juice cytology by placing ENPD tube can be tested repeatedly and that contributes to improving the diagnostic yield of correct diagnosis. Also, it is useful as a definite diagnosis method in early stage because it is easier to detect positive for smaller tumor, furthermore, it is possible to diagnose carcinoma in situ and positive result is detected even in a small cystic leison of branch type IPMC.

P-039

Preoperative 18[F]-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Predicts Early Recurrence After Pancreatic Cancer Resection

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Background: Pancreatic cancer sometimes recurs in the early postoperative period. It is important in deciding the treatment strategy that we can predict this possibility preoperatively. Therefore we reviewed whether 18[F]-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) could predict the recurrence for pancreatic cancer in the early postoperative period.

Methods: We performed FDG-PET/CT preoperatively on 56 cases with invasive ductal pancreatic cancer who then underwent curative resection. We compared the maximum standardized uptake values (SUVmax) obtained by FDG-PET/CT in the group who showed a recurrence within six months postoperatively with the group who had no recurrence in the six postoperative months. Furthermore, we analyzed whether age, sex, preoperative CA 19-9 value, operative method, portal vein resection, presence of postoperative adjuvant chemotherapy, or Stage classification were risk factors for recurrence less than 6 months postoperatively in addition to SUVmax.

Results: Cancer recurred in the first 6 months postoperatively in 22 cases (39.3%). The median SUVmax value of the recurrence group was 7.9, compared with 4.2 in the no recurrence group ($P=0.0042$). As Stage increased, SUVmax also tended to increase, and the relapse-free survival rate was high in patients with low SUVmax. Only SUVmax was a risk factor by the univariate analysis of the palindromic risk factors for recurrence in the first 6 postoperative months ($P=0.025$).

Conclusions: Preoperative SUVmax was higher in the recurrence group for the early postoperative period, and high SUVmax was a palindromic risk factor for an early postoperative recurrence. Therefore, it is thought that recurrence in the early postoperative period is predictable based on SUVmax by FDG-PET/CT obtained preoperatively.

P-040

Impact of 18-Fluorodeoxyglucose Positron Emission Tomography on the Management of Pancreatic Cancer

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Background: We compared the usefulness of positron emission tomography with the glucose analogue 2-deoxy-2-[18F] fluoro-D-glucose (FDG-PET) and multidetector row computed tomography (MD-CT) in diagnosing pancreatic cancer and in determining the patients' suitability for surgery.

Methods: We reviewed the clinical FDG-PET data of 103 consecutive clinically or histologically diagnosed pancreatic cancer patients admitted to our hospital between July 2004 and March 2009.

Results: The detection rates of pancreatic cancer by MD-CT (89%) and FDG-PET (91%) were similar. From the MD-CT findings, 38 patients were judged as operable, and 65, inoperable. Among the inoperable patients, noncurative factors (metastasis to the liver, paraaortic lymph nodes, peritoneum, remote lymph nodes, bones, and other organs and direct invasion of a major artery) were detected by MD-CT and/or FDG-PET. Detection rates of liver metastasis and major arterial invasion by FDG-PET were significantly inferior to those of MD-CT (neither was detected by FDG-PET alone). Remote lymph nodes and bone metastasis were detected in 20 lesions by FDG-PET alone; however, MD-CT indicated other noncurative factors in these patients. All 65 patients could be diagnosed as inoperable without FDG-PET.

Conclusions: The results suggest that FDG-PET is not a suitable imaging modality for either diagnosis or preoperative treatment in pancreatic cancer patients. Currently, MD-CT alone can be used to perform rapid whole-body imaging and even detect small tumors. Therefore, since it is expensive, FDG-PET as a routine diagnostic tool in pancreatic cancer patients must be used with caution.

P-041

Clinical Usefulness of Measuring the Value of KL-6 Antigen in Pancreatic Juice for Diagnosing Malignant IPMN Of the Pancreas and Pancreatic Cancer

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Background and Aim: Our previous immunohistochemical data showed that MUC1 is highly expressed in pancreatic cancer and that IPMN expressing MUC1 is malignant. KL-6 is an antigen of the sialylated sugar chain expressed on MUC1. KL-6 in pancreatic juice has never been measured. We measured the value of KL-6 in pancreatic juice of patients with pancreatic diseases and investigated the usefulness of measuring the value of KL-6 in pancreatic juice for diagnosis of malignant IPMN and pancreatic cancer.

Methods: Pancreatic juice was collected in 14 cases of benign IPMN and 4 cases of malignant IPMN, 13 cases of pancreatic cancer, 10 cases of chronic pancreatitis and 3 cases of gallstones. The value of KL-6 in pancreatic juice of them was measured. Diagnostic ability of KL-6 in pancreatic juice for malignant IPMN and pancreatic cancer was evaluated and compared with that of CA15-3, CA19-9 and CEA.

Results: The values of KL-6 in pancreatic juice were 670+-894 U/mL in the malignant IPMN group and 26+-42 U/mL in the pancreatic cancer group, which were significantly higher than the values in the benign IPMN group (5.2+-3.4) and control group (4.3+-2.3). Sensitivity, specificity and accuracy for diagnosis of malignant IPMN were all 100%, and they were 38%, 100% and 69%, respectively, for pancreatic cancer under a cut-off value of KL-6 in pancreatic juice of 20 U/mL. Diagnostic ability of KL-6 for malignant IPMN and pancreatic cancer was better than that of CA15-3, CA19-9 and CEA.

Conclusion: Measurement of KL-6 in pancreatic juice is useful for diagnosis of malignant IPMN and pancreatic cancer.

Poster 07 Pancreatic Cancer Surgery 1

P-042

Duodenum-preserving Total Pancreatectomy for Pancreatic Neoplasms

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Background: Total pancreatectomy (TP) is sometimes performed to treat low-grade malignant neoplasms that are spreading to the entire pancreas. However, TP impairs quality of life, due to the resulting loss of pancreatic exocrine and endocrine function, and an organ preserving procedure should be chosen to minimize the impact of pancreatic dysfunction. We performed four duodenum-preserving TPs (DPTPs) on patients with low-grade malignant neoplasms of the entire pancreas and we introduce our operative technique and results.

Methods: DPTP is performed with the objective of preserving the arterial arcade of the posterior pancreas so as to maintain good blood flow in the duodenum and common bile duct. Care must also be taken to preserve the splenic artery and vein to protect the spleen. When patients are undergoing a bile duct resection, an end-to-side choledochoduodenostomy is performed to reconstruct the biliary tract.

Results: DPTP with preservation of the spleen, conserving splenic vessels, was performed on a patient with hereditary pancreatic

carcinoma with pancreatic intraepithelial neoplasia-3 (PanIN-3). DPTP with splenectomy was performed on a patient with multiple metastases of the entire pancreas from renal cell carcinoma. DPTP with preservation of the common bile duct and the spleen, conserving splenic vessels, was performed on a patient with minimally invasive carcinoma derived from intraductal papillary mucinous neoplasm (IPMN). DPTP with preservation of the spleen, conserving splenic vessels, was performed on a patient with minimally invasive carcinoma derived from IPMN. No deaths or morbidity occurred. All patients were placed on pancreatic enzyme replacement therapy and given a daily dose of insulin of approximately 30 U. Complete professional rehabiliation was achieved in all patients. All patients except one gained weight, and the hemoglobin A1c (HbA1c) levels have been maintained at around 7%.

Conclusions: DPTP is a useful organ-preserving procedure for low-grade malignant neoplasms spreading within the entire pancreas.

P-043

Recent Experiences with Total Pancreatectomy

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Objective: Total pancreatectomy (TP) for pancreatic cancer had been almost abandoned because of its high morbidity and mortality. However, the number of TP is recently increasing because of improved operative techniques and perioperative management. The aim of this study was to evaluate our recent experiences of TP.

Methods: We retrospectively reviewed postoperative courses of 14 patients who underwent TP between 2001 and 2009 at our institution.

Results: There were 7 pancreatic ductal carcinomas, 4 intraductal papillary mucinous neoplasms (IPMNs), one bile duct cancer, one neuroendocrine tumor and one multiple pancreatic metastasis from renal cancer. Indications for TP were multifocal lesions in the entire gland in 8 patients, previous major pancreatectomy in 4, severe pancreatitis in one, and preexistent hypoplasia of distal pancreas in the remaining one. TP had been performed in 3 patients before 2006, 2 of whom had hospital death caused by hypoglycemia and massive portal vein thromboembolism. In contrast, there has been no fatal complication after TP during recent 3 years. Of 11 patients who underwent TP between 2007 and 2009, 8 patients have been alive to date without any sign of recurrence. All of them are suffering from pancreatic diabetes, but have been treated by diabetic physicians at the outpatient clinic with sufficient nutrient status and quality of life. The other 3 of 11 patients died of recurrent pancreatic cancer but not of TP-related complication.

Conclusions: TP seems to become an effective procedure for cure in selected patients in collaboration with diabetic physicians. TP should be considered when oncological curability can be expected.

P-044

Pancreaticoduodenectomy with a Duct-to-mucosa Anastomosis of Pancreaticojejunostomy With or Without a Stenting Tube Was No Different for Pancreatic Cancer

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Background: The short-term complications after pancreaticoduodenectomy have been gradually decreasing, and recent improvements of operative technique and perioperative management have resulted in an increase in the number of long term survivors after pancreaticoduodenectomy .The aim was to evaluate short-term complications of pancreaticoduodenectomy with a duct-to-mucosa anastomosis of pancreaticojejunostomy without a stenting tube for pancreatic cancer.

Methods: A retrospective study was conducted on a series of 61 patients with pancreatic cancer who underwent PD with duct-to-mucosa pancreaticojejunostomies (but not associated with hepatic resections) from 1990 to 2009. They were classified into two groups of duct-to-mucosa anastomosis of pancreaticojejunostomy with a stenting tube (group A: 16) and without a stenting tube (group B: 45). Outcomes, including complications are reported.

Results: The following results were found for group A: morbidity 18.8%, pancreatic fistula (gradeA) 6.3%, delayed gastric emptying 6.3%, leakage of gastrointestinal anastomosis 6.3%. In group B, there are morbidity 13.3%, pancreatic fistula 0%, delayed gastric emptying 4.4%, biliary fistula 2.2%, intra-abdominal abscess 2.2%, liver disfunction 2.2%, portal vein thrombus 2.2%. All results were non-significant.

Conclusion: Pancreaticoduodenectomy with a duct-to-mucosa anastomosis of pancreaticojejunostomy with or without a stenting tube was no different for pancreatic cancer.

P-045

Prognostic Factors in Resected Carcinoma of the Pancreatic Body and Tail

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Background: Invasive ductal carcinoma in the body and tail of the pancreas is less frequent than pancreatic head carcinoma and its prognosis is worse, because curative resection is difficult and long-term survival is rare. The aim of this study was to evaluate the prognostic significance of clinicopathological factors in patients with resected invasive ductal carcinoma of the body and tail of the pancreas using multivariate analysis.

Methods: We reviewed the medical records of 47 patients with surgically treated invasive ductal carcinoma of the body and tail of

the pancreas between 1985 and 2009. Age, gender, tumor location, diameter, serosal invasion (s), retroperitoneal invasion (rp), portal venous invasion (pv), arterial invasion (a), nervous plexus invasion (pl), lymph node metastasis (n), pancreatic cut end margin (pcm), dissected peripancreatic tissue margin (dpm), residual tumor (R), histological differentiation, tumor infiltration (INF), lymphatic invasion (ly), venous invasion (v), nervous invasion (ne), and chemotherapy were investigated. The accumulative survival rates were calculated using the Kaplan-Meier method. Multivariate analysis was used to determine significant prognostic factors.

Results: The 47 patients (29 males, 18 females) reviewed had a mean age of 65.6 years old (41–83). The total 50% mean survival time was 17 months, and the five-year survival rate was 24%. Five factors, including histological differentiation ($p=0.0076$), ne ($p=0.0173$), s ($p=0.0436$), a ($p<0.0001$), pl ($p=0.0006$), dpm ($p=0.0011$), n ($p=0.0040$) were analyzed as being significant by univariate analysis. Those seven factors were reanalyzed by multivariate analysis. Two factors, a ($p=0.0268$, hazard ratio $=1.349$), and pl ($p=0.0143$, hazard ratio $=1.602$) were found to be the significant prognostic factors.

Conclusion: Our results showed arterial invasion and pancreatic nervous plexus invasion to be the significant prognostic factors for resected invasive ductal carcinoma in the body and tail of the pancreas.

P-046

Surgical Implication of Micrometastasis for Pancreatic Cancer

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Objectives: The clinical significance of micrometastasis to regional lymph nodes for pancreas cancer is controversial in patients who underwent curative resection.

Methods: Nine of 42 patients who underwent macroscopically curative resection of pancreatic head cancer were found to have pN(-) by routine examination. Complete serial section examination of the resected specimens was done to detect micrometastasis in these 9 patients.

Results: A total of 16,505 sections were examined by immunohistochemistry or hematoxylin and eosin staining. Micrometastases were identified in 7 (78%) of 9 patients and 17 (3.6%) of 474 lymph nodes. All micrometastases were found in the pancreas head area. However, the frequency of micrometastases around superior mesenteric artery was 44%. There were no micrometastases to para-aortic nodes. There was a tendency that the patients with micrometastases showed better survival than those with overt nodal involvement ($P=0.053$). Micrometastasis did not provide the poor prognostic factor in patients who underwent optimal regional lymphadenectomy.

Conclusions: Even in overtly pN(-) pancreatic cancer, micrometastases occur high frequently (78%) and widely, including the nodes around superior mesenteric artery. These results provide important pathological information when we consider the preoperative, perioperative, and postoperative strategies, even when patients seem to have no nodal involvement by preoperative examinations.

Poster 08 Pancreatic Cancer Case Report 1

P-047

Symptomatic Early Stage Pancreatic Cancer (Three Case Reports)

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We experienced three cases of early clinical stage pancreatic cancer (UICC stage 1A), acute pancreatitis is associated with these three cases.

Case1: 68 y.o. female with acute onset of abdominal pain was referred to our hospital. A pancreatic cyst was seen in the body of the pancreas although there was no evidence of a solid mass in the CT. Laboratory data showed elevation of CA19-9 and ERCP revealed a narrowing of the main pancreatic duct (MPD) and cytology of pancreatic juice confirmed an adenocarcinoma.

Case 2: A 61 year-old male was hospitalized for pancreatitis. Segmental stenosis of MPD was found on MRCP, hypoechoic mass found on EUS. There was difficult to differential diagnosis for as a cancer mass in CT. Cytological diagnosis of pancreatic juice was suspicious pancreatic adenocarcinoma.

Case 3: A 66 y.o. male was referred to us with abdominal pain and worsening of diabetes mellitus and dilated MPD on the US scan. There was small low density area in pancreas body next to the cyst on the CT, and CA19-9 was slightly elevated. ERCP revealed segmental narrowing of the MPD and cytology confirmed an adenocarcinoma.

In conclusion, all three patients presented with symptons related to pancreatitis. It is difficult to distinguish MPD stricture of pancreatic cancer and pancreatitis. Thus, it appears to be necessary to perform pancreatography and cytology, which may make it possible to diagnose pancreatic cancer at early stage. Furthermore pancreatitis and worsening of diabetes were seen in early stage pancreatic carcinoma. We will present clinicopathological features of asymptomatic and symptomatic early stage pancreatic cancer.

P-048

Pancreatic Mucinous Noncystic Carcinoma, a Rare Subtype of Adenocarcinoma of the Pancreas. A Case Report

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Context: Primary mucinous carcinoma is a rare subtype of adenocarcinoma of the pancreas characterized by production of extensive mucin. Although mucinous carcinoma of other organs such as the

breast, colon, and prostate have been studied extensively, there are only a limited number of reported accounts on mucinous carcinoma of the pancreas.

Case Report: Here we report a case of a mucinous carcinoma of the pancreas in a 66-year-old woman. She presented with weight loss and diabetes which was getting worse. An abdominal ultrasonography demonstrated dilatation of the main pancreatic duct and the common bile duct. An contrast-enhanced computerized tomographic scan demonstrated a large 10-cm mass in the head of the pancreas that involved the duodenum. There was also marked dilatation of the biliary tree, including the intrahepatic ductal system as well as the common bile duct. No radiologic evidence of major vascular or artery invasion by the pancreatic mass was noted. An upper gastrointestinal endoscopic study showed a large cauliflower-shaped tumor exposed in the lumen of the duodenum as well as large volumes of mucin. Mucinous adenocarcinoma was strongly suspect by a biopsy of the tumor. From these findings, we perfomed an operation, subtotal stomach preserving pancreaticoduodenectomy, with the most likely diagnosis of pancreatic mucinous carcinoma or invasive carcinoma derived from a intraductal papillary mucinous neoplasms. Histopathological study of the resected specimen revealed scattered loosely cohesive groups of epithelium and cells with large cytoplasmic vacuoles in a mucinous background, and thus pancreatic mucinous carcinoma was diagnosed.

P-049

A Case of Young Aged Mucinous Cystadenocarcinoma of Pancreas with Osteoclast Like Giant Cell

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The patient was a 27-years-old Japanese woman with abdominal distention and no abdominal pain. She was referred to our institute for farther examination of a giant cystic tumor of the left upper abdomen, suspected of a pancreatic solid pseudopapillary tumor. Her complaint was distention at the upper abdomen without tenderness.Her serum level of CA199 was elevated at 87 U/ml, while CEA and DUPAN-2 was normal range. A computed tomography showed a 12-cm mulutilocular cystic tumor at the tail of the pancreas . A magnetic resonance imaging scan (MRI) of abdomen demonstrated a cystic tumor with various degeneration and hemorrhagic content. The solid compornent in this tumor was stained in dynamic MRI. A distal pancreatectomy accompanied with splenectomy was performed. Macroscopically, the tumor of the pancreas measured 11 × 7.7 × 7.5 cm, was the multilocular cystic tumor filled with degeneration and hemorrhage on cut section. The histological pattern was characterized by mucin-producting columnar ephithelium with ovarian-like mesenchymal stroma. Minimal invasion to its capsule was existed. In some areas, sarcomatous change and osteoclast like giant cells were observed. The pathological diagnosis was minimal invasive mucinous cystadenocarcinoma of the pancreas with osteoclast like giant cells. Young aged mucinous cystadenocarcinoma of pancreas with osteoclast like giant cell is vary rare. 15 cases including ths case of mucinous cystadenocarcinoma of pancreas with osteoclast like giant cell were reported. Ovarian like storoma was pathologically proved in only 5 cases of 15 cases.

P-050

A Case of Undifferentiated Carcinoma with Osteoclast-like Giant Cell of the Pancreas in Whom a Ductal Adenocarcinoma Was Detected in Theremnant Pancreas as a Recurrence

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An undifferentiated carcinoma with osteoclast-like giant cells is a veryrare neoplasm of the pancreas comprising less than 1% of all exocrine pancreatic tumors. We report a resected case of an undifferentiated carcinoma with osteoclast-like giant cells of the pancreas, in whom a ductal adenocarcinoma in the remnant pancreas was removed three years after the first surgery. A 37-year-old woman presented with epigastralgia and was hospitalized.An abdominal ultrasonography and computed tomography showed a well-demarcated mass with a cystic component 4 cm in maximum diameter at the pancreatic head. The patient underwent a pylorus-preserving pancreaticoduodenectomy based on a preoperative diagnosis of a mucinous cystic neoplasm.The tumor grossly contained hemorrhage and necrosis inside, and osteoclast-like giant cells were histopathologically detected in the tumor. The final pathological diagnosis was an undifferentiated carcinoma with osteoclast-like giant cells of the pancreas. Postoperatively, her tumor markers elevated 3 years after the surgery, and a tumor 2 cm in diameter was detected at the remnant pancreas. The clinical diagnosis was a recurrence, and the second surgery was performed based on the localized mass in the remnant pancreas and her positive consent of the second surgery. We performed a partial resection of the remnant pancreas. Histopathologically the recurrent tumor consisted of a poorly differentiated tubular adenocarcinoma. A retrospective pathological analysis showed a component of a poorly differentiated tubular adenocarcinoma in the first osteoclast-like giant cell tumor. Therefore, the final diagnosis was not metachronous multiple carcinoma but a recurrence at the remnant pancreas possibily originated from vascular, lymphatic, or neurogenic metastasis. This case seems important to consider the histogenetic derivation and pathogenesis of the osteoclast-like giant cell tumor of the pancreas.

P-051

Pancreatic Adenosquamous Carcinoma Presenting as Splenic Rupture

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Pancreatic adenosquamous carcinoma is a rare variant of ductal adenocarcinoma, representing only 1–4% of exocrine pancreatic malignancies. The common presenting clinical symptoms of this tumor resemble those of pancreatic ductal adenocarcinoma, including abdominal pain, weight loss, jaundice, and anorexia. Splenic rupture is a very rare presenting sign of pancreatic malignancy, and to the best of our knowledge only 6 cases have been reported previously. Herein, we report a case of pancreatic adenosquamous carcinoma presenting as splenic rupture, and the literature is reviewed in order to define the characteristics of this pathology.

A 58-year-old woman presented left upper quadrant pain with sudden onset. On physical examination revealed presence of shock status. Abdominal computed tomography revealed splenomegaly with a huge mass inside the spleen, and massive fluid collection in the abdominal cavity. After splenic artery embolization, laparotomy was performed. The operative finding revealed intra-abdominal hemorrhage, and rupture of the lower pole of the spleen. Furthermore, a palpable solid mass was observed at the splenic hilum, and distal pancreatectomy with splenectomy was performed. Macroscopic finding revealed pancreatic tail tumor was found at the splenic hilum directly invading the splenic parenchyma. Microscopic examination showed that the tumor comprised squamous cell carcinoma. Furthermore, old and new thrombi were observed inside splenic vessels. These findings were considered to represent invasion of pancreatic adenosquamous carcinoma to the spleen, and rupture of the spleen was attributed to splenic necrosis resulting from cancer invasion and splenic vein obstruction.

P-052

Peutz-jeghers Syndrome Developing Pancreatic Carcinoma in Two of Three Siblings

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We report a case of Peutz-Jeghers synderome (PJS) developing pancreatic carcinoma in two of three siblings (older brother and sister). They had typical features of PJS: family history of autosomal dominant inheritance, mucocutaneous hyperpigmentation, and numerous hamartomatous polyps in the large and small bowel.

An older brother developed locally advanced pancreatic head cancer (poorly differentiated tubular adenocarcinoma) and underwent intraoperative radiotherapy in 46 years old. However, he died of exacerbation of the cancer 1 year later.

A sister developed 3-cm-sized pancreatic tail cancer (poorly differentiated tubular adenocarcinoma) and underwent distal pancreatectomy in 57 years old. At present, she is alive 3 months after the operation.

Patients with PJS have a greater risk of developing several carcinomas at a relatively younger age. Frequent associated carcinomas are gastrointestinal, gynecologic, lung, breast and pancreas cancer. They have a greater than 132-fold increased risk of developing pancreatic cancer and the lifetime risk of the pancreas cancer is about 36 percent by age 60. Approximately 5 to 10 percent of individuals with pancreatic cancer report a history of pancreatic cancer in a close family member. PJS is one of the several known genetic syndromes which have been shown to be associated with an increased risk of pancreatic cancer.

We report a case of PJS developing pancreatic carcinoma in two siblings. Clinicians should collect detailed family history information, pay attention to associated malignancies,and perform periodical screening study in managing PIS patients.

P-053

Adenocarcinoma of the Pancreas Complicated by Obstructive Jaundice in Pregnancy

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Adenocarcinoma of the pancreas in pregnancy remains rare, with few reported cases in the literature. We have experienced a case of a pregnant woman with advanced inoperable adenocarcinoma of the pancreas. A 31-year-old woman at 22 weeks' gestation was admitted to a near hospital with a jaundice. On examination, she was found to be jaundiced, afebrile with minimal right upper quadrant tenderness. Biochemical investigations revealed deranged liver function tests. Abdominal ultrasound revealed common bile duct and intrahepatic duct dilatation. She was then referred to our general hospital for further management. A magnetic resonance cholangio-pancreatography showed intrahepatic, common bile duct and pancreatic duct dilatation down to the head of pancreas. Enhanced multidetector-computed tomography showed an approximately 3.5 cm mass in the head of pancreas. The mass had an unclear border and a poor effect of enhancement with infiltration of major vessels, such as portal vein, inferior mesenteric vein and superior mesenteric artery. In addition, several small nodules were scattered in bilateral lung fields. To confirmed histopathological diagnosis, percutaneous pancreatic biopsy was performed. We clinically diagnosed as advanced pancreas cancer with lung metastases. Percutaneous transhepatic bile duct drainage was performed for treatment of jaundice. A fetus development was observed by pelvic ultrasound. To optimize the survival rates and developmental disability of the fetus and prognosis of mother, the termination of the pregnancy was scheduled at 28 weeks of gestation or later. A female was delivered by nature means at 30 weeks of gesta-

tion. An endoscopic metallic stent was set across the biliary stricture and a systematic chemotherapy by gemcitabine (1000mg/m2) with or without S-1 (100mg/day) was started on postparturtion day11. The chemotherapy had gone on until terminal phase.

Poster 09 IPMN Diagnosis, Treatment

P-054

Reevaluation of International Consensus Guidelines for Management of IPMN from Analyzing Resected Patients with IPMN

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Aim: Our objective was to reevaluate the international consensus guidelines for management of IPMN from analysis of resected patients with IPMN in our hospital.

Methods: Forty resected patients with IPMN between 2000 and 2009 were examined and seventeen parameters (age, gender, abdominal pain, other tumors, history of pancreatitis, jaundice, DM, type of IPMN, location, mural nodule, patulous papilla, tumor size, cyst size, size of the main pancreatic duct, CEA, CA19-9, serum amylase) were investigated for their relation to malignancy.

Results: 28 males and 12 females with IMPN and a mean age of 67.3 years (ranging from 51 to 79 years) were surgically treated at Hyogo Cancer Center (TP 3, PD 24, DP 13). IMPN was classified into three types, main duct type (MD, n=16), mixed type (M, n=12) and branch duct type (BD, n=12), consisting of 19 malignant tumors and 21 benign tumors. Average size of main pancreatic duct was 5.7mm (malignancy 6.1mm vs. benign 5.4mm) and average size of cyst was 32.1mm (malignant 33.7mm vs. benign 30.7mm). In MD-type, 12 of 16 cases were malignant, while 3/12 in M-type and 4/12 in BD-type were malignant. In BD-type IPMN with more than 30mm of cyst in size, only two of 5 were malignant, although all of them had mural nodule.

Conclusion: MD-type IPMN was indicated for surgical resection. On the other hand, in BD-type and M-type IPMNs several factors including mural nodule were considered for surgery.

P-055

The International Consensus Guidelines under Validation for the Treatment of Branch Duct Type Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Backgrounds: Although 6–46% of branch duct type intraductal papillary mucinous neoplasms (BD-IPMN) could develop malignancy, the natural history of BD-IPMN has not been established yet. Because most study variably defined BD-IPMN characteristics, it is inappropriate to suggest definitive guidelines for management.

To clear this ambiguity, in 2006 international consensus guidelines for management of IPMN of the pancreas was proposed. By the guidelines, the patients of BD-IPMN are recommended for resection if they have 1) symptoms related to IPMN, 2) cyst size more than 30 mm, 3) mural nodule, 4) dilated pancreatic duct, and positive cytology. Despites low specificity and positive predictive value, several studies after that validated these guidelines.

Aim: The aim of this study was to define the valuable features of BD-IPMN in aspect of treatment strategy and to establish predictors of malignancy. In addition, predictive value of international consensus guidelines was reevaluated.

Patients and Methods: From May 2000 to July 2009, a total of 135 patients with BD-IPMN were included. Clinical features, radiologic results and surgical pathology were analyzed retrospectively to determine malignant predictors of BD-IPMN.

Results: Maximal diameter of pancreatic duct and mural nodule size measured by endoscopic ultrasonography (EUS) were valuable predictors of malignancy in multivariate analysis. International consensus guidelines showed 100.0% sensitivity, 24.2% specificity and 14.8% positive predictive value of predicting malignancy if applied to our cohort. Two predictors, such as dilated pancreatic duct more than 5.0 mm or mural nodule size more than 6.0 mm increased the malignant predictive power if the values were defined further and applied to international consensus guidelines (p=0.015 & 0.010).

Conclusions: In regard of surgical indication, international consensus guidelines of BD-IPMN showed low positive predictive value of malignancy. Dilated pancreatic duct and mural nodule size measured by EUS seems to be complementary to International consensus guidelines.

P-056

Clinicopatholical Analysis of Intraductal Papillary-mucinous Neoplasms (IPMNs) of The Pancreas

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Aims: Intraductal papillary-mucinous neoplasms (IPMNs) of the pancreas are known as a favorable pancreatic tumor. However some IPMN progress to invasive cancer. We studied IPMNs clinicopathologically and attempted to clarify rate of invasive IPMN.

Methods: Surgically resected 106 IPMNs at Juntendo University Hospital from July, 1984 to November, 2008 were investigated histologically. WHO calsification was selected for histological criteria.

Results: The 27 patients had adenoma with slight atypia, 6 patients had borderline tumor and 37 patients had malignant tumor (6 evere dysplasia/CIS and 31 invasive tumor).

Conclusions: 29%(31 invasive tumors) of IPMN were invasive cancer and should be resected. 59%(63 adenomas) of IPMN and 5.5%(6 borderline tumor) could be observed carefully.

P-057

Concomitant Cancer and Its Prognosis in Patients with Branch Duct Type Intraductal-papillary Mucinous Neoplasms of the Pancreas

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Aim: To examine the coexistence of metachronous and synchronous cancer in branch duct IPMN.

Methods: We reviewed records of 145 patients with branch duct IPMN between January 1991 and April 2008 and assessed the relationship between IPMN and intra- or extra-pancreatic carcinoma and the outcome of IPMN.

Results: The mean observation period was 55.9 mo. Among the 145 patients, the frequency of extra-pancreatic cancer was 29.0%. The frequency of gastric cancer, colon cancer, breast cancer, and pancreatic cancer were 25.5%, 15.7%, 13.7%, 9.8%, respectively. In the end, 20 (13.8%) patients died. The cause of death was extra-pancreatic carcinoma in 40%, pancreatic cancer in 25%, IPMN per se in 20%, and benign disease in 15% of the patients.

Conclusion: The prognosis for IPMN depends not on the IPMN per se but on the presence of intra or extra pancreatic cancer.

P-058

Long-term Follow-up of Branch Duct Intraductal Papillary Mucinous Neoplasm Without Suspected Malignant Potential

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Background: Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is believed to be slow-growing neoplasm with a good prognosis, thus most patients with IPMN, particularly branch duct IPMN (BD-IPMN), are conservatively followed. Another important feature of IPMN is the high frequency of malignant extrapancreatic neoplasms. This study aimed to examine the natural history of BD-IPMN without suspected malignant potential and to estimate the frequency of malignant extrapancreatic neoplasms during follow-up.

Methods: The study included 77 patients with Bd-IPMN without a predictive factor for malignancy (cyst size >30 mm, presence of intramural nodules, or dilated main pancreatic duct) on initial examination. All patients were conservatively followed by imaging modalities over 12 months.

Results: The mean follow-up period was 37.2 months. During follow-up, 7 (9.1%) of 77 patients showed new predictive factors for malignancy as follows: cyst size >30 mm in 4 and the appearance of intramural nodules in 3. 3 of these patients underwent surgical resection; only one patient had malignancy (minimally invasive cancer). On the other hand, 5 (6.5%) of 77 patients were found to have malignant extrapancreatic neoplasms, including gastric cancer (n=2), colorectal cancer (n=1), gallbladder cancer (n=1), and prostatic cancer (n=1).

Conclusion: In followed-up patients with BD-IPMN, considerable attention should be paid not only to the carcinogenesis of BD-IPMN itself but also to the possible occurrence of extrapancreatic malignancies.

P-059

Long-term Follow Up Results of Surgical Resection for Patients with Intraductal Papillary Mucinous Tumors of Pancreas

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Objective: The objective of this study was evaluate the clinocopathological factors, surgical methods and long-term survival in patients with intraductal papillary mucinous tumors of pancreas (IPMT).

Methods: The study included 34 patients with IPMT who pathologically classified the following types:intraductal papillary mucinous adenocarcinoma (IPMC) in 18 (53%), and intraductal papillary mucinous adenoma (IPMA) in 16 (47%). Our 34 IPMT cases are subclassified into three types: the main duct type in 4 (12%), the branch duct type in 28 (82%), and the mixed type in 2 (6%). We analyzed correla-

tion with clinocopathological factors and long term follow up results of these patients retrospectively.

Results: The average 5, 10, 15 and 20-years survival rate was 97/88/88/88% in all IPMT patients of surgical resections. There were no significant difference in 5, 10, 15 and 20-years survival rates for patients with IPMC and IPMA (100/100/100/100% and 94/84/84/84%, respectively) ($p=0.71$). Fifty four percentage of Branch duct type IPMT and 50% of main and mixed duct type IPMT are malignancy. There was significant difference in the cystic diameter of IPMA (3.6 ± 0.7mm) and IPMC (5.6 ± 0.7mm) ($p=0.04$). Partial pancreatectomy was selected in 4 (25%) of IPMA, and surgical margins are assessed intraoperatively in all IPMTs. Tumor recurrence was noticed in one patient (6%) among 16 operated IPMA and in three patients (17%) among 18 operated IPMC. Extra-pancreatic malignancy was found in two IPMA (13%) and seven IPMC (39%).

Conclusions: The long-term follow up results of surgical resection of IPMC has better prognosis than pancreas cancer. The surgeon's close follow up is clearly needed to detect extra-pancreatic tumor.

P-060

A Case of Total Resection of the Residual Pancreas Due to the Recurrence of IPMN After Distal Pancreatectomy

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The patient was a 60-year-old man who had undergone distal pancreatectomy with splenectomy under a diagnosis of IPMN at another hospital 9 years earlier. In June 2009, he visited a local clinic because of upper abdominal pain, and was noted to have an elevated amylase level of 1,914 IU/L. Abdominal ultrasound, CT, and MRI revealed a dilated main pancreatic duct (about 20 mm in diameter) in the pancreatic head. The recurrence of IPMN was suspected, and he was admitted to our department for further evaluation and treatment. ERCP demonstrated a gaping major pancreatic papilla, dilated main pancreatic duct of 20 mm in diameter, and filling defect due to mucin. Pancreatic juice cytology revealed only clusters of mucus-containing cells. These findings led to a diagnosis of IPMN recurrence, and he underwent total resection of the residual pancreas. Histopathological examination showed mucus retention in the dilated main pancreatic duct lined by high columnar epithelium with areas of high-grade dysplasia. On immunostaining, the tumor was MUC1(-), MUC2(+), MUC5AC(+), and MUC6(-). These features led to a diagnosis of IPMN.

P-061

A Nomogram for Predicting the Probability of Carcinoma in Patients with Intraductal Papillary-mucinous Neoplasm – Internal and External Validity –

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Background: The objective of the current study was to develop a model for predicting the presence of carcinoma in patients with intraductal papillary mucinous neoplasm (IPMN) using clinical and laboratory data.

Methods: Data were collected on 81 patients with IPMN who underwent a pancreatic resection between 1989 and 2008 at Aichi Cancer Center Hospital. Variables analyzed included age, sex, laboratory findings (serum amylase, carcinoembryonic antigen and carcinoma 19-9 level), pancreatic juice cytology and imaging studies. Factors associated with the presence of carcinoma were evaluated by univariate and multivariate logistic regression analysis. A nomogram to predict carcinoma was construted and validated internally using the area under the receiver operating characteristic curve (AUC). The nomogram was then validated with an external data set. External validity was assessed using an external data set contributed by Center for Gastroenterology, Teine Keijin-kai Hospital. 30 patients who received a meticulous preoperative examination were analyzed.

Results: Among the 81 patients with IPMNs, 34 (42%) had malignant tumors (non-invasive carcinoma in 22 and invasive carcinoma in 12) and 47 (58%) had adenoma. On multivariate analysis, existing carcinoma was associated with female sex, main pancreatic duct IPMN, nodule size, and pancreatic juice cytology. Based on these variables, a predictive nomogram was developed. AUC for the model was 0.903. The sensitivity and specificity of the model were 94% and 72%, respectively, in the validation study for which the predictive probability of >25% was used to indicate the presence of carcinoma. Applied to another data set, the external validated AUC was 0.701, and the sensitivity and specificity were 88% and 50%, respectively.

Conclusion: The nomogram has high diagnostic predictability for carcinoma in patients with IPMNs.

P-062

Epidemiology of Intraductal Papillary Mucinous Neoplasms of the Pancreas: Gender Differences between 3 Geographic Regions

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Patients with IPMN are being reported in increasing numbers worldwide. The purpose of this study is to examine the demographic variables of age and gender of patients with IPMN from USA, Europe, and Asia.

Methods: A Pubmed search for publications related to IPMN from January 1991 to December 2009 yielded 335 articles. Of these, we selected 35 studies where >30 patients were reported, and where, in addition to age and gender being described, there was surgical pathological confirmation of IPMN. Ten studies were from the USA, 13 studies were from Japan, 5 from Korea, 1 from Taiwan, and the remaining 6 from France and Italy. Patients were categorized as having main duct (or combined) IPMN, branch duct IPMN, or non-classified IPMN.

Results: Of 4056 patients, 489 had main duct IPMN, 854 branch duct IPMN and 2713 were not classified; 2366 patients were from Asia, 1151 from the USA, and 539 from Europe. The male-to-female ratios of main duct IPMN were 3, 1.1, and 1.5, respectively in Asia, USA, and Europe ($P<0.001$); for branch duct IPMN the respective numbers were 1.8, 0.76, and 0.66 ($P<0.001$), and for non-classified IPMN 2.1, 1.2, and 1.3, respectively ($P<0.001$). No differences were found when comparing USA and Europe. Average age ranged from 62.3 to 67.3 years, with no statistical difference between groups.

Conclusion: While age at diagnosis is similar, there is marked geographic variation in the gender distribution of IPMN, with a significantly higher male predominance of both main and branch type IPMN in Asia compared to the USA and Europe.

Poster 10 Cystic Pancreatic Tumor 1

P-063

Intraductal Papillary Mucinous Neoplasm That Was Difficult to Differentiate from a Mucinous Cystic Neoplasm. Report of Two Cases

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Intraductal papillary mucinous neoplasms (IPMNs) are characterized by cystic dilatation of pancreatic ducts, whereas mucinous cystic neoplasms (MCNs) are large septated cysts with no connection to the ductal system and are characterized by the presence of an ovarian-type stroma (OS) and mucin. We report two cases of IPMN located in the body or tail of the pancreas in which it was difficult to make the differential diagnosis from MCN.

Case 1: A 61-year-old woman was admitted because a cystic lesion in the tail of the pancreas had increased in size. A CT scan had shown a unilocular cyst that measured over 35 mm in diameter and had a thick capsule. Endoscopic examination showed no communications between the cystic lesion and the pancreatic duct, no mucin extrusion from the ampulla of Vater, no dilation of the pancreatic duct, and no solid lesions in the cyst. A diagnosis of MCN was made, and distal pancreatectomy was performed. Microscopic examination revealed that the cystic lesion contained a gastric-type IPMN, and no OS was detected.

Case 2: A-65-year old woman was admitted because two cystic lesions over 40 cm in diameter had been detected. One multilocular cyst was located in the tail of the pancreas, and communicated with the pancreatic duct, whereas the other unilocular cyst was located in the body of the pancreas, and had a thick capsule, and it did not communicate with the pancreatic duct. We diagnosed the lesion in the body as MCN and the lesion in the tail as IPMN. Histological examination of both cystic lesions revealed branched-type IPMN.

Conclusion: The differential diagnosis between IPMN and MCN should be made carefully in women with a unilocular cystic lesion that has no communication with the pancreatic duct.

P-064

A Resected Case of Small Mucinous Cystadenoma Communicating with Main Pancreatic Duct

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A 77-year-old female was pointed out a tumorous lesion of the body of the pancreas on abdominal CT. Pancreatography was not informative because of unsuccessful canulation into main pancreatic duct (MPD). Abdominal ultrasoundsonography showed septal structure in the tumorous lesion. Distal pancreatectomy was performed. Gross section of the tumorous lesion showed multi-cystic or -locular structure,1.8 x 1.5cm in size, in its largest dimension,communicating with MPD. A capsule-like structure was seen around the lesion. Histologically each cystic/locular lesion was lined by mucinous epithelium with minimal atypia. MPD communicated with the lesion. There was the proliferation of spindle cells immunohistochemically positive for estrogen and progesterone receptors, corresponding to so-called ovarian-like stroma (OLS). Pathological diagnosis was mucinous cystadenoma. Microscopical serial sections showed protrusive growth of OLS into the lumen of the MPD, resulting in stenosis but presented no destruction of the duct. Ductal stenosis in mucinous cystadenoma may be caused by growth of ovarian-like stroma.

P-065

A Case of Acute Pancreatitis Due to Intracystic Hemorrhage of Mucinous Cystadenocarcinoma of Pancreas

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A-31-year-old woman was admitted to our hospital because of sudden left hypochondrium and left back pain. Pancreas enzymes including amylase, lipase and trypsin were elevated and an abdominal computed tomography (CT) scan showed peripancreatic fat stranding. Abdominal Ultrasonography, CT and magnetic resonance imaging (MRI) revealed an encapsulated multilocular cystic mass 5 cm in diameter in the pancreatic tail and one of the cystic lesions with intracystic hemorrhage. We diagnosed pancreatitis due to cystic tumor of pancreas and treated it, and left hypochondrium and left back pain disappeared. Serum level of amylase was normalized and she was discharged from the hospital. We planed distal pancreatectomy because we suspected the cystic lesion was mucinous cystic neoplasm. Ten days later, she was rehospitalized because of reactivation of panceatitis. We treated pancreatitis again, and distal pancreatectomy was performed. Histological examination revealed mucinous cystadenocarcinoma of pancreas with ovarian-type stroma. To our knowledge this is rare case of acute abdomen due to pancreatitis that follows intracystic hemorrhage of mucinous cystadenocarcinoma of pancreas.

P-066

A Case of Intraductal Papillary Mucinous Carcinoma of the Pancreas Penetrating to the Duodenum

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A 74-year-old woman was admitted to our hospital complaining of back pain. An enhanced computed tomography (CT) showed swelling of the pancreas head and dilatation of the main pancreatic duct. Duodenal endoscopy revealed the presence of a fistula between the main pancreatic duct and the duodenum. Endoscopic retrograde pancreatography (ERP) through the fistula showed a filling defect, 1 cm in diameter, in the main pancreatic duct. Per oral pancreatoscopy showed a papillary tumor in the main pancreatic duct. The preoperative diagnosis was an intraductal papillary mucinous neoplasm (IPMN) of the pancreas head with penetration to the duodenum. Imaging modalities, CT, ERP, and intraductal ultrasonography (IDUS) showed severe atrophy of the pancreas tail and suggested that the papillary tumor diffusely spreaded in the main pancreatic duct with mucosal extension from the head to the body of the pancreas. She underwent pylorus-preserving, spleen-preserving total pancreatectomy with D2 lymph node dissection. Resected specimens demonstrated the presence of mucin producing papillary tumor in the main pancreatic duct and penetration to the duodenum. Microscopic examination showed no lymph node metastasis, however the main tumor in the main pancreatic duct invaded to the duodenum nearby the ampulla of Vater. The final pathological diagnosis was invasive intraductal papillary mucinous carcinoma (main duct type). IPMN with penetration to the other organs are rare and we herein report our case with some discussion using the reported literatures.

P-067

A Case of Xanthogranulomatous Pancreatitis

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Xanthogranulomatous inflammation is characterized histologically by clumping of foam macrophages and infiltration on inflammatory cells. Xanthogranulomatous cholecystitis is well documented in many reports, and is known to mimic carcinoma on imaging study. However, xanthogranulomatous pancreatitis is very rare and clinicopathological features are not enough described. We report a case of xanthogranulomatous pancreatitis with a cyatic lesion of the pancreas. A 55-year-old man was referred to our hospital with a complaining of upper abdominal pain. On admission, physical examination revealed no abnormal findings. Laboratory data including tumor marker such as CEA, CA19-9, DUPAN-2, and Span-1 also revealed no significant abnormal findings. Gastroduodenal fiberscopy showed gastric cancer at the angle of stomach, and biopsy specimen showed poorly diffentiated adenocarcinoma. Abdominal computed tomography and endoscopic ultrasoundscopy showed the cystic tumor of the pancreas head. We could not deny the malignancy of the pancreas, pancreaticoduodenectomy was chosen for cure. Operative findings showed gastric cancer and the mass lesion of the pancreas head which contained dark serous fluid. Pathological findings of the pancreas head showed xanthogranulomatous inflammation with numerous foamy histiocytes without malignant findings. His post operative course was well, and he has remained well. Herein we report a rare case of xanthogranulomatous pancreatitis which was difficult to differentiate from pancreas cystic tumor, with a review of the literatures.

Poster 11 Other Pancreatic Tumor

P-068

Eleven Cases of Resection Pancreatic Metastases

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Background: Pancreatic metastases occur in very advanced malignancies. These metastases are considered operable only when there are no other metastases or the metastases are limited.

Methods: We have performed eleven resections of pancreatic metastases between 1990 and 2009. We examined their clinico-pathological features.

Results: Five patients suffered from renal cell carcinomas. Other primary tumors were as follows: rectal cancer, colon cancer, lung cancer, thyroid cancer, leiomyosarcoma and hemangiopericytoma. The pancreas was the first metastatic organ in seven cases. Median time from the primary tumor resection to the first recurrence was 9.2 years (0.0–26.1). Median time from the primary tumor resection to the pancreatic metastasis was 11.4 years (0.0–26.1). The average age at pancreatic resection was 61.6 years (39–79). Solitary metastasis of pancreas was found in nine cases. The following operations were performed: four pancreatoduodenectomies, three distal pancreatectomies, two total pancreatectomies, one middle pancreatectomy and one enucleation. Median follow up time was 2.0 years. Recurrences in other organs were detected in six cases after pancreatic surgery. Only one patient had a recurrence in the remnant pancreas.

Conclusion: Pancreatic metastasis is a systemic disease, and new metastatic lesions tend to apper in other organs soon after pancreatic resection. But we sometimes experience a disease controlled case after pancreatic surgery in the slow growing malignancy such as renal cell carcinoma. It will be important to determine the type of cases that would most benefit from surgical resection.

P-069

A Case with a Solitary Pancreatic Metastasis from Leiomyosarcoma of the Back

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In September 2003, a 70-year-old man had undergone surgical resection of the mass, 2cm in diameter, in the back. He had been diagnosed with leiomyosarcoma and had undergone extended resection. He was followed up postoperatively at an outpatient clinic.

In July 2009, he was admitted with bulging in the right groin area and diagnosed as right inguinal hernia. Preoperative abdominal computed tomography scan showed a low density mass, 2cm in diameter, in the body of the pancreas accidentally.

Both ultrasonography and endscopic ultrasonography showed a hypoechoic mass, 2cm in diameter, and revealed the dilatation of the distal main pancreatic duct. An T1-weighted magnetic resonance image showed a mass with low signal intensity, and T2-weighted also showed with low signal intensity. Endscopic retrograde cholangiopancreatography revealed severe stenosis of the main pancreatic duct in the pancreatic body.

Pancreatic body cancer was suspected, therefore distal pancreatectomy with splnectomy was performed. Histological examination revealed the lesion was metastasis of the leiomyosarcoma.

Immunohistochemically, tumor cells were positive for alpha-smooth muscle antigen and desmin, while s-100 protein, c-kit, and CD34 were negative. MIB-1 labeling index using PCNA antibody was 69%. These findings was compatible with that of leiomyosarcoma.

Pancreatic metastais from other primary malignancies are rare, especially from leiomyosarcoma. We present here in an interesting case of metastatic leiomyosarcoma of the pancreas body.

P-070

Ampullary Gangliocytic Paraganglioma with Regional Lymph-node Metastasis

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Gangliocytic paraganglioma (GP) is generally considered to be a benign peri-ampullary lesion, although it is unclear whether it should be classified as a hamartoma or a neoplasm. Here, we present a GP case with lymph-node metastasis. A 16-year-old male complained of exertional dyspnea. His laboratory data revealed a marked anemia, while upper endoscopy revealed a polypoid ampullary tumor without dilatation of the biliary or pancreatic duct. Pancreaticoduodenectomy with lymph-node dissection was performed because there was the swelling of peri-pancreatic lymph-nodes. Histologically, the tumor consisted of three types of cells: epithelioid, gangliocytic, and spindle cells. In addition to these typical components of GP, a distinct glandular component was included. There was frequent invasion of tumor cells into lympho-vascular vessels, and this was associated with lymph-node metastases, although mitotic figures were indistinct. These lymph-node metastases were histologically similar to the primary tumor. Therefore, GP may be a true neoplasm with metastatic capacity. Pre- and intra-operative investigations for lymph-node or distant metastasis are required for adequate resection of this tumor.

P-071

A Case of Solid-pseudopapillary Neoplasm of the Pancreas with Liver Metastasis

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A 63-year-old woman was admitted to our hospital because of a large mass in the pancreas and multiple nodules in the liver. She complained of epigastralgia and right upper quadrant pain. Physical examination revealed no abnormal findings. Blood chemistry tests were within normal range except for elevation of γ-GTP. A serum level of NSE was slightly elevated, but serum levels of CEA, CA19-9, AFP and PIVKA-II were not elevated. Abdominal computed tomography, ultrasonography and endoscopic ultarasonography revealed a large solid and cystic mass in the pancreatic tail and right hepatic lobe. The cytology of pancreatic juice obtained during ERP was class II. The biopsy of the liver tumor led to the suspicion of solid-pseudopapillary neoplasm (SPN). One month after percutaneous transhepatic portal embolization, diatal pancreatectomy and splenectomy were performed. Another month later, right hepatic lobectomy was performed. On histological examination, the neoplastic cells were eosinophilic with round to oval nuclei and presented pseudopapillary pattern. Immunohistochemically, the neoplastic cells were negative for AE1/3, chromogranin-A, trypsin but diffusely expressed vimentin. Furthermore, the neoplastic cells were strongly nuclear positive for beta-catenin. The diagnosis of SPN was confirmed. SPN with liver metastasis is rare, and in this case, radical operation could be performed.

P-072

Granulomatous Inflammation of the Pancreas with Circumportal Pancreas and Retroportal Main Pancreatic Duct: Report of a Case

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We report an incidental combination of two rare pancreatic conditions: granulomatous inflammation of the pancreas and circumportal pancreas with retroportal main pancreatic duct. An 80-year-old woman had back pain from 2008 and developed epigastralgia in December 2009. Ultrasonography showed a hypoechoic area (2 cm in the daimeter) in the neck-body of the pancreas at a neighboring hospital and she was referred to us for the further examination and treatment. Computed tomography showed a mass lesion in the body of the pancreas without enhancement. The mass did not invade into the surrounding tissues. Magnetic resonance imaging demonstrated a mass in the body of the pancreas of low intensity. MRCP displayed obstruction of the main pancreatic duct in the body of the pancreas without dilatation of the main pancreatic duct distal to the mass. Distal pancreatectomy and splenectomy was performed under the tentative diagnosis of pancreatic body cancer. When cutting the pancreas at the neck of the pancreas, the processus uncinatus back of the portal vein was found to be consecutive with the pancreas body (circumportal pancreas) and the main pancreatic duct to be located behind the portal vein (retroportal main pancreatic duct). Histological examination of the mass of the pancreas showed granulomatous inflammation containing epitheliod cells and multinucleated giant cells, suggesting the diagnosis of sarcoidosis of the pancreas. There was no caseous necrosis. The granulomatous lesion was also found in the peripancreatic lymph nodes and the spleen.

Her postoperative course was uneventful and was discharged on POD 22.

We, herein, report an incidental combination of two rare disorders: granulomatous inflammation of the pancreas and circumportal pancreas with retroportal main pancreatic duct

P-073

The Imaging of Intrapancreatic Lipomas

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Aim: Lipomas of the pancreas are rare benign tumors. The purpose of this study is to examine the imaging of intrapancreatic lipomas in three patients.

Patients and Methods: The medical records and imaging studies of three patients with intrapancreatic lipoma in our hospital were reviewed retrospectively. The patients were all men, 71, 72 and 76 years old. In all three cases, the lipoma was revealed incidentally on imaging obtained for other reasons. All three patients had US, enhanced CT, MRI and EUS. We examined these findings of imaging. Histologic confirmation was not obtained in any of the cases. But imaging follow-up was done in all patients.

Results: CT scans showed well-circumscribed pancreatic masses composed of fat in all three patients, representing lipomas. The lipoma measured a maximum of 14mm, 16mm, and 23mm. In all three patients, the lipoma were located in the pancreatic body. MR images of these patients showed the lipomas were high-intense on T1-weighted and T2-weighted MR images. US and EUS images showed low echoic lesions, we needed to differentiate with cystic mass lesions like SCN. No pancreatic or biliary dilatation was noted in any patients. In all patients, a follow-up imaging obtained showed no significant change in the pancreatic lipoma.

Conclusions: CT scans and MRI imagings were diagnostic, showing well-circumscribed masses within the pancreas composed almost entirely of fat. Pancreatic lipomas are rare, usually incidental tumors, and conservative management is often indicated.

Poster 12 Others 1

P-074

Interventional Treatment with Arterial Embolization for Intractable Pancreatic Fistula

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Background: Postoperative pancreatic fistula (POPF) is a most striking complication after pancreatic resection. POPF would lead not only prolongation of the hospital stay but also lethal morbidity or surgical mortality.

Objectives: We report a patient with intractable POPF treated successfully with arterial embolization.

Case Report: A 58-year-old man was referred to our hospital for epigastralgia, high fever and appetite loss. He was a heavy drinker and suffered from repeated pancreatitis with persistent abdominal pain for 4 years. Computed tomography revealed that the pancreatic pseudocyst was widely connected to gastrocolic ligaments, right thoracic cavity, and mediastinum. Based on his general condition and radiological findings, surgical strategy was decided. The operative findings were as follows: hard pancreas was palpable and adhered to portal venous system and mesocolon tightly. Therefore pancreatic body could not be dissected from the peripancreatic tissue. En bloc resection of distal pancreas and pseudocyst were planned, but we were obliged to performed drainage of the pseudocyst and partial resection of pancreas. POPF occurred on next day. Medical treatment could not heal POPF, and MRSA was isolated from the pancreatic fluid. To eliminate pancreatic exocrine function, arterial embolization of splenic artery was performed on 22nd hospital day. Thereafter, POPF disappeared immediately. The patient discharged on the 42nd day. Without abdominal pain, exacerbation of pancreatitis and complicated diabetes, the patient has been painless for 30 months.

Conclusion: Arterial embolization may be considered an effective treatment for patients with persistent POPF fails to respond to conservative management.

P-075

Middle Pancreatectomy with Pancreaticojejunostomy by No Stenting Technique for Pancreatic Neoplasms

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Background: A middle pancreatectomy (MP) is sometimes performed to treat benign or low-grade malignant neoplasms in the neck or body of the pancreas. The aim of MP is to preserve pancreatic exocrine and endocrine function. However, MP requires two times of transaction of the pancreas and reconstruction of the distal pancreatic remnant. Therefore, the pancreatic fistula may occur after MP rather than after pancreatoduodenectomy or distal pancreatectomy. The aim of this study is to evaluate surgical results after MP.

Methods: A group of 60 patients who underwent MP for pancreatic neoplasms between 1991 and 2008 were investigated in this study, retrospectively. Transection of the pancreas was performed by a scalpel and reconstruction of the distal pancreatic remnant was performed by pancreaticojejunostomy.

Results: Intraductal papillary mucinous neoplasm (IPMN) was found in 32 patients (adenomas 17, borderline lesion 7, non-invasive carcinoma 5, invasive carcinoma 3), neuro-endocrine tumor (NET) in 15 patients, serous cystadenoma (SCA) in 10 patients and mucinous cystic adenoma (MCA) in 3 patients. Pancreaticojejunostomy without a stent tube was performed in 49 patients and 11 patients underwent pancreaticojejunostomy with a stent tube. Mortality rate was 0%. According to the ISGPF criterion, no pancreatic fistula with grade C was occurred. Moreover, no pancreatic fistula with grade B at the

pancreaticojejunostomy was occurred. However, pancreatic fistula with grade B at the proximal pancreatic cut end was occurred in 20% of the patients. Pancreatic exocrine and endocrine insufficiencies were not seen.

Conclusions: MP is a safe procedure for the treatment of benign or low-grade malignant neoplasms in the pancreatic neck or body, however, improvement of the treatment of the proximal pancreatic cut end is needed in case of the wide transaction.

P-076

Novel Pancreato-enteric Reconstruction with Bioabsorbable Polymer Sheet and Biocompatible Bond

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Background: Pancreato-enteric reconstruction (PER) often induces severe complications because of pancreatic juice leakage. While many techniques have been developed to prevent this leakage, there has yet to be a standard technique for the PER itself. The leakage of pancreatic juice is mostly caused by pancreatic damage by the suture needle. Our group invented a novel method for PER by sutureless anastomosis using a bioabsorbable polymer sheet (BAPS) and biocompatible bond (BCB). In this study we used animals to investigate whether this method is available for clinical use.

Methods: Hybrid pigs were laparotomized under general anesthesia. The body of the pancreas was divided and the craniad stump was closed by suture. The main pancreatic duct at the caudal stump was cannulated and indwelled with a 24 Fr plastic tube. A BAPS coated with BCB was rolled and fixed around the caudal pancreatic stump into a cylinder and anastomosed to the duodenal side wall without suturing the pancreas. The BCB was composed of a cross-linking agent synthesized from organic acid and a biological polymer confirmed to be of high-strength and low toxicity in clinical use. The BAPS was composed of polylactic acid and polycaprolactone. Ten weeks after the operation, the pigs were re-laparotomized.

Results: All of the operated pigs survived until sacrifice without pancreatic juice leakage or intra-abdominal infection. The BAPS could not be identified on macroscopy. The pancreatic stump was tight on the duodenum. Part of the pancreas was observed in the duodenal lumen. The histological study revealed that the pancreatic stump and duodenal wall were continuous and that the main pancreatic duct opened into the lumen of the duodenum in spite of the profuse infiltration of inflammatory cells.

Conclusion: We propose that our method of sutureless PER with BAPS and BCB may be feasible for clinical use.

P-077

Controlled Release of Basic Fibrosis Growth Factor Causes Rapid Healing of Pancreaticojejunostomy with Potent Angiogenesis and Apoptosis Induction in Granulation Tissue

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We examined the healing process following the novel approach to investigate significance of administration of basic growth factor (bFGF) incorporated in gelatin hydrogel (GH) microspheres in the anastomotc healing of the pancreaticojejunostomy (PJ). 28 dogs received a jejunal subserosal injection of 10 microgram bFGF-GH (n=16) or GH alone (n=12). Sequential analysis of the healing process was performed on day 4, 7, 21, 28. Histologic observations revealed an abundant granulation tisuue at the border zone in the bFGF-GH group on day 7 and the GH alone group on day 21. Marked neovascularization and dense collagen deposition were detected in both groups on day 28. Collagen content and breaking strength showed no significant difference between both groups on day 28. A higher value of TUNEL index and a rapid decline in the number of vimentin-positive cells was detected since day 21 in the bFGF group. The MVD in the bFGF-GH was a higher value since day 7. Basic FGF-GH administration can cause a repid healing of PJ and may contribute to improvement of quality of the healing with potent angiogenesis and promotion of apoptosis induction.

P-078

3-D Angiography Using Multidetector-row CT Images to Perform Pancreatoduodenectomy Safely Following Dissection of the Inferior Pancreaticoduodenal Artery

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Background/Purpose: During a PD it is important to fully understand the arcade of blood vessels in the head of the pancreas before the surgery to reduce intraoperative bleeding. There are two ways to locate the IPDA: to measure the distance between the origin of the SMA and that of the first jejuna artery (FJA) or to measure the distance between the origin of the middle colic artery (MCA) and that of the FJA. In this study, we measured both distances using 3D models of arteries constructed with MD-CT images and discussed which

distance can be more easily measured to help determine the location of the IPDA.

Methods: 141 patients underwent 64 -MD-CT to acquire early arterial phase images. The distance between the SMA origin and the FJA origin and the distance between the MCA origin and the FJA origin were measured.

Results: In patients whose IPDA formed a common trunk with the FJA or arose directly from the SMA, the IPDA or the common truck was located in parallel with the SMA at a very short distance of approximately 18 mm from the MCA origin towards the center. The distance between the SMA origin and the IPDA was significantly longer (approximately 36 mm). However, in patients whose AIPDA and PIPDA arose separately, the distance between the AIPDA origin and the MCA origin was approximately 18 mm, the distance between the AIPDA origin and the PIPDA origin was approximately 19 mm, and the distance between the PIPDA origin and the SMA origin was 19 mm.

Conclusions: Considering that the distance between the IPDA origin and the MCA origin was short, it was demonstrated that it is effective to locate the MCA origin to determine the location of the PIPDA.

P-079

Comparison of Sclerosing Cholangitis with Autoimmune Pancreatitis and Infiltrative Extrahepatic Cholangiocarcinoma: MDCT Findings

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Purpose: To compare MDCT findings between cases of sclerosing cholangitis with autoimmune pancreatitis (SC-AIP) and infiltrative extrahepatic cholangiocarcinoma (IEC).

Materials and Methods: We retrospectively assessed MDCT findings from 16 IEC and 13 SC-AIP cases. MDCT findings were analyzed with regard to location, length, wall thickness, contour, stricture wall enhancement pattern, proximal duct diameter, and presence of diffuse concentric thickening in the proximal duct and gall bladder wall thickness.

Results: Stricture length, stricture wall thickness, and proximal duct diameter were significantly smaller for SC-AIP compared with IEC ($P<0.001$). SC-AIP was correlated with stricture location in both the intrapancreatic and hilar hepatic bile ducts, concentric stricture contour, and diffuse concentric thickening of the proximal bile duct ($P<0.001$). Overall values of sensitivity, specificity, and accuracy used to distinguish between SC-AIP and IEC for stricture wall thickness of <3.0mm and concentric contour were 76.9%, 93.8%, 86.2% and 100%, 87.5%, 93.1%, respectively.

Conclusion: Concentric contour and stricture wall thicknesses of <3.0mm may help to distinguish between SC-AIP and IEC.

P-080

A Novel Heterophilic Antibody Interaction Involves IgG4

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The immunoglobulin (Ig) subclass IgG4 has become of interest by being increased in autoimmue pancreatits and other IgG4-related systemic diseases, recently recognized as new disease entities. IgG4 has a unique binding capacity to IgG Fc, like a rheumatoid factor, but this binding occurs by a high affinity Fc-Fc interaction. Because human IgM rheumatoid factor binds to various animal IgGs, we sought to clarify whether or not human IgG4 has the same ability. By an ELISA procedure, human IgG4 showed a variable reactivity to animal IgGs, reacting very intensely with rabbit and mouse IgGs, but weakly with sheep, horse and rat IgGs. By Western blotting, human IgG4 binding to rabbit IgG was via the Fc piece of the IgG4 molecule, as for human IgG. In addition, ELISA showed that each patient with autoimmune pancreatitis with a high serum IgG4 concentration had high serum level of IgG4 that could bind to rabbit IgG, and the serum level of IgG4 that bound to rabbit IgG was closely correlated with the serum IgG4 concentration. The present study shows that human IgG4 does bind to various animal IgGs by a Fc-Fc interaction, and such an interaction may have a promising utility, or conversely may interfere with some assay systems when there is a high serum IgG4 concentration.

P-081

Examination of the Immunological Difference in LPSP and IDCP

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Objectives: Histopathologically, most of autoimmune pancreatitis in Japan is lympoplasmacytic sclerosing pancreatitis (LPSP) and IgG4-positive plasmacytic involvement is suggested in LPSP. Whereas IDCP (idiopathic duct-centric chronic pancreatitis) in Europe and United States, characterized by neutrophilic infiltratin, is rare in Japan. For the purpose of elucidating an immunological difference and significance of IgG4, we examined immunological difference in our clinical cases between LPSP and IDCP.

Subjects and Methods: Nineteen patients with the tumor-forming type of pancreatitis were operated from 1992 to 2007. We examined 9 cases of LPSP, 1 case of IDCP, and 9 patients with alcoholic chronic pancreatitis served as control. The numbers of immunohistochemically identified IgG1-, IgG4-, and Foxp3-positive cells

contained within the portal tracts selected in each specimen were counted under five different high power fields (HPF), and the ratio between IgG1, IgG4, and Foxp3-positive cells and infiltrated mononuclear cells was calculated in each case.

Results: The resected LPSP cases showed significantly increased (1) Foxp3-positive Tregs (15.3cells/HPF), (2) IgG4 positive cells (20.0cells/HPF), (3) IgG4/IgG1 ratio (2.7) but decreased (4) IgG1 positive cells (7.6cells/HPF) compaired with alcoholic chronic pancreatitis (1) 1.7cells/HPF (2) 2.1cells/HPF (3) 0.18 (4) 12.1cells/HFP. However, IDCP case showed (1) 9.7cells/HPF, (2) 8.0cells/HPF, (3) 0.4, (4) 20.7cells/HPF, respectively. In the group of patients with LPSP, Foxp3/HPF and IgG4/HPF are positively correlated ($p<0.05$; $R=0.67$).

Conclusions: Tregs in the patients with LPSP and IgG4 are positively correlated. LPSP and IDCP seem to be completely different disease.

Poster 13 Acute Pancreatitis Treatment

P-082

The Factor Associated with Severity Progression of Acute Pancreatitis

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The clinical course of AP is diverse according to initial presentation. MAP at the beginning is usually uneventfully recovered. However small group of MAP progress to SAP. SAP progress to mortality upto 20%. During first week, progression of severity is crucial to prognosis of AP. However, there is little data to evaluate severity progression of AP. AIM The aim of study are to analyze the clinical course of AP during 1week of admission and to analyze factors that affect the severity progression of AP.

Methods: Medical records of 177 AP pts were reviewed retrospectively. Severity of AP was classified by Atlanta on 48 hr after adm and at 1 wk after adm. Pts were classified into MM (MAP to MAP), MS (MAP to SAP), SM (SAP to MAP), SS (SAP to SAP).

Result: 48hrs from adm, 138 pts were MAP (78%) and 39 pts were SAP (22%). After 1 wk of adm, 2 pts from the MAP group progressed to the SAP (MS) and 11 pts from the severe AP still remained in the same group (SS). Five pts from the SS expired within one wk and 1 pt of 6 SS group died of sepsis after 90days of adm. To evaluate factors that affect the disease progress of MM, MS, SM, and SS, univariate analysis was done. Alcohol ($P=0.04$), DM ($P=0.03$), and fluid therapy within 48hrs ($P<0.01$) were significant factor in the MM and SS. In the SM and SS, HTN ($P=0.04$), renal failure ($P=0.01$) were correlated to the disease progress. Multivariate analysis showed that only alcohol was correlated to the disease progress ($P=0.03$). Statistical analysis showed that the SS had more underlying diseases than the SM and this correlated with more organ failure and poor disease progress ($P<0.01$).

Conclusion: Very little portion of MAP progress to SAP. Co=morbidity patients should be intensively cared because of high possibility of serious disease progression.

P-083

Analysis of Late Onset Complications of Acute Pancreatitis in Japanese

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Introduction: Acute pancreatitis is local and systemic disease. The fatality rate of acute pancreatitis is still high. The early-onset complications of acute pancreatitis are multiple organ failure (MOF), disseminated intravascular coagulation (DIC), peritonitis. The late-onset complications of acute pancreatitis are infected pancreatic necrosis, pancreatic abscess, pancreatic pseudocyst. We examined the incidence and mortality of late-onset complications, and the colleration with the severity of acute pancreatitis.

Methods: The patients with acute pancreatitis (n=1240) were evaluated (the results from of the natiowide survey of acute pancreatitis). Sex, age, severity of acute pancreatitis, imaging studies, therapy, mortality and incidence of late onset complications were estimated.

Results: Male 818 and Female 420 patients were assessed, mean age was 54.4 years old. The patients with severe acute pancreatitis were 337 (male 245 and female 92, mean age was 55.6 y.o), moderate acute pancreatitis were 205 (male 136 and female 69, mean age was 55.6 y.o) and mild acute pancreatitis were 693 (male 432 and female 259, mean age was 53.4 yo). The patients with infected pancreatic necrosis were 33, the mortality was significantly higher than the patients without infected pancreatic necrosis. The incidence of infected pancreatic necrosis in the patients with severe acute pancreatitis was significantly higher than the patients without severe acute pancreatitis. The patients with pancreatic abscess were 33, the mortality was significantly higher than the patients without infections pancreatic necrosis. The incidence of pancreatic abscess in the patients with severe acute pancreatitis was significantly higher than the patients without severe acute pancreatitis. The patients with pancreatic pseudocyst were revealed same tendency.

Conclusion: The severity of acute pancreatitis and mortality of the patients with infected pancreatic necrosis and pancreatic abscess was high. We also report the trend of these late onset diseases of acute pancreatitis.

P-084

Brain Damage in Severe Acute Pancreatitis

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Pancreatic encephalopathy (PE) is a very rare neurological complication in pancreatic disorders. Pancreatic encephalopathy, which is one of multiple organ dysfunction syndrome, generally occurs in early stage of severe acute pancreatitis and has a high mortality. However, its pathogenesis is not clear till now, treatment is complex.

We examined 18 severe acute pancreatitis patients with encephalopathy. The encephalopathy is diagnosed in 13 patients during 2–3 days after admission, in 5 patients - after 15–16 days. In patients blood we measured TNF-alpha, IL-1beta, IL-6, malondialdehyde, endothelin-1. Diffusion-weighted MRI and FLAIR MRI used for diagnostic. Control group was served 15 patients without encephalopathy.

In all patients with severe acute pancreatitis we notes increase in blood cytokines, malondialdehyde, and endothelin-1. At the same time at 13 patients with encephalopathy levels TNF-alpha and IL-6, malondialdehyde, and endothelin-1 were is higher. Positive correlation between these indicators and brain lesion was defined. Diffusion-weighted MRI scans showing bilateral diffuse high intensity lesions in the pons, middle cerebellar peduncles and cerebral deep white matter. FLAIR MRI scans showing bilateral diffuse high intensity lesions in the pons, middle cerebellar peduncles and cerebral deep white matter. 5 patients did not differ from control group, Wernicke encephalopathy was diagnosed. For treatment of pancreatic encephalopathy Mexidol was applied successfully. Wernicke encephalopathy was treated by Thiamin.

The brain lesion in acute pancreatitis should be diagnosed in time. Treatment should be differentiated.

P-085

Nafamostat Mesylate for Prevention of Post-ERCP Pancreatitis in Different Doses

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Background and Aim: Pancreatitis is a major complication of endoscopic retrograde cholangiopancreatography (ERCP). Continuous infusion of nafamostat mesylate (20mg), a protease inhibitor, may prevent post-ERCP pancreatitis in low risk groups. This study assessed the efficacy of nafamostat mesylate (50mg) for prevention of post-ERCP pancreatitis in high risk groups.

Methods: From January, 2005 to December, 2009, a total of 956 patients who were performed ERCP were analyzed. Patients were infused with 500 mL of 5% dextrose solution with 20mg (group 2, 350 patients) or 50mg (group 3, 252 patients) of nafamostat mesylate or without nafamostat mesylate (group 1, 354 patients). Serum amylase and lipase levels were checked before ERCP, 4 and 24 hours after ERCP, and when clinically indicated. The incidence of post-ERCP pancreatitis was analyzed. After ERCP, patients were classified as high-risk if they had a history of acute pancreatitis, suspected sphincter of Oddi dysfunction, difficult cannulation, precut sphincterotomy, trans-papillary balloon dilatation or multiple pancreatic duct injections; the remainers were classified as low-risk.

Results: The overall incidence of acute pancreatitis was 4.9%. There were a significant difference in the incidence of PEP among treatment groups (7.4% vs 3.3% vs 3.5%, respectively, $p=0.024$). There was no significant difference between group 2 and group 3 (3.3% vs 3.6%, respectively; $p=0.904$). Subgroup analysis showed that, in low-risk patients, the rate of PEP was significantly different (8.0% vs 3.3% vs 2.5%, respectively, $p=0.044$). In high-risk patients, the rate of PEP was not significantly different among treatment groups (6.5% vs 3.6% vs 7.5%, respectively; $p=0.486$).

Conclusions: Nafamostat mesylate prophylaxis (20mg or 50mg) is partially effective in preventing post-ERCP pancreatitis. In high risk patients, preventive effect of nafamostat mesylate is not significant.

P-086

Pancreatic Pseudocyst Penetration to The Duodenum;Reports of Three Resolved Cases

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Pancreatic pseudocyst is sequelae caused by acute pancreatitis, and can be complicated by infection, intracystic hemorrhage and rupture with high mortality. We report three cases of pancreatic pseudocyst infection with spontaneous penetration to duodenum resolved by various clinical courses. Case 1: A 77 year old woman presented with epigastralgia, and diagnosed acute pancreatitis. Fluid transfusion and antibiotic administration did not improve the pain.CT suggested pancreatic pseudocyst infection. Gastrointestinal endoscopy and EUS revealed a fistula between the pseudocyst and the duodenal bulb, and pus was observed. Conservative therapy continued, and pseudocyst disappeared. Case2: A 30 year old man presented with general upper abdominal pain. The patient was diagnosed as and was treated for severe acute pancreatitis, and was complicated by an infected giant pancreatic pseudocyst. Gastrointestinal endoscopy showed pus secretion from a fistula at the duodenal bulb,and it was suspected to communicate with the pseudocyst. ERCP revealed the giant pseudocyst at the tail. Endoscopic nasal pancreatic drainage tube was used to treat the pseudocyst, and it disappeared over time. The tube was removed with no recurrence of the pseudocyst. Case 3: A 60 year old man was treated for severe acute pancreatitis. A giant pancreatic pseudocyst formed one month after the treatment. 9 month later, he presented with fever, and was diagnosed with the pseudocyst infection. EUS guided pseudocyst drainage was performed. The symptom and blood chemistry data improved, and CT showed reduction in the cyst size. Contrast study of extra drainage tube and endoscopy revealed a fistula at the descending part of the duodenum,and it was conceived as a result of penetration of pseudocyst infection. At our institution, primary therapy for pancreatic pseudocyst infection is either endoscopic

transpapillary or transgastric drainage. We report the three cases with literature review on spontaneous penetration of pancreatic pseudocyst infection.

P-087

Pancreatic Stenting After Early Endoscopic Removal of Bile Duct Stones in Patients with Predicted Severe Acute Biliary Pancreatitis Might Prevent Local Complications

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Background: Early endoscopic retrograde cholangiopancreatography (ERCP) is the established treatment for the predicted severe acute biliary pancreatitis (SABP). However, even after successful intervention, systemic and local complications of SABP develop in 15–65% of patients and the possibility that the procedure itself may contribute to these grave clinical outcomes cannot be excluded because the risk of post-ERCP pancreatitis per se reaches 5–15%. We designed this study to evaluate if drainage of pancreatic juice might improve consequences by pancreatic stenting after removal of bile duct stones (BDS).

Methods: Prospective observation study was carried out from October 1, 2007 to March 31, 2009 in patients hospitalized for predicted SABP at Donngguk University Ilsan Hospital and Seoul National University Bundang Hospital. They received ERCP within 48 hours once the diagnosis was made. After stone removal, the placement of a small-caliber plastic pancreatic stent was tried for every patient.

Result: A total of 41 patients were recruited. All of them received appropriate BDS extraction on the initial session of ERCP and pancreatic stenting was successful in 32 (82.9%) of them. There was no mortality in successful stenting group (SS), and pseudocyst developed in one patients. Also, none died in failed stenting group (FS), and there were one case of pseudocyst and one infected necrosis. The incidences of local complications were significantly lower in SS than in FS (P-values $< .05$).

Conclusion: Early ERCP with BDS removal can be life-saving in patients with predicted SABP and additional pancreatic stenting might prevent local complications.

P-088

Proximally Migration of Pancreatic Duct Stent Since 1~4 Years After Transduodenal Papillectomy, and Attempted Endoscopic Retrieval in Two Patients

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We report herein two patients, one's stent migrate proximally for 4 years and the other is primary placed for one year, caused by postoperative complications of transduodenal papillectomy. We discussed these cases with reference of previous published reports.

A 71 year old man underwent transduodenal papillectomy for the adenoma of Vater. As a postoperative complication, duodenal obstruction was shown temporally, and the patient improved conservatively. After 4 years later the patient attacked acute pancreatitis. Abdominal CT was obtained a pancreatic duct tube migrate into the pancreas. Consequently we attempted endoscopic retrieval with a endoscopic biopsy forceps. Since then pancreatitis did not occur.

And a 72 years old woman underwent transduodenal papillectomy for the adenoma of Vater that was suspected the infiltlatation into the bile duct. 8 days after the operation, the patient complained abdominal pain and fever. Intestinal contrast showed a minimum leakage of duodenal suture. The patient concervatively improved and making satisfactory progress. For one year she remained without symptoms. A pancreatic duct stent was found endoscopically that stayed in primary place and not migrated. We successfully retrieved with a endoscopic forceps.

P-089

A Pancreatic Pseudocyst-portal Vein Fistula Presented by Liver Abscess and Treated by Endoscopic Stent Insertion in Acute Pancreatitis Patient

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A pancreatic pseudocyst-portal vein fistula is a very rare and potentially fatal complication of acute pancreatitis. Most patients reported present symptoms of acute pancreatitis or serious complications such as sepsis or sever fat necrosis. However, it is very rare that the fistula was found due to symptoms associated with the hepatic abscess and closed by endoscopic pancreatic stent insertion, as in our case.

Case Report: A 54-year-old man presented to the hospital with right upper abdominal pain and mild fever (37.9). On admission, the physical examination revealed right upper quadrant tenderness and

the laboratory findings showed a slight increase in the amylase, lipase levels and the within normal limits of liver function test. The CT findings were as follows: a 5 x 6 cm cyst in the head of the pancreas, a marked fusiform dilatation of the portal vein filled with a low-density substance suspected as a thrombosis adjacent to the pseudocyst, and an irregular marginated intrahepatic abscess in the S6 segment of the liver. When percutaneous transhepatic portography was performed, the contrast injected into the portal vein leaked into the pseudocyst. The analysis of aspirated fluid from the portal vein showed an increased amylase (78707 U/L) and lipase (>50,000 U/L), which confirmed the formation of a pancreatic pseudocyst-portal vein fistula. ERCP showed that the pseudocyst communicated with the main pancreatic duct from the stricture site and the portal vein was delineated via the pseudocyst-portal vein fistula, in the late phase.

While performing the ERCP, a 9-cm 7-fr ERPD (Geenen® pancreatic stent, Cook, NA, USA) was inserted into the main pancreatic duct passing through the stricture site. The follow-up CT two months later showed a significant decrease in the amount of portal vein thrombosis and the size of the pseudocyst, and complete resolution of the hepatic abscess.

P-090

Two-stage Treatment: Percutaneous Drainage and Open Necrosectomy in Severe Acute Pancreatitis

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Background: Percutaneous drainage is a possible first stage for the treatment in severe acute pancreatitis.

Aim: To assess patient's selection, techniques and results of peripancreatic fluid collection (PFC), pancreatic abscess (PA) treatment using ultrasound guided percutaneous catheter drainage (PCD); to find predictors of successful outcome.

Patients and Methods: We treated 291 patients (222 male, 69 female) with severe necrotizing pancreatitis. The most common cause of the pancreatitis were alcohol abuse and gallstone disease (62.5% and 20.6%). Percutaneous drainage was used for those patients, with 2–3 cm or wider peripancreatic fluid collection (72 patients) or pancreatic abscess (15 patients). Multivariate regression analysis determined predictors of PCD success. Variables entered into the analysis included: type, diameter, and location, complexity of PFC and PA, and drainage technique (pigtail or trocar).

Results: No complications were found related to this intervention. Fifty patients with PFC (69.4%) were recovered without surgery after a 14.8 days average time of drainage. The remaining 22 patients with PFC underwent a late (14–30 days of admission) open necrosectomy. Ten patients with PA were recovered without open surgery.

Conclusions: We suggest the percutaneous peripancreatic drainage as a first intervention for acute fluid collection or pancreas abscess in patients with severe pancreas necrosis. If septic symptoms or MOF developed in spite of drainage open necrosectomy (2 stage) is mandatory. PCD should be considered as the initial therapy in selected patients with PFC and PA, and as a staging method for the resolution of sepsis prior to surgery.

Poster 14 Chronic Pancreatitis Diagnosis

P-091

Can Oxidative Stress Markers Indicate Any Proof of the EUS Findings of Chronic Pancreatitis in the Early Stage?

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Background and Aim: Although endoscopic ultrasonography (EUS) is considered the most sensitive modality for the diagnosis of chronic pancreatitis (CP), the evidence that EUS findings correlate with histological changes is not enough. By the way, oxidative stress is well-known as one of the cause of CP. The aim of this study was to evaluate whether oxidative stress markers can be the evidence of EUS findings suggestive of CP or not.

Patients and Methods: Twelve patients diagnosed as CP and 6 patients suspected of early CP clinically were enrolled. EUS findings were referred to the EUS criteria of CP. The correlations between the number of EUS findings in the early CP suspected patients and the value of oxidative stress markers (glutathione, thioredoxin and SOD) were examined. And then we also evaluated the relationship between changes of the number of EUS abnormalities and of the value of oxidative stress markers in 7 patients who were demonstrated EUS more than twice (including both CP and suspected early CP).

Results: EUS findings correlate with thioredoxin ($rs=0.82$, $P=0.017$). And there was a correlation between the change of the number of EUS findings and of the SOD value ($rs=0.81$, $P=0.014$).

Conclusion: Thioredoxin may be one of the evidence of EUS findings that would be seen in an early stage of CP. The activity of the CP might be evaluated by EUS and SOD. Therefore oxidative stress markers may be the foundation for diagnosis of early CP.

P-092

A Difficult Case in Diagnosis of Focal Autoimmune Pancreatitis

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Recently, the number of patient with autoimmune pancreatitis (AIP) has increased. The diagnosis of focal AIP out of pancreatic tumor is very difficult in some cases, especially in ruling out of pan-

creatic cancer. Here, we report a case of focal AIP, showing the globular shape very similar to pancreatic cancer. A 59-year-old woman was referred to our hospital for a further examination of a pancreatic tumor detected during the medical checkup. Ultrasonography (US) revealed a hypoechoic tumor in the pancreatic body, 10 mm in diameter, however, it was not detected by contrast-enhanced computed tomography and magnetic resonance imaging. Endoscopic US (EUS) revealed the tumor as a well-defined hypoechoic lesion with irregular border and hyperechoic foci and strand of pancreatic parenchyma. Endoscopic retrograde pancreatography showed the normal main pancreatic duct without dilatation or narrowing. Fluorine-18-fluorodeoxyglucose positron-emission tomography revealed the abnormal uptake in the pancreatic body. (The maximum standardized uptake value: 2.02) After these examinations, although focal AIP was most likely, we were not able to rule out pancreatic cancer, because we couldn't get enough sample by EUS guided fine needle aspiration/biopsy (EUS-FNAB) for histological diagnosis, and the level of serum IgG4 was within the normal range. Therefore, a distal pancreatomy was underwent after the informed consent. The resected tumor, appeared grossly as a white mass, was diagnosed lymphoplasmacytic sclerosing pancreatitis by histological study. (IgG4 positive plasma cell >10/HPF). In our case, EUS findings were the most reliable basis to diagnose pancreatic tumor as focal AIP, although the diagnosis was not established in imaging study.

P-093

Involvement of ICOS and IL-10 Positive Regulatory T Cells in the Development of Autoimmune Pancreatitis

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Background & Aim: Autoimmune pancreatitis (AIP) have several immunologic and histologic abnormalities, including increased levels of serum IgG4 and storiform fibrosis with infiltration of lymphocytes and IgG4-positive plasmacytes. Among the involved organs showing extrapancreatic lesions, bile duct is the most common, exhibiting sclerosing cholangitis (IgG4-SC). However, the role of IgG4 is unclear. Recently ICOS is paid attention to the key molecule of IL-10 secretion from Tregs. We analyzed the Tregs to clarify the role of IgG4 production in AIP.

Subjects and Methods: We obtained pancreatic tissue from 6 AIP and 6 cases of chronic pancreatitis. Hepatic tissue was sectioned from 16 IgG4-SC patients and 26 patients with PSC. We studied infiltrating IgG4-positive cells and Tregs in the pancreas and liver by immunohistochemistry. ICOS positive and IL-10 producing Tregs were analyzed from peripheral blood by flow cytometry.

Results: Tregs were increased in the pancreas with AIP (24.6±18.0 cells/HPF) compared with controls (5.1±4.3 cells/HPF). The numbers of IgG4-positive plasmacytes were significantly higher in AIP (18.6±10.3 cells/HPF) than in controls (1.1±0.7 cells/HPF). However, there were no significant differences in CD3+, CD4+, or CD79+ cells between the AIP and controls. In the liver, IgG4-positive plasmacytes were significantly higher in IgG4-SC (16.6±7.7 cells/HPF) than in PSC (4.0±0.7 cells/HPF). Tregs in the patients with IgG4-SC (5.4±1.5 cells/HPF) were also significantly increased compared with PSC (2.0±0.3 cells/HPF). In the patients with IgG4-SC, the numbers of infiltrated Tregs were significantly positively correlated with IgG4-positive plasma cells (R=0.75). ICOS+Tregs (3.45±1.58%) were significantly increased in comparison with healthy control (1.57±0.69%), alcoholic chronic pancreatitis (1.71±0.98%) and idiopathic chronic pancreatitis (1.80±0.86%). IL10+ICOS+Tregs (3.81±1.52%) in LPSP were significantly increased compared with healthy control (1.38±0.64%). In patients with the untreated AIP, IL-10 producing Tregs and IgG4 also positively correlated (R=0.53).

Conclusion: In AIP, Tregs may affect the switching of B cells to IgG4-producing plasmacytes.

P-094

Retrospective Clinicopathologic Study of the Patients with Chronic Pancreatitis Clinically Suspected of Pancreatic Carcinoma: What Percentage of Them Can Be Diagnosed as Autoimmune Pancreatitis Immunohistochemically?

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Background/Purpose: Between 1979 and 2008, 57 patients underwent pancreatic resection for alcoholic chronic pancreatitis (ACP, 18 patients) confirmed clinically and histologocally or non-alcoholic chronic pancreatitis (NACP, 39) clinically suspected of pancreatic carcinoma. We reviewed the histopathologic and immunohistochemical findings for the surgically resected specimens to elucidate the pathogenesis of chronic pancreatitis respectively and assess what percentage of NACP was linked with autoimmune pancreatitis (AIP).

Methods: All resected pancreas sections were fixed in 10% formalin and were sliced serially at 5- to 8-mm intervals in a plane at right-angles to the main pancreatic duct (MPD). All the slices were processed according to standard procedures for hematoxylin eosin-stained histologic preparations and were examined microscopically. Forty cases, reliably excluding 8 ACPs and 9 NACPs with little inflammatory cells infiltration, are now under immunohistochemical study by IgG4 staining to determine AIP or not.

Results: (1) NACP could be classified according to inflamed area in the pancreas as followed: 1) Ductitis (ductal wall thickening at MPD or 1st/2nd branch) with/without periductal fibrosis in 11 patients, 2) Focal pancreatitis in 10 patients, 3) Santorini pancreatitis (pancreatitis at the pancreatic tissue along the duct of Santorini, mostly spreading to minor papilla and/or duodenal wall) in 7 patients, 4)So-called groove pancreatitis in 4 patients, 5) Diffuse pancreatitis (pancreatic head-body or body-tail) in 7 patients. (2) Pancreatitis with duct epitherial hyperplasia (DEHP) 1)6/11, 2)8/10, 3)3/7, 4)0/4, 5)0/7. (3) AIP (pancreatitis with periductal lymphoplasmacytic infil-

tration) 1) 0/11, 2)3/10, 3)0/7, 4)1/4, 5)7/7 (IgG4 staining is now under study)

Conclusion: (1) Major pathogeneses of NACP are DEHP (17/39), AIP (11/39), and Unknown (11/39). (2) DEHP is mostly observed in Focal Pancreatitis (8/10). (3) AIP is observed in all Diffuse Pancreatitis (7/7).

P-095

Efficacy of Camostat Mesilate Against Dyspepsia Associated with Non-alcoholic Mild Pancreatic Disease Based on the Rosemont Criteria

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Background: The management of dyspepsia remains challenging. The aim of the present study was to examine the potential efficacy of camostat mesilate, a protease inhibitor, against dyspepsia associated with non-alcoholic mild pancreatic disease.

Methods: Between April 2002 and September 2008, patients with upper abdominal pain suggesting pancreatic disease, without a history of alcohol consumption and who exhibited no abnormalities regarding serum amylase and lipase, ultrasonography, CT and upper gastrointestinal endoscopy, were prescribed 200 mg camostat mesilate three times daily for 2 weeks. The patients were subjected to endoscopic ultrasonography (EUS) while under treatment and were distributed into those who had 4 or more suggestive findings of chronic pancreatitis (suspected pancreatic disease group), 2 or 3 (equivalent group) and those with one or no findings (control group). EUS findings were assessed based on the Rosemont criteria. Patients having major criteria on EUS were excluded. Symptom severity was recorded before and after treatment using a 10-cm visual analog scale (VAS).

Results: Ninety-five patients completed the 2 week treatment period and EUS examination; 34 were in the suspected pancreatic disease group, 31 were in the equivalent group and 30 served as controls. The mean VAS score before and after the administration of camostat mesilate was 5.1 (1.9) and 1.5 (1.4) in the suspected pancreatic disease group, 4.5 (1.6) and 3.9 (1.4) in the equivalent group, and 4.2 (1.6) and 3.7 (1.8) in the control group; a significant improvement of VAS score was observed in the suspected pancreatic disease group ($p < 0.001$).

Conclusions: Camostat mesilate may serve as a therapeutic agent for patients with dyspepsia associated with mild pancreatic disease, who do not habitually drink alcohol.

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P-096

Management of Pancreatolithiasis – A Japanese Multicenter Study

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Japanese multicenter study of pancreatolithiasis was performed to investigate clinicopathological features and to exhibit treatment strategy for pancreatic stones. A retrospective study was performed on 899 patients (752 men and 122 women). Treatment methods included extracorporeal shock wave lithotripsy (ESWL) in 452 cases, surgery in 133 cases and endoscopy alone in 68cases. Fragmentation of stones after ESWL was achieved in 92.4% cases. However, stones were completely cleared in 49.4% cases after ESWL alone. Complete stone clearance rate was lower after ESWL than after endoscopy. However, symptom relief rate after each treatment was over 90%. The incidence of early complications after surgery was significantly higher than after ESWL. On the other hand, the incidence of late complications was higher after ESWL than after endoscopy or surgery, although not significantly. Stone recurrence after ESWL and endoscopy were significantly more frequently than after surgery. After ESWL, abdominal pain recurred significantly more frequently than after surgery. Most recurrence of stones and abdominal pain after ESWL and endoscopy were occurred within three years. In conclusion, first-line treatment for pancreatic stone should be ESWL alone or with endoscopy because of its minimally invasiveness and low incidence of early complication. Surgical treatment should be performed on cases in which ESWL and endoscopy have failed.

P-097

Appraisal of the Modified Beger Procedure (Imaizumi Modification) for Chronic Pancreatitis

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Background: We developed the Imaizumi modification of the Beger procedure, a duodenum-preserving pancreatic head resection. The Imaizumi modification allows for removal of more of the subtotal pancreatic head than in the conventional Beger procedure, including the intrapancreatic bile duct, for chronic pancreatitis with common bile duct stenosis. A retrospective study was performed to evaluate the efficacy of the Imaizumi modification compared to a pylorus-preserving pancreaticoduodenectomy (PPPD), based on the early and late postoperative results.

Methods: A group of 15 patients who underwent the Beger procedure with the Imaizumi modification to treat chronic pancreatitis from 1997 to 2007 was investigated retrospectively. This group was compared to a group of 22 patients who underwent PPPD from 1997 to 2007. The median follow-up period was 3.9 years (range 3.3–6.1 years) for the Imaizumi modification group and 4.3 years (range 3.3–8.7 years) for the PPPD group.

Results: A pancreatic fistula formed in 7% of the Imaizumi modification patients (PPPD 5%), pain relief was achieved in 93% (PPPD 95%), complete professional rehabilitation was achieved in 73% (PPPD 68%), insulin dependent diabetes mellitus was present in 46 versus 40% before the procedure (PPPD 64 versus 41% before the procedure), and body weight improved in 73% (PPPD 50%). No significant differences were found between the two groups for the early postoperative complications and the late postoperative outcome 3 years after the procedure. However, the Imaizumi modification group exhibited an encouraging tendency to have a lower rate of new-onset exocrine and endocrine insufficiency than the PPPD group.

Conclusions: Imaizumi modification of the Beger procedure, including intrapancreatic bile duct resection, represents a useful alternative for the treatment of chronic pancreatitis with an inflammatory mass and bile duct stenosis in the pancreatic head.

P-098

A Case of Common Bile Duct Stricture due to Pancretic Duct Stenting for Chronic Pancreatitis

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A 44-year-old man was treated by endoscopic pancreatic stenting for pancreatic duct stenosis due to chronic pancreatitis. The stent was exchanged endoscopically at intervals of 3-4 months. After about 1 year, he suffered obstructive jaundice. Endoscopic and radiologic examinations revealed that the intra-pancreatic portion of his common bile duct was stenosed. The biopsy of this legion revealed no malignancy and the serum level of tumor markers were normal. Therefore, we diagnosed common bile duct stricture because of oppression from panceartic duct stent to common bile duct. He was treated by endoscopic bile duct stenting and is making satisfactory progress.

Common bile duct stricture due to pancreatic duct stenting is rare complication. We would like to consider the mechanism of this complication and the treatment of it.

P-099

Two Cases of Pancreatic Ductal Strictures Associated with Chronic Pancreatitis Treated with Endoscopic Pancreatic Stenting

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Pancreatic ductal stricture with chronic pancreatitis (CP) is one of an important cause of pain. Currently, several studies have shown that interventional endotherapy provides partial or complete relief of pancreatic pain. We, here, reported two cases of pancreatic ductal strictures with CP treated with endoscopic pancreatic stenting.

Case 1 is a 50-year-old man diagnosed as CP in 2001, and then he was hospitalized for several times for pancreatic pain. In 2008, he was referred to our hospital to treat CP. He presented light pain at upper abdomen. Laboratory tests showed elevated serum amylase and lipase levels. Abdominal CT showed a pseudocyst at pancreas head, and the dilatation of main pancreatic duct (MPD) at proximal site to the pseudocyst. ERP demonstrated a pseudocyst and stricture of MPD at pancreas head. We placed a 5-French pancreatic stent with side holes, and replaced by a larger stent every three months. Finally, we placed a 10-French stent. Then the pseudocyst and stricture of MPD gradually disappeared. Since the first interventional endotherapy, he complained no abdominal pain and serum amylase and lipase have been within normal level.

Case 2 is a 25-year-old man. He was hospitalized for acute pancreatitis in 2008, and then repeated hospitalization for treatment of abdominal pain. In 2009, he was referred to our hospital. He presented light pain at upper abdomen. In the laboratory tests, serum lipase levels slightly elevated. ERP demonstrated a pseudocyst and stricture of MPD at pancreas body. Endoscopic pancreatic stenting was performed similar to case 1. Finally, we placed a 10-French pancreatic stent. Since the first interventional endotherapy, he was free from abdominal pain.

In conclusion, the interventional endotherapy could offer an excellent therapeutic alternative in patients with pancreatic duct stricture associated with CP.

P-100

Three Cases Suffered from Inflammation of a Vein and Allergy Symptoms After Administering the Generic Drug of Proteinase Inhibitors Due to Attack of Pancreatitis

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Recently public concern about generic drugs is increasing. Generic drugs have the same ingredients as those of original drugs, but the medicinal additives are different from original drugs. In addition unknown substances contained in generic drugs are different from original drugs. There are some reports of generic drugs causing serious side-effects in particularly injectable preparations. We report three cases which experienced adverse effects after using generic drugs in our hospital.

A 45-year-old woman was administered 200 mg of Panabate® (a generic drug of gabexate mesilate) intravenously for the treatment of acute pancreatitis.

A 51-year-old woman was administered 10 mg of Nafamostat MEEK® (a generic drug of nafamostat mesilate) intravenously due to chronic pancreatitis. A 62-year-old woman was administered 10 mg of Nafamostat MEEK® (a generic drug of nafamostat mesilate) intravenously due to suspected chronic pancreatitis.

Our hospital had adopted the generic drug instead of the original drug (FOY® or Futhan®) .

The First case developed inflammation of the left cephalic vein. The Second case developed inflammation of the right cephalic vein after administering 10 mg of Nafamostat MEEK® (a generic drug of nafamostat mesilate) intravenously in the first thirty minutes. She recovered from the symptom four hours after stopping administration. She had never developed this symptom by the original drug (10mg of Futhan®). Third case developed nausea and exanthema after administering 10 mg of Nafamostat MEEK® (a generic drug of nafamostat mesilate) only a slight drip intravenously. These symptoms continued four days.

Generic drugs bring significant cost benefit to our society against rising medical costs.

But on the other hand, we experienced possibilities of side-effects of generic drugs.

When we administer drugs including generic drugs,we must premeditate the possibilities of side-effects.If the side effects occurred, it is important for us to respond promptly.

P-101

Relationship Between Serum IgG4 Levels Before Treatment and Recurrence of Autoimmune Pancreatitis After Steroid Therapy

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Background and Aim: Autoimmune pancreatitis (AIP) is characterized by high serum IgG4 levels, complications involving extrapancreatic lesions, and responsiveness to steroid therapy. We investigated whether AIP patients' recurrence rate after steroid therapy is associated with their serum IgG4 level.

Methods: The serum IgG4 levels of 41 AIP patients treated in our department between 2003 and 2009 were measured, and the patients were divided into two groups at a cut-off value of 135 mg/dl. The recurrence rates after steroid therapy in the two groups were then compared.

Results: All 31 patients in the high-IgG4 group were over 50 years old, but three of the 10 patients in the normal-IgG4 group were under 50 years old. Imaging examinations of the pancreas showed no significant differences between the two groups. Twelve patients (38.7%) in the high-IgG4 group had extrapancreatic lesions, and one of the 10 patients (10.0%) in the normal-IgG4 group had extrapancreatic lesions. Eight patients (25.8%) in the high-IgG4 group experienced a clinical recurrence of pancreatic and/or extrapancreatic lesions, and their serum IgG4 levels rose before the clinical recurrence. None of the patients in the normal-IgG4 group except one patient who had ulcerative colitis as a complication experienced a recurrence of AIP after the completion of steroid therapy. A patient in the normal-IgG4 group who had ulcerative colitis experienced a recurrence of the ulcerative colitis during the steroid tapering period, but there was no evidence of recurrence of the AIP lesion in the pancreas.

Conclusion: AIP patients with high IgG4 levels before treatment are more likely to experience a recurrence of pancreatic and extrapancreatic lesions of AIP than patients with normal IgG4 levels. The recurrence rate and pattern seems to depend on the serum IgG4 level before steroid therapy.

P-102

A Case of Retroperitoneal Fibrosis Two Years after the Completion of Steroid Therapy for Autoimmune Pancreatitis

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A 67-year old man visited our hospital with the chief complaint of jaundice. Laboratory examinations revealed cholestatic liver dysfunction and high levels of serum IgG4 and rheumatoid factor. Computed tomography (CT) revealed enlargement of the pancreas and stenosis of the lower bile duct. Endoscopic retrograde pancreatography demonstrated irregular narrowing of the main pancreatic duct. Percutaneous transhepatic cholangiograpy showed severe stenosis of the lower common bile duct. These findings could lead to the diagnosis of autoimmune pancreatitis (AIP), and treated with prednisolone (PSL) for 48 weeks. The enlarged pancreas and the stenosed lower bile duct were immediately improved with steroid therapy.

Two years later, follow-up CT revealed the appearance of left hydronephrosis and abnormal soft tissue around left common iliac artery without obvious abnormality of the pancreas and the bile duct. In consideration of the occurrence after AIP, we diagnosed these clinical features as retroperitoneal fibrosis related to AIP, and PSL was re-administered for 24 weeks. The findings of hydronephrosis and soft tissue around common iliac artery had disappeared until five months after the restart of PSL therapy.

We report this instructive case suggesting that retroperitoneal fibrosis may occur following the remission of AIP after completion of steroid therapy.

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P-103

Characteristics and Prognosis of Invasive Pancreatic Ductal Adenocarcinomas Originating from a Branch Pancreatic Duct

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Objective: To clarify the early advancement of invasive pancreatic ductal adenocarcinomas (IPDACs) originating from a branch pancreatic duct (BPD), and to analyze its influence on the prognosis.

Materials: 7 resected IPDACs in which the carcinoma invasive area was 2 cm or smaller and no cancer lesion was present in the main pancreatic duct (MPD), therefore, the carcinoma apparently arose from a BPD (B group).

Methods: Regarding the advancement, the histological morphology and distribution of PanIN-3 lesions were investigated. The morphology was classified into flat (F), low papillary (LP), and mixed (FLP) types. The distribution was investigated by counting PanIN-3 lesions in interlobular BPD near and distant from the MPD (central (C) and peripheral (P) inter-BPD, respectively). To evaluate the involvement of these advancements in the prognosis, their relationships with the following prognostic factors were analyzed: TNM, recurrence and survival rate. As the control, 28 resected IPDACs with 2cm or smaller tumors with lesions present in the MPD (NB group) were investigated.

Results: In the B and NB groups, the morphology of PanIN-3 lesions was F/FLP/LP in 3/4/0 and 5/14/9 ($p=0.178$), the mean numbers of lesions in C-inter-BPD were 1.7 and 4.3 ($p=0.015$), those in P-inter-BPD were 2.7 and 2.6 ($p=0.505$), T was 1/2/3/4 in 1/0/6/0 and 9/0/19/0 ($p=0.644$), 6(86%) and 8(29%) were N(+) ($p=0.001$), and stage was IA/IB/IIA/IIB/III/IV in 0/0/1/6/0/0 and 4/0/16/8/0/0 ($p=0.047$), and recurrence occurred in 6 (86%) and 13 (56%) ($p=0.017$), the median postoperative disease free period were 15.6 and 56.4 months, and the 3-year survival rates were 50 and 70%($p=0.2852$), respectively.

Conclusions: The cancer development site was a peripheral BPD distant from the MPD in the B group, and the morphology of PanIN-3 lesions was F type in many cases. Lymph node metastasis occurred at a high rate in IPDACs originating from a BPD, and recurrence occurred after a short period, showing poor prognosis.

P-104

Semaphorin 4D Involves in the Regulation of Cell Motility in Pancreatic Cancer by Tumor-stromal Interaction

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Introduction: Semaphorins are a large family of proteins that provide axonal guidance in neuronal tissues and regulate cell motility in many types of cells. Recent articles reported that Semaphorin 4D (Sema 4D) enhanced in vitro motility and invasiveness through its receptor Plexin B1, and increased in vivo metastasis potential in breast cancer. In the present study, we investigated the clinicopathological significance of Sema 4D and Plexin B1 expression in pancreatic ductal adenocarcinoma and the regulation of cell motility through the Sema 4D - Plexin B1 signaling pathway.

Material & Methods: The mRNA expression level of Sema 4D and Plexin B1 were evaluated by Quantitative Real Time PCR from 12 surgical specimens. Expression of Sema 4D and Plexin B1 were also evaluated immunohistochemically from 90 patients. Using pancreatic cancer cell lines, the expression of endogenous Plexin B1 protein was investigated by western blotting. As functional analysis, scratch assay were carried out.

Results: The mRNA expression level of Sema 4D and Plexin B1 were significantly high in cancer tissues compared to normal pancreas tissues. Immunostaining showed that Sema 4D strongly expressed in lymphocytes and macrophages, as previously reported. Ninety two percent (83 out of 90 cases) pancreatic cancer samples overexpressed Plexin B1 compared to normal pancreas tissues. Endogenous Plexin B1 protein were detected in eight pancreatic cancer cell lines, with a variety of expression levels. Sema 4D stimulation significantly induced cell migration.

Discussion: Here we show that Sema 4D involves in the regulation of cell motility through its receptor Plexin B1. And the results of immunostaining suggest that Sema 4D could play a role in the interaction between tumor cells and tumor microenvironment in pancreatic cancer tissues. As many attempts are now ongoing to target the tumor stroma, these findings provide a new insight into molecular targeted therapies for pancreatic cancer.

P-105

New Cancer-stromal Interaction Between Floating Fibroblasts and Pancreatic Cancer Cells

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Backgrounds: Cancer-stromal interaction plays a critical role in tumor invasion and metastasis. The cancer-related fibroblasts were reported to exist in the blood of patients with lung cancer. Also, orthotopically co-transplanted stromal cells were observed in the metastatic site. Furthermore, bone marrow-derived mesenchymal cells were reported to initiate the pre-metastatic niche. These data suggest that floating fibroblasts may be involved in cancer-stromal interaction.

Aims & Methods: To elucidate the implication of floating fibroblasts in caner-stromal interaction, we used two pancreatic cancer cell lines and primary fibroblasts from 5 patients with pancreatic cancer and compared biological characteristics between floating- and adherent-cultured fibroblasts using quantitative RT-PCR, migration and invasion assays, in vitro microarray, and in vivo experiments.

Results: Floating-cultured fibroblasts significantly enhanced migration and invasion of pancreatic cancer cells compared with adherent-cultured fibroblasts ($P < 0.05$). Floating-cultured fibroblasts expressed significantly higher levels of CD10 mRNA (> 7.5-fold), MMP3 (>21.5-fold) and MMP9 (> 81.2-fold) mRNA, and lower level of alpha-SMA mRNA (<100-fold) than those of adherent cultured fibroblasts. Also, floating-cultured fibroblasts showed higher levels of MMP9 activity than adherent-cultured fibroblasts. In the present in vivo model, co-transplantation with floating fibroblasts enhanced the growth rate of subcutaneous tumors compared with the adherent fibroblasts.

Conclusion: Floating-cultured fibroblasts may enhance malignant behavior of pancreatic cancer cells.

P-106

Usefulness of Fluorescence in situ Hybridization for Detection of Pancreatic Cancer Cells

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Background and Aim: The aim of this study was to assess the relative sensitivities and specificities of fluorescence in situ hybridization (FISH) and routine cytology for the detection of malignancy in pancreatic carcinoma.

Materials and Methods: Brushing specimens of tumor cut surface were collected from 30 cases of pancreatic cancer and 5 cases of chronic pancreatitis surgically resected in Hiroshima University Hospital from 2006 to 2010. Carcinoma tissue was confirmed in the brushed cut surface by histological and cytological examination. The FISH assay was done using a mixture of fluorescently-labeled probes to the centromeres of chromosomes 3, 7, and 17 and chromosomal band 9p21 (Abbott UroVysion) to identify cells having chromosomal abnormalities including polysomy and/or chromosomal deletion. A case was regarded as polysomy if four or more cells exhibited three or more centromeres signals of two or more chromosomes in 25 cells examined. A case was regarded as chromosomal deletion if twelve or more cells exhibited deletion of 9p21 in 25 cells examined.

Results: Polysomy, chromosomal deletion and chromosomal abnormalities were noted in 28 (93%), 6 (20%) and 29 (96%) of 30 cases of pancreatic cancer, respectively. On the other hand, No polysomy or chromosomal deletion were detected in 5 cases of chronic pancreatitis. The sensitivity and specificity of FISH for brushing specimens of the discrimination between pancreatic cancer and chronic pancreatitis was 100% and 83%, respectively. There was no significant correlation between grade of polysomy and various clinicopathological factors including lymph node metastasis, lymphatic involvement, venous involvement, peri-neural invasion or histological grade of pancreatic cancer.

Conclusion: FISH is significantly more sensitive than and nearly as specific as conventional cytology for the detection of pancreatic cancer. FISH may improve the clinical management of patients who are being evaluated for malignancy in pancreatic cancer.

P-107

Gene Expression Levels as Predictive Markers of Outcome in Pancreatic Cancer After Gemcitabine-based Adjuvant Chemotherapy

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Background: The standard palliative chemotherapy for pancreatic ductal adenocarcinoma (PDAC) is gemcitabine-based chemotherapy; however, PDAC still presents a major therapeutic challenge. The aim of this study was to investigate the expression pattern of genes involved in gemcitabine sensitivity in resected PDAC tissues and to determine correlations of gene expression with treatment outcome.

Methods: We obtained formalin-fixed paraffin embedded (FFPE) tissue samples from 70 patients with PDAC who underwent pancreatectomy in our institution from 1992 to 2007. Forty of 70 patients recieved gemcitabine-based adjuvant chemotherapy. We measured *human equilibrative nucleoside transporter-I* (*hENT1*), *deoxycytidine kinase* (*dCK*), *cytidine deaminase* (*CDA*), and *ribonucleotide reductase subunits M1 and M2* (*RRM1* and *RRM2*) mRNA levels by quantitative real-time RT-PCR, and determined combined score (GEM score), which was calculated based on the expression levels of *hENT1*, *dCK*, *RRM1*, and *RRM2* expressions. We investigated the association between the expression levels of individual genes and of the GEM score with survival time using univariate and multivariate analyses. Furthermore, by determining the mRNA levels of these genes in endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) cytological specimens, we investigated the feasibility of individualized chemotherapy.

Results: High *hENT1* ($P=0.011$), high *dCK* ($P=0.0095$), low *RRM1* ($P=0.041$), low *RRM2* ($P=0.030$), and low GEM score ($P=0.0002$) groups had a significantly longer survival in gemcitabine treated group. A low GEM score (<2) was an independent predictive marker for poor response to gemcitabine-based adjuvant chemotherapy, with a relative risk of 5.677, as shown by multivariate analysis ($P=0.0002$). Altered expression levels of these genes were distinguishable in microdissected neoplastic cells from EUS-FNA cytological specimens.

Conclusion: Quantitative analyses of *hENT1*, *dCK*, *RRM1*, and *RRM2* mRNA expressions using FFPE tissue samples may be useful to predict the gemcitabine-sensitivity of patients with PDAC.

P-108

Radiation Enhances Oncolytic Effect of a hTERT Promoter-dependent Conditionally Replicative Adenovirus in Pancreatic Cancer Cells

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Background & Aim: Oncolytic virotherapy is a promising approach for treating pancreatic cancer, however, clinical trials revealed that it is difficult to eradicate pancreatic tumors with oncolytic virotherapy alone. The aim of the present study is to examine the effect of combination therapy of radiation and oncolytic virotherapy on pancreatic cancer.

Methods: Pancreatic cancer cells were treated with human telomerase reverse transcriptase (hTERT) promoter-dependent conditionally replicative adenovirus (Ad5/3hTERT), which replicate selectively in tumor cells expressing hTERT, radiation, or the combination with them. We evaluated the inhibitory effect on cell proliferation with PI assay. Quantitative RT-PCR was performed to evaluate the expression of hTERT and Cyclin E1 (G1/S-specific marker) in the cells treated with radiation and Ad5/3hTERT. In addition, virus replication was evaluated in the cells treated with radiation.

Result: Combination therapy (radiation and Ad5/3hTERT) significantly inhibited the cell proliferation compared with each single therapy (each, $P<0.05$). Radiation up-regulated relative levels of hTERT mRNA expression, suggesting that virus E1 expression was increased via activation of hTERT promoter. Cyclin E1 expression was increased in the cells transfected with virus E1-expressing plasmid. Furthermore, virus replication was significantly increased in the cells treated with radiation. Taken together, these data suggest that radiation-enhanced virus E1 expression contributes to increase of viral replication via induction of S phase.

Conclusion: Current data showed that radiation synergistically enhanced oncolytic effect of Ad5/3hTERT in pancreatic cancer cells in vitro, and may provide an optimal therapy for controlling pancreatic cancer.

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P-109

Expression of Nanog, Oct3/4, Sox2, c-Myc, and Klf4 in the Human Pancreatic Cancer

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Introduction: Oct3/4, Sox2, c-Myc, and Klf4;(Yamanaka 4 factors) introduce pluripotent differentiation and high proliferative capacity in a coordinated manner. Nanog is also a master gene of pluripotency. On the other hand, Klf4 and c-Myc are known as cancer-related genes. In this study, we studied the expression of these transcription factors in pancreatic cancer, and compared it to the clinicopathological factor of the patients.

Methods: Nanog, Sox2, c-Myc, Oct-4, and Klf4 expressions were analyzed by tissue array (TMA1150) in 34 pancreatic cancer patients who underwent the surgery at our department from 1988 to 2005.The patients consisted with Stage1;1, Stage2; 5, Stage3; 15, Stage 4a; 6, and Stage 4b; 7. Gene expressions were evaluated by the combination of the immunohistological intensity and distribution.The final decision was made by two pathologists. Survival curves were plotted using the the Kaplan-Meier method and Log-Rank test.

Results: The positive rate of each genes were as follows. Nanog; 10 /26 (38.5%), Oct3/4; 3 /16 (17.6%), Sox2; 3 /15 (20.0%), c-Myc; 21 /22 (95.5%), and Klf-4; 6 /15 (40.0%). There was no clear relationship between each gene and clinicopathological factors. Nanog expression of the patients who had performed R0,1 resection (n=23) was significantly associated with overall survival (p=0.04). The patients (n=10) with Nanog higher expression had a longer survival time (median survival=34 months) compared to patients (n=13) with lower expression (median survival=15 months).

Conclusions: In pancreatic cancer, high rate of c-Myc expression were observed,and Nanog expression might have prognostic impact for pancreatic cancer.

P-110

PEGylated Adenovirus Vectors with Cancer Targeting Ligands Improve Specificity of Adenovirus Vectors for Tumor Cells in Pancreatic Cancer

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Backgrounds: Adenovirus vectors are expected to be an attractive strategy in cancer therapy, but they have some obstacles for clinical use. One is induction of immune responses, and the other is low transfer gene expression in tumor tissue. On the other hand, it is known that polyethylene glycol (PEG) modification (PEGylation) is a technique to extend circulating time of therapeutic peptides or proteins in blood and induce enhanced permeability and retention (EPR) effect in tumor tissue and reducing immune responses.

Purpose: To overcome problems of conventional adenovirus vectors, we established cancer-specific targeting PEGylated adenovirus vectors and investigated their specificities to tumor cells in pancreatic cancer.

Methods: We determined optimized PEG modification ratio to adenovirus vector, and constructed PEGylated AdlacZ (PEG-AdlacZ). Then, we conjugated several cancer-targeting ligands (CTL) to PEG-AdlacZ, and generated CTL-PEG-AdlacZ. We investigated characterizations of CTL-PEG-AdlacZ by dynamic light scattering (DLS) and in vitro functions of CTL-PEG-AdlacZ in pancreatic cancer cell lines.

Results: The optimized PEGylated ratio was over 25:1 (PEG:AdlacZ). We constructed CTL-PEG-AdlacZ by conjugating with CTL-PEG to AdlacZ at a 25:1 molar ratio. The average size of CTL-PEG-AdlacZ is approximately 140 nm. We measured the transgene expression levels induced by CTL-PEG-AdlacZ using X-gal staining, and found that lacZ expression was transduced selectively in targeted pancreatic cancer cells.

Conclusion: We successfully constructed PEGylated adenovirus vectors which had ability to target cancer cells selectively. This strategy might improve the efficiency of gene therapy and be a new strategy for cancer therapy.

P-111

Antitumor Effect of R1507, a Novel IGF-1R Monoclonal Antibody, on Human Pancreatic Tumor Cells Cultured in vitro

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The IGF-1R (IGF receptor type 1) pathway is frequently deregulated in human tumors and has become a target of interest for anti-

cancer therapy. Roche R1507 is a fully humanized IGF-1R monoclonal antibody. We evaluated the effects of R1507 on the growth of several pancreatic tumor cell lines in vitro. We found that the 20 pancreatic tumor cell lines and immortalized pancreatic ductal cell line HPDE-E6E7-c7 expressed IGF-1R moderately analyzed by qRT-PCR. Next we evaluated the effect of R1507 on the growth of pancreatic cancer-derived cell lines in vitro. The growth inhibitory effect of R1507 against several pancreatic cell lines as indicated by IC50 value, was dozens of times more potent than Gemcitabine and 5-FU at 24 hr exposure. On the other hand R1507 has little inhibitory effect on HPDE-E6E7-c7, normal tissue control, suggesting it has little side effect. But there is less growth inhibitory effect at 48–72 hr exposure, probably because of the lack of immune system to kill cells following antibody-antigen interaction in the culture condition. Next we evaluated combined R1507 and Gemcitabine, and R1507 and 5-FU on the pancreatic tumor cell lines in vitro. Combined R1507 and Gemcitabine are superior to gemcitabine alone each at the concentration of 0.5 x IC50 in the 24 hr treatment of human pancreatic tumor cell line AsPC-1, SUIT-2 and MIA-Paca-2. In conclusion, R1507, used alone or combined with gemcitabine, is a promising anticancer drug on human pancreatic cancer cells evaluated in vitro. In vivo evaluation of antitumor effect of R1507 on human pancreatic cancer cells using subcutaneous and orthotropic transplantation models of nude mice is ongoing.

P-112

Anti-tumor Effect of Angiotensin II Type 1 Receptor Antagonist Which Has Synergic Effect with Gemcitabine Administration on Orthotopic Rat Pancreatic Cancer Model

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Objective: Angiotensin II type 1 receptor (AT1) stimulates the growth and angiogenesis of pancreatic cancer. We investigated that anti-tumor effect of AT1 antagonist and its synergic effect with gemcitabine (GEM) on orthotopic rat pancreatic cancer model.

Methods: Lewis rat orthotopic pancreatic cancer model was prepared with DSL-6A/C1. To examine the effect of gemcitabine and AT1 antagonist (Losartan; Los) on Lewis rat ductal pancreatic adenocarcinoma cell line (DSL-6A/C1), proliferation was determined by MTT assay. The animals were treated with GEM (100mg/kg/weekly) and/or Los (100mg/kg/daily) for 4 weeks. Animal survival and AT1 expression on pancreatic cancer tissue were evaluated.

Results: Expressions of AT1 on DSL-6A/C1 cell line and in pancreatic cancer tissue were confirmed by Western blot analysis. MTT assay showed that DSL-6A/C1 cell proliferation was significantly reduced by co-cultured with GEM and/or Los in a dose-dependent manner ($p<0.05$). Mean survival time (59.6 ±13.4days) was significantly improved by treatment with GEM (89.6±21.8days; $p=0.0005$), Los (76.9±18.7days; $p=0.013$), or GEM+Los (102.6±16.5days; $p<0.0001$) ($n=12$ each groups). Although there was no significant difference in survival curves between GEM/Los combination therapy and GEM, GEM/Los combination therapy significantly improve survival compared with Los alone ($p=0.014$).

Conclusion: These observations suggest AT1 antagonist has anti-tumor effect on rat pancreatic cancer model. Furthermore, concomitant use of AT1 antagonist with GEM may be a useful therapeutic strategy for pancreatic cancer.

P-113

Clinical and Immunologic Evaluation of Dendritic Cell-based Vaccination in Combination with Gemcitabine/S-1 in the Patients with Advanced Pancreatic Cancer

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Background and Objective: Pancreatic cancer has a poor prognosis. Tumor-specific cytotoxic T lymphocytes (CTLs) can be activated in vivo by dendritic cell (DC)-based vaccination. However, clinical responses to the immunotherapy with DC vaccination have only been observed in a minority of patients with solid cancer. In the current study, the clinical and immunologic efficacy of the DC vaccine pulsed with the peptide(s) derived from pancreatic cancer-associated antigen(s) in combination with gemcitabine/S-1 has been evaluated in the patients with advanced, inoperable pancreatic cancer.

Patients and Methods: Eighteen patients with advanced, inoperable pancreatic cancer refractory to standard treatment were entered the study. DCs generated from CD14+ monocytes from leukapheresis by 6-day cultivation with granulocyte macrophage-colony stimulating factor and interleukin-4, were matured by OK-432, a streptococcal agent, and were pulsed with the pancreatic cancer-associated antigen(s). These DCs (1 x 107) were intradermally administered 7 times at 14-day intervals concomitantly combined with gemcitabine and/or S-1.

Results: Of the 18 patients, complete response (CR) was observed in 2 (11.1%), partial response (PR) in 7 (38.9%), stable disease (SD) in 5 (27.8%), progressive disease (PD) in 4 (22.2%). Response rate was 50%. Survival rate, quality of life, performance status were markedly increased. In 3 patients, immunologic responses have been analyzed. Numbers of regulatory T cells were decreased after DC vaccination in all 3 patients examined. In 2 of 3 patients, Numbers of WT1-tetramaer positive CD8+T cells were increased after the therapy. Severe side effects of more than grade 3 which were assessed in accordance with NCI-Common Toxicity Criteria v.2.0, were not observed.

Conclusions: It was strongly suggested that the DC vaccination pulsed with cancer associated-peptide(s) in combination with gemcitabine and/or S-1 was safety and effective in the patients with the inoperable pancreatic cancer refractory to standard treatment.

P-114

Abberant Signaling Pathways in Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Background and Aim: Intraductal papillary mucinous neoplasms of the pancreas (IPMNs) are characterized by intraductal growth of mucin-secreting neoplastic cells with varying degrees of atypia and various type of papillae. Some IPMNs are associated with invasive carcinoma composing of tubular or mucinous adenocarcinoma. The molecular mechanisms of the development and progression of IPMN are poorly understood. We investigated aberrant multiple signaling pathways involving EGFR, MAPK and AKT in IPMNs.

Materials and Methods: We studied 92 IPMNs including 39 of those of low-grade/adenoma and 53 of those of high-grade/carcinoma. Expressions of EGFR, MAPK, phosphorylated MAPK (p-MAPK), AKT and phosphorylated AKT (p-AKT) were investigated by immunohistochemistry.

Results: Significant expressions of EGFR, MAPK, p-MAPK, AKT, and p-AKT were observed in 82.1%, 94.9%, 100%, 0%, and 0% of 39 low-grade IPMNs, and 96.2%, 96.2%, 81.1%, 9.4%, and 7.6% of 53 high-grade IPMNs, respectively. EGFR expressions in high-grade IPMNs were significantly prevailed than those in low-grade IPMNs ($p=0.023949$). Moreover, EGFR expressions in nuclei were significantly different between IPMNs of low-grade and those of high-grade (0% vs 20.75%, $p=0.002443$). Morphological types of papillae of IPMNs were not associated with any of the expressions.

Conclusions: Aberrant signaling pathways may be actively involved in development and progression of IPMNs.

P-115

A Large-series, Multicenter Analysis of Polymorphic Variants in Cancer-associated Genes in Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Accumulating evidence has shown that intraductal papillary mucinous neoplasms (IPMNs) are associated with pancreatic and extrapancreatic malignancies at a high incidence (~30%), raising a possibility of genetic event(s) susceptible to the development of neoplasms, such as a germline mutation/variant in cancer-prone gene(s). In an attempt to determine common genetic variants linked to IPMNs, we conducted a large-scale, multi-center screening study for single nucleotide polymorphism (SNP) in patients with IPMNs. We genotyped 20 SNPs in 260 individuals with IPMN and 499 healthy controls. The target SNPs analyzed were those previously identified as cancer-associated genes, including TP53, MTHFR, PPARG, IGFBP3, STK15, MBD4, ADPRT, XRCC1, OGG1, APC, MMP2, STCH, ODC, MMP7, ADH1B, ALDH2, POU5F1P, STKI11, SPINK1, and PRSS1. Our analyses, however, showed no significant association of any SNPs with IPMN. Thus, common variants in these cancer-associated genes are unlikely the target for IPMNs, suggesting that other genetic and/or epigenetic alterations may influence the development of this specific type of neoplasm.

Poster 18 Pancreatic Cancer Chemotherapy

P-116

The Usefulness of The Second Line S-1 Chemotherapy Following Gemcitabine (GEM) for Unresectable Pancreatic Cancer

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Background and Aim: To treat unresectable pancreatic cancer (UPC), we have used GEM since April 2001, and S-1 for the second line chemotherapy since August 2006. The aim of this study is to clarify the present state and the usefulness of S-1 for the second line chemotherapy.

Patients and Method: From April 2001 to December 2009, we treated 112 UPC patients with the first line GEM-monotherapy. They were divided into group A (before the introduction of S-1) and group B (after the introduction of S-1), and group B was further divided into group B1 (switching over S-1) and group B2 (GEM-monotherapy). We compared the patients' characteristics and the survival time between group A and B, and between group B1 and B2. Next, we evaluated the prognostic factors using the Cox proportional hazards model.

Results: The response rate of GEM-monotherapy was 15.2%. The medium survival time (MST) of group A and B was 4.3 and 8.2 months respectively ($p=0.0041$). The rate of PS >1 patient at the time of GEM-refractory was 30.0% in group B1 and 97.2% in group B2 ($p<0.0001$). MST of group B1 (11.0 months) was longer than group B2 (6.9 months) ($p=0.0025$). The following prognostic factors are extracted on multivariate analysis, locally advanced ($p<0.0001$, hazard ratio: 0.307 [95% CI: 0.178–0.530]), increased CA19-9 during GEM-therapy ($p=0.0111$, 1.934 [1.163–3.218]), improvement and/or retainment of PS during GEM-therapy ($p=0.032$, 0.365 [0.186–0.713]), frequency of GEM administration >6 times ($p=0.0231$, 0.217, [0.058–0.811]), PS at GEM-refractory >1 ($p=0.0028$, 2.990 [1.456–6.139]), switching over S-1 ($p=0.0032$, 0.416 [0.232–0.745]).

Conclusion: The second line S-1 chemotherapy may prolong the patients' prognosis. However, the patients of poor PS at the time of GEM-refractory showed unfavorable prognosis. A S-1 shift before the PS exacerbation may be a possible option to prolong prognosis especially in the patients with increasing CA19-9 during GEM-monotherapy.

P-117

Feasibility of Combination of S-1 Administration Prior to Gemcitabine Therapy as a Second-line Therapy for Unresectable/ Recurrent Pancreatic Cancer: A Single Institute Experience

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Background: No established second-line treatment exists for patients with advanced pancreatic cancer. We have shown in the previous studies (Pancreas, 33:142–147, 2006. Anticancer Res, 28:179–186, 2008.) that the combination of the administration of 5-fluorouracil (5-FU) prior to GEM has been considered as a promising strategy for pancreatic cancer. We evaluated the feasibility of this combination chemotherapy as a second line treatment for unresectable/recurrent pancreatic cancer.

Methods: Eligibility criteria: histologically or cytologically proven pancreatic ductal carcinoma previously treated with GEM as first-line therapy, measurable disease, age above 20 yrs, good performance status (0–2 in PS) with expected life more than 2 months, normal renal, liver, and bone marrow function, capable oral intake, and written informed consent. S-1 (80 mg/ m2/day) was orally administrated from day 1 through day 5,and day 8 through day 12, and GEM (1,000 mg/m2, div/30min) was administrated on day 6 and 13, and one week rest every 3 weeks. The primary efficacy endpoint was disease control rate defined as CR, PR, or stable disease (SD) according to RECIST.

Results: 29 pts (14 male, 15 female) were enrolled (median age, 65.0 yrs). 9 pts were considered to be unresectable and 20 pts were recurrent pancreatic cancer after curative surgery (7: liver, 9: lung, 7: lymph node). Median number of courses administrated was 7 (range 1–22). Grade 3–4 toxicities were neutropenia (48%), leucopenia (41%), thoronbocytopenia (14%), and anorexia (10%). Disease control rate was 62% (1(3%) CR, 5 (17%) PRs, and 12 (41%) SDs. Median progression-free survival time was 4.1 months (range 0.5–18.5M). Median survival time was 16.2 months (range 1–32.9M).

Conclusion: The combination chemotherapy with pre-administrated S-1 and GEM is well tolerated and is active for the second-line treatment of advanced pancreatic cancer after GEM.

P-118

The Effectiveness of Paclitaxel for Gemcitabine-refractory Pancreatic Cancer

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Background and Aims: Gemcitabine showed significant improvement of cancer-related symptoms and survival. However, almost all pancreatic cancer cannot be cured with gemcitabine-based first-line chemotherapy. Thus, salvage chemotherapy after gemcitabine is necessary for patients who maintain a good performance status. We evaluated the efficacy and feasibility of paclitaxel in patients with gemcitabine-refractory pancreatic cancer. We also evaluated the correlation between the decline in tumor marker and the response rate.

Patients and Methods: Thirty patients histologically diagnosed as pancreatic cancer and received a paclitaxel regimen as salvage chemotherapy were analyzed retrospectively. Paclitaxel treatment was performed with 80 mg/m2/week for continuous three weeks followed by one week rest and was continued until failure defined by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Adverse events were evaluated by Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Tumor marker response was evaluated with monthly measured CA 19-9, CEA, and DUPAN-2.

Results: Totally 272 weekly paclitaxel treatments were performed. The median administration per patient was 8 (1–22) times. Five patients required a dose reduction. The median overall survival from the start of paclitaxel treatment was 6.7 (1.2–18.8) months. The response rate was 10% (3/30 patients) and the disease control rate was 46.7% (14/30 patients). Though grade 3–4 hematological and non-hematological toxicities were seen in 7 and 6 patients, respectively, adverse events were manageable conservatively. We found a significant correlation between the disease control rate and the decline of tumor marker within two months after the beginning of paclitaxel ($p=0.01$). Patients with tumor marker decline tended to have a longer survival.

Conclusion: Weekly administration of paclitaxel in patients with gemcitabine-refractory pancreatic cancer was well tolerated and effective. It should be considered as salvage chemotherapy after gemcitabine failure in patients with good performance status.

P-119

A Phase II Study of Personalized Peptide Vaccination Combined with Gemcitabine for Non-resectable Pancreatic Cancer Patients

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The present multicenter phase II study was conducted to confirm the safety of, and clinical and immune responses to personalized peptide vaccination with gemcitabine (GEM) as the first line therapy in patients with non-resectable pancreatic cancer. Patients with histologically or cytologically proven pancreatic adenocarcinoma with at least one measurable metastatic lesion were eligible for the study. Other eligibility criteria included: age of 20–80 years, ECOG performance status (PS) of 0 or 1, and adequate organ function. Pre-vaccination peripheral blood mononuclear cells (PBMCs) and plasma were prepared to examine cellular and humoral responses to 14 and 16 peptides in human leukocyte antigen (HLA)-A24+ or -A2+ patients, respectively. Only the reactive peptides (maximum of 4) were administered weekly at 3 mg/peptide. GEM was administered at 1,000 mg/m^2 per week for 3 weeks, followed by 1 week of rest. Twenty-one patients with untreated and non-resectable pancreatic cancer were enrolled. The combination therapy was generally tolerated. Boosting of cellular and humoral responses to the vaccinated peptides was observed in the post-vaccination (eighth) PBMCs and plasma from 14 of 18 and 13 of 18 patients tested, respectively. The best clinical responses were 7 cases of partial response, 9 cases of stable disease, and 5 cases of progressive disease. Median survival time of all 21 patients was 9.0 months with a one year survival rate of 38%. Immune boosting in both cellular and humoral responses was well correlated with overall survival with a hazard ratio of 0.13 (95% CI, 0.03 to 0.59; log-rank $p=0.008$). This study could be recommended for further stages of clinical trials because of safety, boosting of immune responses, and potential clinical benefits.

P-120

Clinical Comparative Study of Operation, Intra-arterial Chemotherapy, Chemoradiation and Chemotherapy (Gemcitabine) for Stage IVa Pancreatic Cancer

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Purpose: This time We have acomparative study about operation (OP), intra-arterial chemoradiation (IACRT), chemoradiation (CRT) and chemotherapy (CT) (Gemcitabine only) for Stage IVa pancreatic cancer. And consider about standard selection of treatment for panceatic cancer.

Methods: 248 cases of Stage IVa pancreatic cancer from 2003 to 2006 were studied. Comparative study of clinical effect (prognosis) were studied about OP 154, IACRT 16, CRT 32, CT 46 cases. About IACRT, Gemcitabine 400–1000mg/body and CDDP 10mg/body were performed through the intra-arterial reservoir once/2 weeks. About CRT, after 45Gy radiation, Gemcitabine 1000mg/m^2 were performed. About CT, Gemcitabine 1000mg/m^2 were performed.

Result: About the Clinical result of OP, IACRT, CRT, CT, each MST was 990.5days, 665.0days, 434.2days, 425.6 days, and each survival rate for 2 years was 44.3%, 18.8%, 9.4%, 4.3%. And we studied effect for prognosis (OP, IACRT, CRT, CT) about the grade of retroperitoneal plexus infiltration (PL+ or ± or -).

Conclusion: Prognosis of OP was better than the others. Next was IACRT, CRT and CT. OP and IACRT were worse prognosis for PL+ rather than PL-.

P-121

Prognostic Factor for LAPC Patients Treated with CRT

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Backgrounds/Aims: The prognostic factors have not been well studied in LAPC patients treated with CRT. The aim of this study was to evaluate the prognostic factors that could expect long-term survival in LAPC patients treated with CRT.

Methods: From January 1995 to December 2007, 118 patients (70 men, 48 women; median age 62 years) with LAPC were treated with CRT in one tertiary institution. Seventeen patients (14.4%) received 5-FU based CRT, 17 patients (14.4%) received paclitaxel-based CRT, and 84 patients (71.2%) received gemcitabine-based CRT. Various factors were classified into three groups, such as patient factors, tumor factors, and treatment factors, and were analyzed.

Results: One hundred patients (84.7%) completed the scheduled CRT. Eighteen patients (15.3%) showed therapeutic response (complete response plus partial response), 66 patients (55.9%) showed stable disease, and 34 patients (28.8%) showed progressive disease. Median overall survival of all patients was 11.6 months (95% CI: 10.2–13.0 months). Among patient factors, univariate analysis revealed that younger age (<65 years), good performance (ECOG 0–1), abdominal pain, less weight loss (<5 Kg), and normal hemoglobin (>11 g/dL) were good prognostic factors. Among tumor factors, tumors with N0 stage and low level of CA19-9 (<2000 U/mL) showed good prognosis. Among treatment factor, completion of CRT, paclitaxel or gemcitabine-based CRT, therapeutic response, decrease of CA19-9 level, and operation after CRT were good prognostic factors. Multivaiate analysis revealed that good performance (ECOG 0–1), low level of CA19-9 (<2000 U/mL), clinical response (CR+PR+SD), decrease of CA19-9 level (>30% drop), operation after CRT were independent good prognostic factors for LAPC patients treated with CRT.

Conclusions: Baseline CA19-9 itself was an independent prognostic factor and follow up of it after completion of CRT could predict long-term survivors in LAPC patients treated with CRT.

P-122

Characteristics of Four Long-term Survivors with the Resection of Pancreatic Cancer Treated with Neoadjuvant Chemoradiotherapy and Portal Infusion Chemotherapy

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Recent data suggest that a multimodality approach consisting of surgery combining neoadjuvant chemoradiotherapy could improve local control and survival in patients with pancreatic cancer. Since 2003, we have performed neoadjuvant chemoradiotherapy and adjuvant portal infusion chemotherapy after extended pancreatectomy for patients with potentially resectable pancreatic adenocarcinoma. Patients received a continuous infusion of 5-FU and unfractionated heparin accompanied by MMC and CDDP and concurrent radiotherapy (NCRT), followed by surgical resection of the pancreatic tumor. After resection, continuous intraportal infusion of 5-FU and unfractionated heparin accompanied by systemic infusion of MMC and CDDP (PIC) was performed. Until now, we have 4 patients who survived over 5years and analyzed the clinicopathological features of them. According to the Response Evaluation Criteria in Solid Tumor (RECIST) scale, one case showed a partial response and 3 cases were in stable diseases. Pathological staging was Stage 0 in one and Stage III in 2 and IVb in one. The status of the residual tumor after surgery was R0 in 2 and R1 in 2. In 2 cases, carcinoma in situ in the pancreatic ducts existed beyond the main tumor lesions. Lymph node metastasis didn't exist in these four cases. According to the evaluation of the histopathological response criteria by Scodan RL. et al (Am J Clin Oncol 2008; 31: 545–52), major response was present in one, moderate response in one, and minor response in 2. Moreover, based on the classification of response criteria in breast cancer, there were Grade1a in one, Grade 1b in 2 and Grade2 in one. These findings suggested that RECIST scale and Scodan's criteria do not always correspond to the prognosis of these cases. This combined modality therapy of NCRT and PIC might improve the prognosis of pancreatic cancer after surgery. We need further investigate the relationship between the outcome and histological responses.

P-123

Three Cases of Advanced Pancreatic Cancer Received Preoperative Chemotherapy – The Histological Evaluation of Its Anti-tumor Effect –

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We present three cases of resected locally advanced pancreatic adenocarcinoma after chemotherapy.

Histopathlogical evaluation of response is based on the amount of viable cells among the whole lesion including necrosis, fibrosis, and existence of macrophage. We defined the percentage of viable cancer areas among the whole lesion area at the maximum cut surface of the lesion as a shrinkage rate.

Case 1: A 64-year old woman was diagnosed as locally advanced pancreas carcinoma with the portal vein and gastric wall invasion. After four courses of chemotherapy (TS-1/Gemcitabine), we performed pancreaticoduodenectomy with portal vein reconstruction. Pathological finding showed that a small amount of adenocarcinoma cells were scattered in fibrous tissue, and the shrinkage rate was 98%.

Case 2: A 47-year old woman was diagnosed as locally advanced pancreas carcinoma with the portal vein and gastric wall invasion. After four courses of chemotherapy (TS-1/Gemcitabine), distal pancreatectomy with portal vein reconstruction was performed. Histological examination showed well differentiated adenocarcinoma surrounded by fibrous tissue and mucinous lake without cancer cells, and the shrinkage rate was 55%.

Case 3: A 37-year old man was clinically diagnosed as carcinoma of the forth portion of duodenum with invasion to pancreas and portal vein system. After four courses of chemotherapy (Docetaxel/CDDP/TS-1), we performed pancreaticoduodenectomy combined with resection of the forth portion of duodenum, left adrenal, and transverse colon. Histology revealed that invasive ductal carcionam of the pancreas was invaded to the duodenum wall and fibrous tissue spread over the retropancreatic tissue, and the shrinkage rate was 45%.

All three patients were possible to received a histologically R0 resection after chemotherapy. Preoperative chemotherapy can be thus an alternative treatment for the borderline resectable pancreatic carcinoma. Further studies are necessary to establish the effective preoperative chemotherapy regimen and the methods of histopathological assessment of preoperative therapy for pancreatic cancer associated with favorable prognosis.

Poster 19 Pancreatic Cancer Surgery 2

P-124

Prognostic Factors in Patients with Locally Advanced Pancreatic Body Cancer Undergoing Distal Pancreatectomy with En-bloc Celiac Axis Resection (DP-CAR)

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Objective: The purpose of this study was to investigate prognostic factors in patients who underwent Distal Pancreatectomy with en-bloc Celiac Axis Resection (DP-CAR) for locally advanced pancreatic body cancer and to reconsider indication of this procedure.

Methods: Between 1998 and 2008, 50 patients underwent DP-CAR for locally advanced pancreatic body cancer without distance metastasis, when the gastroduodenal artery and the superior mesenteric artery were likely to be preserved. Prognostic factors were defined by univariate and multivariate analyses.

Result: According to Japan Pancreatic Society (JPS) staging system, the numbers of patients of III, IVa, and IVb disease were 9, 32, and 9 patients, respectively. The median operative time was 458 minutes. The median blood loss was 970ml. Histopathological negative surgical margins were achieved in 46 patients (92%). The predominant postoperative complication was pancreatic fistula (46%). Two patients died of postoperative complications: acute myocardial infarction and multiple organs failure. The median survival time was 25 months and disease specific 1-, 3-, and 5-year survival rates were 78%, 40%, and 30%, respectively. Multivariate analysis revealed that operative time, postoperative hospital stay, and preoperative C-reactive protein (CRP) level were the independent negative prognostic factors for survival.

Discussion: As elongation of operative time and postoperative hospital stay showed strong correlations with tumor invasion to other organs (stomach, jejunum, etc.), treatment strategy for tumors invading other organs would be reconsidered. Also elongation of postoperative hospital stay had a strong negative correlation with the opportunity of adjuvant chemotherapy.

Conclusions: DP-CAR could provide comparatively good prognosis for the patients with locally advanced pancreatic body cancer, with the estimated disease specific 5-year survival rate of 30%, and the median survival time of 25 months. Treatment strategy for patients with tumors such as invading other organs would be reconsidered.

P-125

Lymph Node Metastasis and Survival of Patients with Carcinoma of the Body and Tail of the Pancreas

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Backgrounds/Objectives: Carcinoma of the pancreas is characterized by neural invasion and lymph node metastasis. However, there are insufficient studies characterizing the role of lymphatic metastasis on clinical outcome in pancreatic body and tail carcinoma. The aim of this study was to assess the impact of lymph node metastasis on patient outcome in pancreatic body and tail carcinoma.

Methods: Eighty-four cases of adenocarcinoma of the body and tail of the pancreas who underwent pancreatectomy were selected for analysis in this study. The correlation between the location, the number, and the ratio of metastatic lymph nodes and the survival of patients was investigated.

Results: Forty-two patients with lymph node metastasis had significantly worse prognosis (P=0.0324). Although the anatomic location of metastatic lymph nodes had no significant influence on survival, prognosis of patients with five or more metastatic lymph nodes was significantly poorer than that of patients with less than five metastatic nodes (P=0.0186). In addition, patients with a metastatic lymph node ratio of 0.2 or more had the worst prognosis compared to both patients with a metastatic lymph node ratio of less than 0.2 (P=0.0001) and patients without lymph node metastasis (P<0.0001).

Conclusions: Our results indicated that the number and the ratio of metastatic lymph nodes, rather than the anatomic location, are the major determinants of poor patient survival on the contrary to the current staging strategy.

P-126

The Impact of Vessel Invasion on Prognostic Factor in Carcinoma of the Body and Tail of the Pancreas

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Objectives: Involvement of the splenic artery (SA) and vein (SV) is frequently observed in carcinoma of the body and tail of the pancreas, but its correlation with various other clinicopathologic factors and prognosis has not been explored in detail. A retrospective study was performed to determine the prognostic implications of invasion to the splenic vessels in pancreatic body and tail cancer.

Methods: Fifty-one patients who had undergone distal pancreatectomy for invasive adenocarcinoma of the body and tail of the pancreas were discreetly selected from the prospective data base for analyses. Cases that required extended surgery due to invasion of the major vessels such as the portal vein, common hepatic artery, celiac artery and superior mesenteric artery were excluded. Correlation between invasion of the splenic vessels and prognosis and other clinicopathologic factors were analyzed.

Results: Seventeen patients with invasion of the SA had a significantly inferior prognosis compared with those without the invasion (P=0.0067), whereas invasion of the SV, observed in 24 patients, did not affect prognosis. Additionally, invasion of the SA significantly correlated with tumor size >2cm, anterior serosal infiltration, perineural invasion and SV invasion (P=0.0440, P=0.0406, P=0.0460 and P=0.0173, respectively). In univariate analysis, SA invasion, lymph node metastasis and anterior serosal infiltration were identified as significant poor prognostic factors. In multivariable analysis, only SA invasion was an independent prognostic factor (odds ratio 2.611, P=0.0196).

Conclusions: Our results indicated that the invasion of the SA, but not that of the SV, is a crucial prognostic factor in pancreatic body and tail cancer.

P-127

Appleby Operation for Carcinoma of the Body and Tail of the Pancreas

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Background/Purpose: Appleby operation was first reported in 1953 and enabled us to completely clear the pancreatic cancer with the lymph nodes, especially along the celiac axis, in a patient with pancreatic cancer in the body and/or tail of the pancreas. We retrospectively reviewed our clinical experiences of four patients with Appleby operation for pancreas cancer in the body or tail.

Methods: This retrospective report consisted of four Japanese patients who underwent Appleby operation for advanced pancreatic cancer in the body or tail of the pancreas July 1997 and April 2009.

Results: The four patients were three men and one woman with the mean age of 67.5 years. In all the four patients,preoperative imaging revealed pancreatic cancer with possible invasion to the artery (splenic artery in 3, celiac artery in 3 and common hepatic artery in 3) of the pancreas cancer. The mean operative time was 472min (range: 295–653). Residual tumor status (R) was R2 in one patient, R1 in two patients and R0 in another. Histologic examination of the resected specimens showed adenocarcinoma of the pancreas in three and SCC in another. Arterial invasion was confirmed in two patients (splenic artery and celiac artery in both). Three of the four patients had lymph node metastasis.Final stage was stage III in two patients and stage IVa in the other two patients. Pancreatic fistula developed in two patients. All of four patients had the local recurrence or the distant metastasis 2–8 months after the operation. Three patients who had R1 or R2 resection died within 10 months after operation.

Conclusion: From our experiences of the four patients, we conclude that the indication of Appleby operation for locally advanced pancreatic carcinoma remains limited at the present and would be advocated for patients with possible R0 resection using this radical operation.

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Vascular Variations Encountered During Pancreatoduodenectomy for Periampullary Malignancies

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Introduction: The presence of vascular variations increases the risk of hemorrhage and ischemia during pancreatoduodenectomy for periampullary malignancy. We report our recent experience with these variations.

Methods: The Database of the HPB Unit was searched for aberrant vascular anatomy as well as other anatomic variations that were identified during pancreaticoduodenectomy between January 2007 and January 2010.

Results: 57 patients underwent a pylorous preserving pancreatoduodenectomy during this time period. 42 patients (73.7%) had pancreatic adenocarcinoma, 10 patients (17.5%) had distal common bile duct cholangiocarcinoma, and 5 patients (9%) had carcinoma of the ampulla of Vater. Thirty six (63.2%) were male and 21 female (36.8%), with a median age of 64 years (range 49–85). During laparotomy, a total of 9 anatomic vascular variations were identified (15.8%). An accessory right hepatic artery from the superior mesenteric artery (SMA) was found in 4 patients (7%), a replacing right hepatic artery from the SMA was found in 4 patients (7%) and one patient presented with the Kelaiditis syndrome and a duplicated superior mesenteric vein (1.8%). The accessory right hepatic artery was injured in two patients during the surgical procedure and was primarily repaired. These injuries did not influence the patient's intraoperative blood transfusion requirements, overall morbidity or hospital stay.

Conclusions: In the present series, aberrations of the right hepatic artery were in accordance to the numbers reported in the literature with a slightly higher preponderance of an accessory compared to a replacing right hepatic artery from the superior mesenteric artery. Meticulous identification and preservation of the regional aberrant vascular anatomy should be attempted.

Poster 20 Pancreatic Cancer Case Report 2

P-129

Neoadjuvant Chemoradiotherapy and Pancreaticoduodenectomy for Locally Advanced Pancreatic Head Cancer with Extrapancreatic Nerve Plexus Invasion

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Background: With currently available surgical techniques, patients with borderline-resectable pancreatic head cancer are at high risk for a margin-positive resection.

Patient: A 69-year-old man was diagnosed as locally advanced pancreatic head cancer with extrapancreatic nerve plexus invasion (encased >180°). He underwent a course of chemoradiotherapy (CRT) with a total 50.4Gy radiotherapy and S-1 (100mg/body) chemotherapy. Combined chemotherapy of gencitabine (GEM) (800mg/m^2) and S-1 (100mg/body) was continued after CRT. After 3 courses of chemotherapy, the tumor shrank to 1.5cm diameter and the invasion of extrapancreatic nerve plexus improved. The response of tumor to neoadjuvant CRT followed by combined chemotherapy of S-1 and GEM was PR. The patient underwent pancreaticoduodenectomy and reconstruction of SMV with no residual tumor. The histopathological finding showed atrophy of acini and extensive fibrotic tissue were observed in the pancreatic head, and no cancer tissue were observed in the extrapancreatic nerve plexus. The patient was still alive without recurrence 12 months after first visiting our institution.

Conclusion: Neoadjuvant CRT followed by combined chemotherapy of S-1 and GEM was effective for locally advanced pancreatic cancer, and it may improve survival in patients with locally advanced pancreatic head cancer because of a higher rate of R0 resections.

P-130

Platinum-based Doublet Chemotherapy for Small Cell Carcinoma of the Pancreas: Report of a Case and Review of Literature

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Small cell carcinoma (SCC) of the pancreas is a rare malignancy with poor prognosis. Reported that most patients with SCC of the pancreas died within 1year after diagnosis, detailed data on effectiveness of chemotherapy is lacking. A 61-year-old man complaining of general fatigue, body weight loss and jaundice had a medical examination in a clinic. Laboratory findings revealing hepatobiliary enzymatic elevation and anemia, the patient was transferred to our hospital. Computed tomography (CT) and magnetic resonance imaging showed dilated common bile duct and main pancreatic duct compressed by a 6.5-cm mass, adjacent to the pancreas head to porta hepatis, with multiple liver masses and lymphadenopathy. The histological features by endoscopic ultrasound- guided fine needle aspiration biopsy for the diagnosis included the presence of round, uniform and small cells, which were occasionally indented mitosis and positive for CAM5.2, synaptophysin and trypsin, but negative for chromogranin A. Then, the tumor was diagnosed as SCC of the pancreas (T3N2M1: clinical stage IVb). As the first-line treatment a 21-day cycle of cisplatin 100 mg/m^2 (days 1) and etoposide 160 mg/m^2 (days 1–3) had been started, the dose of which had been decreasing gradually because of the hematologic toxicity. After 4 cycles CT evaluation showing the progression of the primary mass and the emergence of new lesions in the liver, a 28-day cycle of cisplatin 60 mg/m^2 (days 1) and irinotecan 60 mg/m^2 (days 1,8,15) was performed as second-line chemotherapy. Although the therapy evaluation was partial remission after 1 cycle, the dose of chemotherapy had been decreasing as same reason so as to be progress disease after 3 cycles. In conclusion, platinum-based doublet chemotherapy may improve the outcome in selected patients with advanced SCC of the pancreas, but further results are needed. In the meantime, the therapy should still be considered investigational.

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An Autopsy Case of Peritonitis Carcinomatosa with Pancreatic Cancer Treated by Intraperitoneal Administration of CDDP

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At present, as there are no effective therapeutic regimes for control of ascites due to peritoneal carcinomatosis, malignant ascites frequently affects quality of life in pancreatic cancer patients. A 61-year-old man with complaints of upper abdominal pain was transferred to our hospital for further examination and therapy in December 2008. A computed tomography scan of the abdomen demonstrated a pancreatic head mass with small calcifications. EUS guided FNA confirmed the diagnosis of tubular adenocarcinoma of the pancreas. After 4 courses of chemotherapy with gemcitabine, development of massive ascites was noted. Cytologic examination of the peritoneal fluid showed class-V adenocarcinoma and the patient was diagnosed as peritonitis carcinomatosa. In May 2009, he was given 100mg/body of CDDP intraperitoneally after informed consent was obtained. Adverse reactions were Grade-2 nausea, vomiting, and loss of appetite. After the therapy, the patient achieved temporary relief of symptoms but 2 months later, abdominal fullness and anorexia deteriorated again. Upper gastrointestinal endoscopy and ultrasonography revealed duodenal obstruction due to tumor involvement and massive ascites. He was treated by gastroduodenal stent placement with informed consent, and subsequently underwent 2 sessions of intraperitoneal chemotherapy with CDDP. Although he required paracentesis several times, the distressing symptoms subsided following these treatments. For third line chemotherapy, 80mg/body/day TS-1 was given orally, but was stopped because of Grade-3 stomatitis and bruising with Grade-3 thrombocytopenia. The patient subsequently developed DIC and died of gastrointestinal hemorrhage. Autopsy revealed a thickening of the mesentery and the peritoneum, and there was a solitary disseminated nodule measuring 1mm in diameter. No other nodules or findings of peritoneal dissemination were observed macroscopically. Stent patency was maintained at the stenotic lesion of the duodenum. The tumor was present at the head of the pancreas and had invaded to the stomach, transverse colon and duodenum.

P-132

Anaplastic Carcinoma of Pancreas with Tumor Thrombus – A Case Report

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Anaplastic carcinomas of the pancreas is uncommon disease. It has been representing only 0.5–7% of all pancreatic cancers. In addition, pancreatic cancers with tumor thrombus are rare. We report a resected case of anaplastic carcinoma of the pancreas with portal vein tumor thrombus. A 77-year-old Japanese man was referred for an abdominal giant tumor, found during an examination for back pain. Laboratory data showed leukocytosis and elevated CRP level, but tumor marker such as CEA and CA19-9 was not elevated. Abdominal CT showed a giant tumor which size was 10cm in diameter, at the pancreatic body and tail, and the tumor accompanied by the slight contrasting effect with necrotic change on the inside of the tumor. Magnetic resonance imaging (MRI) revealed a cystic-solid lesion with hyper-intensity on both T1-weighted and T2-weighted image. Moreover, there was a tumor thrombus in the splenic vein extending into the main portal vein. To get a histopathological evidence, endoscopic ultrasound-guided fine-needle aspiration biopsy was proceeded, the tumor was diagnosed as poorly differentiated adenocarcinoma. The patient underwent a distal pancreatectomy, combined with resection of spleen. The tumor involved the pancreatic body and tail, the resected specimen revealed an irregular, grayish-white mass, inside of the tumor was uneven, accompanying with some bleeding on the part. Tumor thrombus completely occluded the splenic vein, but could be dragged it out with loose adhesion to the vein. Tumor was composed of large polygonal or large spindle-shaped cells, these cells showed diffuse infiltration. On immunohistochemistry, tumor cells was positive for cytokeratin AE1/AE3, but negative for CA19-9, alpha-smooth muscle actin, and desmin. Together these findings, we diagnosed the tumor as anaplastic carcinoma of the pancreas.

P-133

A Case of Intramural Pseudocyst of the Duodenum Caused by Carcinoma of the Head of the Pancreas

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We present a case of intramural pseudocyst of the duodenum caused by carcinoma of the head of the pancreas.

A 60-year-old woman with obstructive jaundice and suspicious of pancreatic cancer was referred to our hospital. Computed tomography revealed a solid mass with a diameter of 30mm in the pancreatic head, which was compatible with pancreatic cancer, and a cystic lesion, 45mm in size, around the second portion of the duodenum, next to the solid mass. Trans-duodenal fine needle aspiration of the cyst under endoscopic ultrasonography was performed, which revealed adenocarcinoma in cytology. Pancreaticoduodenectomy was performed to remove both the solid mass and cystic lesion. Specimen pancreatography demonstrated communication between the pancreatic duct and the cyst. Cut surface of the resected specimen revealed a whitish mass in the pancreatic head and a cyst in the duodenal wall. Pathologically, the mass in the pancreatic head was invasive ductal carcinoma. The cystic lumen was not covered by epithelial cells, but cancer was scattered in the cyst wall.

This patient has been alive for two years without recurrence. There have been few reports describing pseudocyst in the duodenal wall caused by pancreatic cancer.

P-134

Invasive Ductal Carcinoma of the Pancreas Tail with Noninvasive Growth Through the Nondilated Main Pancreatic Duct and Macroscopically Cystic Invasive Carcinomatous Glands

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Noninvasive growth forming macroscopically dilated cystic pancreatic ducts is a fundamental feature of intraductal papillary mucinous neoplasm (IPMN), from which invasive carcinomas can arise. However, some invasive ductal carcinomas also show a macroscopically cystic feature simulating IPMN. We experienced two cases of invasive ductal carcinomas of the pancreas tail with noninvasive growth through the main pancreatic duct without dilation at the body

side, and with collection of macroscopically cystic carcinomatous glands infiltrating at the spleen side, which resembled some IPMN-derived invasive carcinomas. Both cases were examined by serial whole sections cut in round slices with hematoxylin eosin and elastica stains, and immunohistochemistry for mucin core proteins. These cases were different from IPMN or IPMN-derived invasive carcinomas in that they lack macroscopic dilatation of the pancreatic ducts, and the macroscopically dilated cystic carcinomatous glands seemed to be invasive but not intraductal. The intraductal component of the carcinomas showed papillary growth of neoplastic epithelia consistent with atypia of PanIN-3. Both intraductal and invasive components predominantly showed gastric mucin phenotype (MUC5AC+, MUC6 focally +, MUC2- or + in scattered small number of cells). Recognition of these pancreatic carcinoma cases is important in the following two points: 1) The presence of such cases should always be kept in mind as differential diagnosis of IPMN in imaging and pathological diagnoses. 2) The histogenesis of these cases might be placed in the intermediate between two major histogenetic pathways of pancreatic carcinomas (one from microscopic precursors called PanIN and the other from macroscopic precursors of IPMN), i.e. invasive carcinomas derived from semi-macroscopic extension of the intraductal lesion of the main pancreatic duct.

Poster 21 Cystic Pancreatic Tumor 2

P-135

Incidence of IPMN and Mucinous Cystic Tumours and Malignancy in a Single Series of Resected Pancreatic Cystic Tumors

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Introduction: IPMN and Mucinous Cystic Tumors (MCT) involve 10–13% of all cystic lesions and only 1–2% of pancreatic malignancies. There has been a recent increase in the frequency and the incidence of malignancy.

Material and Methods: Patients diagnosed according to the OMS classification (2000), at our institution from January 2002 and December 2009 were included.

Results: 99 patients were included. Average age of 56,2 (7–95). F:M ratio of 1.9:1. 65 F and 34 M. 40 were malignant cystic lesions, 59 were benign. There were 16 IPMN (16,2%) and 68,8% of these were treated surgically. M:F incidence for IPMN was 3:1. 53,8% were localized in the main pancreatic duct and 92,3% were in the head of the pancreas. There was one case of mixed presentation. 4 (25%) were benign, average size 3,0 (1,7–3,8cm). 12 (75%)were malignant with average size of 5,5 (4,5–9cm). There was one borderline case of 3,5cm localized distally. 4 cases (25%) were associated with acute pancreatitis. There were 12 MCT (12,1%). 3(25%) were benign with average size of 11,3cm (4–13cm). 9 (75%) were malignant, average size 4.6cm (2,5–9cm). All of them were distal and occurred in F patients. They were all removed.

There were 10 duodenopancreatectomies and 15 distal pancreatectomies. Mortality was 0 in this series.

Conclusion: 78,6% of IPMN and MCT tumors were malignant or pre malignant. 25% of IPMN were associated to acute pancreatitis 75% of IPMN were malignant. Mucinous type tumors had better prognosis than tubular type, and 75% of MCT were malignant. No lymph node involvement in all cases. Incidence of IPMN has increased in last 5 years. We validate Sendai's recommendations of the importance of a multidisciplinary team, to better understand the different tumor variants in order to deliver adequate and early therapy. The low mortality of our series suggests considering surgery early.

P-136

Two Cases of Main Duct Intraductal Papillary Mucinous Neoplasm Detected by Medical Checkup

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Intraductal papillary mucinous neoplasms (IPMNs) are being increasingly identified, often as incidental findings. Abdominal US findings, such as main pancreatic duct (MPD) dilatation or pancreatic cysts, are indicative of IPMNs or pancreatic cancers. There were 12,228 checkups involving abdominal US performed at Daido Hospital from December 2006 to January 2010. 176 checkups (1.43%) found MPD dilatation or pancreatic cysts. Of these, 2 cases were finally identified as main duct IPMN. The details of these 2 cases are as follows:

Case 1: A 70-year-old woman was found to have MPD dilatation. Abdominal computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) showed diffuse MPD dilatation. Mural nodules were detected inside MPD by EUS and intraductal ultrasonography (IDUS). Papillary growth could be clearly seen by peroral pancreatoscopy (POPS). We diagnosed this case as a main duct IPMN, and pylorus-preserving pancreaticoduodenectomy was performed. The final diagnosis was main duct IPMN.

Case 2: A 62-year-old man was found to have MPD dilatation, in particular the head. Mural nodules were detected inside MPD by EUS and IDUS. Therefore, subtotal stomach-preserving pancreaticoduodenectomy was performed. The final diagnosis was main duct IPMN.

Conclusion: We identified two cases of main duct IPMN via medical checkups. It is important to pick up on the findings, such as MPD dilatation or pancreatic cysts in order to detect main duct IPMN.

P-137

A Case of Peritoneal Recurrence of Invasive Carcinoma Derived from IPMN After Distal Pancreatectomy

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A 62-year-old man who underwent distal pancreatectomy and partial resection of transverse colon with diagnosis of cystic tumor of pancreas tail in July 2007. Histology, the tumor was invasive carcinoma derived from IPMN. Chemotherapy using gemcitabine was administered. 11 months after the operation, abdominal contrast-enhanced CT showed a cystic tumor in the subdiaphragm and CEA increased to 15.2ng/ml. Combination chemotherapy using gemcitabine and S-1 was administered under the diagnosis of peritoneal recurrence. CEA decreased to normal level, but 19 months after the operation, CA19-9 increased to 187.7U/ml . Then, radiotherapy a total of 40Gy was performed. 22 months after the radiotherapy, though chemotherapy using S-1 was continued, CA19-9 re-increased to 134.2U/ml. Abdominal contrast-enhanced CT and PET detect no other recurrence lesion, tumor resection was performed in January 2010. The patient is still alive with combined modality therapy 3.5 year after initial surgery, though the tumor was local advanced pancreatic carcinoma and he got a peritoneal recurrence after surgery.

P-138

Histological and Mucin Analysis Between Three Cases of Intraductal Oncocytic Papillary Carcinoma and One Case of Intraductal Papillary Mucinous Carcinoma

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We report histological and mucous analysis in three cases of intraductal oncocytic papillary carcinoma (IOPC) and one case of intraductal papillary mucinous carcinoma (IPMC). Histopathological examination revealed that IOPC and IPMC were lined by flat to low-papillary columnar cells coexisted with high-grade dysplasia that corresponds to carcinoma in situ and resembles to the carcinoma originating from gastric foveolar epithelium. Cancer cells were architecturally complex and showed arborizing papllae and cribrifom formations with fibrovascular stalks. Cancer cells were composed of eosinophilic or clear cytoplasm, and the cytological atypia was relatively mild. Oncocytic cells with abundant granular eosinophilic cytoplasm showed arborizing papillary proliferation with intraepithelial lumina in IOPC cases. High-grade dysplastic cells and oncocytic cells were collided in the lumen of one case of IOPC. Also, hyaline globules were observed in two of three IOPC cases and one IPMC case. Based on the cytological and structural appearances, IOPC and IMPC were almost similar except for the appearance of oncocytic cells. Immunohistochemistry of mucin revealed that the staining pattern of MUC-1, MUC-5AC and MUC-6 was identical in these cancers. In addition to the histological similarity, mucous analysis also suggests that the histogenesis of IOPC and IMPC is common and IOPC and IMPC may arise from the gastric type intraductal papillary mucinous adenoma.

P-139

Lymphoepithelial Cyst of the Pancreas in a Woman: Report of a Case

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A lymphoepitherial cyst is a rare benign lesion of the pancreas and usually seen in adult men. We report a rare case of lymphoepitherial cyst of the pancreas in a woman.

A 44-year-old Japanese woman underwent abdominal ultrasonography (US) as a routine medical checkup. It showed a cystic lesion, measuring 6cm in diameter, in the tail of the pancreas. Computed tomography revealed a cystic lesion (60mm*65mm) with a septum that was enhanced in the arterial phase. The main pancreatic duct was not dilated. Enhanced magnetic resonance imaging and magnetic resonance cholangiopancreatography (MRCP) showed a cystic condition, measuring 60mm, in the tail of pancreas, which was not connected with the pancreatic duct. Serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 levels were within normal limits. Distal pancreatectomy with splenectomy was performed under the tentative diagnosis of mucinous cystic neoplasm. Histologic examination of the resected specimen showed a cystic lesion lined by mature or metaplastic-like squamous epithelium. Hyalinizes fibrous capsule contained the lymphoid tissue forming scattered lymphoid follicles. Histologic diagnosis was lymphoepithelial cyst of the pancreas.

Although lymphoepitheial cyst is a rare benign pancreatic lesion, usually seen in men, it should be considered as a differential diagnosis of pancreatic cystic lesions in female. We report a rare lymphoepithelial cyst of the pancreas in an adult woman.

Poster 22 Pancreatic Endocrine Tumor

P-140

Endocrine Tumor of the Pancreas. Serotonin Secreting Tumors Tighten the Main Pancreatic Duct

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Background: Serotonin secreting tumor is one variant of the endocrine tumor of the pancreas.

Methods: Among thirteen endocrine tumor of the pancreas, there were four tumors diffusely immunoreactive to serotoin.

Results: The patients were three male and one female, the mean age of four patients was 56.2 years (38–72). All four tumors were solitary, and three located in the body of the pancreas, while one in the head to neck of the pancreas. Abdominal ultrasonography showed localized hypoechoic solid masses in all four tumors, the size of the lesion were seven to 21 mm in diameter (mean 14mm). CT scan showed localized masses, and prominent enhancement by the contrast medium. By magnetic resonance imaging (MRI), T1-weighted image showed the isointensity masses in all four tumors, while T2-weithted image showed high intensity mass in one and low intensity masses in three, respectively. Endoscopic retrograde cholangiopancretography revealed the blunt obstruction of the main pancreatic duct in two cases, and the severe main pancreatic duct stenosis and the dilataion of the dital pancreatic duct in two cases. The performed operations were all middle pancreatectomy along with pancreatico-jejunostomy.

Histological examination revealed all four tumors were those of endocrine tumor of the pancreas, and the three of them had dominant fibrous stroma, while the other one tumor showed medullary appearance. One tumor showed the lymphatic invasion, while the other three tumor showed no vasucular invasion. Immunohistochemichally, the four tumors were diffusely positive for serotonin, and focally immunoreactive to insulin, glucagon, somatostatin, and/or ACTH antibodies.

Conclusion: Serotonin secreting tumors were relatively small size, while they proliferate around the main pandreatic duct, therefore they tend to tighten the main pancreatic duct, and showed the unique pancreatography imaging, so called club like appearance. Low intensity masses by T2-weithted MR image histologically revealed those of dominant fibrous stroma.

P-141

Two Case Reports of the Serotonin-positive Pancreatic Endocrine Tumors Which Caused Obstruction of the Main Pancreatic Duct

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Context: We report two cases of the pancreatic endocrine tumor that caused the obstruction of the main pancreatic duct (MPD). That tumors were not revealed by an endoscopic ultrasonography (EUS), a contrast-enhanced computed tomography (CT) and a magnetic resonance image (MRI) before operation.

Case 1: A 49 year-old asymptomatic male was referred to our institution the dilation of the MPD revealed by the abdominal ultrasonography. But no tumor was demonstrated by EUS, CT and MRI. The diameter of the main pancreatic duct was over 20mm at the body and no dilation at the head. Although we couldn't confirm malignancy through cytology nor imaging, pancreatic cancer was strongly suspected. A pancreaticoduodenectomy was performed and pathological examination revealed a 5x3mm endocrine tumor which showed immunohistochemical staining to serotonin. Fibrosis was present around the MPD that seemed to cause stricture.

Case 2: A 32 year-old male with no symptom had elevated serum amylase, and US demonstrated the dilation of MPD. No tumor was revealed by CT and MRI. Pancreatic cancer was suspected due to the stricture and dilation of the MPD. A middle pancreatectomy was performed and pathological examination revealed an endocrine tumor sized 5 x 4 mm. The tumor cells showed immunohistochemical staining to serotonin.

Conclusion: we report two cases of serotonin-positive pancreatic endocrine tumors that caused stricture of the MPD in spite of small tumor cells.

P-142

A Rare Case of Insulinoma with Difficulty – How Can We Decide Resection Area? –

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Endogenous hyperinsulinaemic hypoglycaemia in adults is most commonly caused by an insulinoma. Islet hyperplasia is rarely reported. To the best of our knowledge the presence of both insulinoma and hyperplasia has hardly been reported before.

A 59-year-old woman was admitted to our hospital due to loss of her consciousness. Her fasting plasma glucose and serum immunoreactive insulin levels were 33mg/dL and 38.5 microU/mL, respectively. A dynamic abdominal CT scan revealed a hypervascular tumor at the pancreas tail, which size was 2.6cm in diameter. ASVS (arterial stimulation and venous sampling) by injecting calcium gluconate revealed that insulin levels in the hepatic vein extremely increased

from basal insulin levels by injecting calcium to distal splenic artery. On the other hand, when we inject to proximal splenic artery, insulin levels also increased, but didn't as much as when inject to distal splenic artery. Insulin levels didn't change after injection from SMA (superior mesenteric artery) or GDA (gastro duodenal artery).

A laparoscopic spleen preserved tail pancreatectomy was performed. However, her plasma glucose levels were not still normalized, nor insulin levels were. It was followed by body-to-tail pancreato-splenectomy, and plasma glucose levels and insulin levels turned into normal. Postoperative course is uneventful. At post operative day 15 she left hospital. The pathological examination diagnosed the tumor at pancreas tail insulinoma. However, we cannot point out any tumor at that pancreas body, which was resected additionally, but only islet hyperplasia there.

We report an even rarer entity of concurrent insulinoma and islet hyperplasia.

P-143

Analyses of Lymph Node Metastases in Pancreatic Neuroendocrine Tumors Based on the Tumor Size and Hormonal Production

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Background: Because of the low incidence of pancreatic neuroendocrine tumors (pNETs), there have been few reports regarding the necessity of lymph node dissection.

Aim: To evaluate the risk of lymph node metastases of pNETs based on the tumor size and hormonal production

Object: The study subjects were 60 pNETs resected at our department over the last two decades. The characteristics of 11 pNETs with lymph node and/or liver metastases at the time of surgical resection (malignant group; 18%) were compared with those of 49 pNETs without metastases (benign group; 82%).

Results: There were 27 non-functioning tumors (45%), 23 insulinomas (38%), 6 gastrinomas (10%), 2 glucagonomas (3.5%), and 2 PPomas (3.5%). According to the WHO classification, 6 gastrinomas were categorized as uncertain behavior of well differentiated endocrine tumors in 3 and well differentiated endocrine carcinomas in the others. Malignant group had a higher prevalence of gastrinoma (27% vs. 6%, P=0.03) and a tendency to have a larger tumor size than benign group (37 mm vs. 19 mm, P=0.05). In details, malignant group consisted of 2 gastrinomas with small size and 9 non-gastrinomas including 2 cases of insulinoma 15mm or larger in size. Only 2 of 25 pNETs (8%) with the tumor size of less than 15mm had lymph node metastases, and both of these were gastrinoma, while there were 9 cases having metastasis in the other 35 pNETs (26%) with the size of 15mm or larger.

Conclusion: All cases of gastrinoma, and non-gastrinoma with the tumor size of 15 mm or larger would be the indication for pancreatectomy with lymph node dissection.

P-144

Advanced Non-functioning Pancreatic Neuroendocrine Carcinoma with Distant Metastasis: Case Report of Two Cases

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Pancreatic neuroendocrine tumours (NETs) are rare neoplasms of the pancreas. We report two cases of advanced non-functioning pancreatic neuroendocrine carcinoma. Patient #1. A 49-years-old woman was referred to our hospital because of the treatment of the tumor of the pancreatic head with multiple liver tumors. Pathologic examination by needle biopsy of the liver tumor revealed neuroendocrine tumor (NET), and we diagnosed malignant pancreatic NET with multiple liver metastases. Although systemic chemotherapy (Dacarbazine/Gemcitabine) was performed on 5 cycles, liver metastases showed progression. Then, 2 sessions of transarterial chemolipiodolization (CDDP) for liver metastases was performed, the lesions were not recognized by PET-CT. Therefore, she underwent PPPD after 2 months (14 months after the introduction of chemotharpy). Postoperative pathologic examination revealed well-differentiated neuroendocrine carcinoma. She is under medical treatment for liver recurrences (57 months after the introduction of first line chemotharpy). Patient #2. A 84-years-old man suffered abdominal pain for 1 months. An abdominal CT showed the tumor of the pancreatic body. He was referred to our hospital for the surgical therapy. He underwent distal pancreatectomy. Because the intraopeartive pathologic examination of a para-aortic lymph node revealed to be malignancy, only the regional dissection of the pancreas was performed. Postoperative pathologic examination revealed well-differentiated neuroendocrine carcinoma with a lymph node metastasis. He is well 5 months after the surgery. In conclusions, the preoperative diagnosis of advanced pancreatic NET including pathological differentiation is difficult. Further development of diagnostic and treatment modalities would offer potential to prolong survival disease-free survival for patients with pancreatic NET.

Poster 23 Endocrine, Exocrine

P-145

Nutritional Management and Diabetes Control in Older People with Pancreatic Insufficiency

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Background: Malnutrition is a common problem in older people with pancreatic exocrine insufficiency. In addition, they need diabetes control while avoiding hypoglycemia if they also suffer from pancreatic endocrine insufficiency. Aging might compromise physical function. Aging also decreases food intake and changes tastes gradually.

Aim & Methods: To determine adequate nutritional assessment for older patients with pancreatic insufficiency, we have studied the clinical characteristics of 14 patients with pancreatic insufficiency aged 70 or over.

Results: All of patients required treatment with pancreatic enzyme. They required an average daily dose of 9.4 (6 to 12) g Berizym® to reduce steatorrhea below 5g of fecal fat. 13 cases of patients required treatment with insulin. They required an average daily dose of 24.1 (6 to 63) units to achieve HbA1c below 7% without symptomatic hypoglycemia. The average Body Mass Index (BMI) of patients was 19.3 kg/m2. The mean change of body weight was less than 0.5 kg in last three months. They also tend to have low levels in serum nutritional markers such as prealbmin, but tend to have small changes of them in last three months.

Conclusion: Dynamically assessments of nutrition seem warranted for older patients with pancreatic insufficiency.

P-146

A Noble Transdifferentiation Method Using Small Molecular Compounds Induce Insulin-producing Cells from Hepatocyte with Different Origin

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Type 1 diabetes mellitus can be ameliorated by pancreatic islet cell transplantation, but this treatment is restricted by the scarcity of islet cell source due to limited replication capacity of pancreatic cells. In the present study we tried to transdifferentiate the cultured hepatic cells to the pancreatic cells by several agents that induce hepatic dysfunction. Two marker plasmids containing a fluorescent gene with liver specific promoter (Albumin-GFP) or pancreas specific promoter (Elastase-DSRED) respectively were constructed and introduced into the human hepatoblastoma cell (HepG2). Using this cell line, we analyzed the phenotypic change of HepG2 to some pancreatic cells. Transdifferentiation of the HepG2 to pancreatic lineage was investigated by reverse transcriptase polimerase chain reaction (RT-PCR), immunostaining and fluorescence analysis. Three of tested agents could convert the green fluorescence of the HepG2 cells to red within two weeks after treatment, indicating the induction of elastase gene expression.RT-PCR analysis demonstrated expression of pancreatic gene markers such as insulin, amylase, and elastase.

Immunostaining confirmed the expression of amylase, glucagon and insulin. To check whether a similar transdifferentiation mechanism is also works in normal cells, we induced mouse ES cells containing Albumin-GFP to liver cells by treatment of Activin A and retinoic acid. By culturing the induced cells in Lanford medium, they showed GFP fluorescence, indicating the albumin gene expression and differentiation into hepatocytes. Then, we transdifferentiated them by one of the three agents and confirmed their expression of amylase, insulin, and glucagon by immunostaining. Moreover, we performed transdifferentiation of primary rat hepatocytes by another one of the three agents and confirmed the induced expression of amylase, insulin, and glucagon by immunostaining. The new transdifferentiation method of hepatocyte to pancreatic cells developed in this study represents one possible source of beta cells for islet transplantation.

P-147

The Prevalence and Severity of Micro Vascular Complications in Patients with Pancreatic Diabetes

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The objective of the study was to determine the prevalence and severity of micro vascular complications (retinopathy, nephropathy, neuropathy) in patients with pancreatic diabetes (PD). Cross-sectional comparative studies comparing prevalence and severity of micro vascular complications in PD patients versus primary diabetic patients were included after a database search. Four cross-sectional comparative studies of references and our cases with PD caused by chronic pancreatitis were included. The prevalence and severity of diabetic micro vascular complications were similar among PD patients and primary diabetic patients. Chronic hyperglycemia and the duration of diabetes mellitus had influence on micro vascular complications rather than genetic factors (body mass index, hypertension, serum total cholesterol). Improvement of glycemic control need for control of micro vascular complications in PD patients.

P-148

Expression of Transcription Factors Pdx-1, Ptf1a, and Ngn3 During Acute Exocrine Pancreatic Injury and Regeneration After Arginine-induced Acute Necrotizing Pancreatitis in Rats

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Background: During organogenesis, terminal differentiation of pancreatic cells is regulated by the sequential expression of a network of transcriptional regulators such as Pdx-1 (pancreatic stem/progenitor cell marker), Ptf1a (exocrine precursor cell marker)and Ngn3 (endocrine precursor cell marker). In this study, we evaluate how these transcript factors express during acute exocrine pancreatic injury and regeneration after arginine-induced acute necrotizing pancreatitis in rats.

Methods: Male Wistar rats (200–230g) were used for experiments. Acute necrotizing pancreatitis was induced by a single intraperitoneal injection of L-arginine monohydrochloride (500 mg /kg body weight). Control rats were treated with injections of saline. Animals were sacrificed on days 2, 3, 4, 5, 7 after the injection. The mRNA expression of Pdx1, Ptf1a, and Ngn3 was examined by RT-PCR. We also investigated the pdx-1 expression using immunohistochemistry. Cell proliferation was assessed by BrDU incorporation.

Results: In this model, the exocrine pancreas was severely damaged at day 2 and the formation of duct-tubular complexes occurred at day 3. From day 4, the regeneration of exocrine pancreas occurred. In control pancreas, the mRNA of Pdx-1 was not expressed and by immunohistochemistry, Pdx-1 was expressed strongly only in islet cells. The mRNA expression of Pdx-1 was up-regulated after exocrine injury, and by immunohistochemistry, Pdx-1 positive cells increased in duct-tubular complexes. The mRNA expression of Ptf1a was down-regulated after injury and then up-regulated during regeneration of exocrine pancreas. No remarkable change in the number of islet cells and the mRNA level of Ngn3 was seen for all the period.

Conclusion: This study shows that the process of exocrine pancreas regeneration may recapitulate that of normal development.

P-149

Investigation of the Cutoff Value for the Diagnosis of Exocrine Pancreatic Insufficiency in Both the Benzoyl-L-Tyrosyl-[l-^{13}C]Alanine Breath Test and the BT-PABA Test

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Background: We defined the exocrine pancreatic insufficiency as the cases with more than 5g of fecal fat excretion per day with meals including fat more than 40g/day. With the 300mg Benzoyl-L-Tyrosyl-[l-^{13}C] Alanine breath test, we could diagnose the exocrine pancreatic insufficiency by $^{13}CO_2$ peak value. We defined the cut-off value by mean-1.5SD in healthy controls (41.2permil). The case with lower value than 41.2permil was classified as positive case, exocrine pancreatic insufficiency. On the other hand, with the BT-PABA test, the pancreatic exocrine function was assessed by the urinary excretion rate of PABA from 6-h urine collection. The case with lower value than 70.0% was classified as hypofunction of exocrine pancreas. We investigated the cutoff value for the diagnosis of exocrine pancreatic insufficiency with the BT-PABA test.

Method: We performed both the breath test and the BT-PABA test in 6 patients with exocrine pancreatic insufficiency and 24 controls.

Result: In the breath test, the mean peak value of $^{13}CO_2$ were significantly lower in patients with exocrine pancreatic insufficiency (21.9permil) than controls (52.9permil), and exocrine pancreatic insufficiency could be detected with high sensitivity (100%) and specificity (91.7%). In the BT-PABA test, the mean urinary excretion rate of PABA (6 hours) were significantly lower in patients with exocrine pancreatic insufficiency (34.0%), than controls (77.6%). For the diagnosis of exocrine pancreatic insufficiency with the BT-PABA test, we use the cut-off value by mean-1SD (71.0%), mean-2SD (64.4%), and mean-3SD (57.8%) in healthy controls. Each sensitivity

was 100%, 100%, and 83.3%. Each specificity was 66.7%, 87.5%, and 91.7%.

Conclusion: We thought the cutoff value in the BT-PABA test by mean-2SD in healthy controls (64.4%) was appropriate for the diagnosis of exocrine pancreatic insufficiency.

P-150

Fluid Secretion from the Pancreatic Duct in PCK Rats

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Autosomal recessive polycystic kidney disease (ARPKD) is caused by mutations in the PKHD1 gene encoding fibrocystin which is localized to primary cilia. The PCK rat is a spontaneously-generated model of ARPKD. Each pancreatic duct cell has a single cilium but its function is not well understood. In this study we examined fluid secretion from interlobular pancreatic ducts isolated from PCK rats and in vivo pancreatic fluid secretion in anesthetized PCK rats. Interlobular ducts were isolated by microdissection and cultured overnight. During the culture both ends of the duct segments sealed spontaneously thus isolating the luminal space from the bath. The isolated ducts were superfused with HCO_3^--buffered solution at 37°C and the fluid secretory rate into the lumen was measured by videomicroscopy. The rate of basal secretion was not different among ducts isolated from homozygote (*pck*/*pck*) rat, ducts from heterozygote (+/*pck*) rat, and ducts from wild-type (+/+) rat. The sequential application of 0.1 nM and 10 nM secretin induced dose-dependent increases in fluid secretion from ducts of all genotypes. The rate of secretin (10 nM)-stimulated fluid secretion in pck/pck ducts was significantly faster than that in +/*pck* and +/+ ducts. Secretin (0.03, 0.1, 0.3 and 1.0 nmol/kg body weight/h) was infused intravenously via the femoral vein of anesthetized rats. Pancreatic juice and bile were collected separately via the respective canulae. Basal and stimulated fluid secretion with a low dose (0.03 nmol/kg/h) of secretin in pck/pck rats were significantly smaller than those in +/+ rats. The fluid responses to higher doses of secretin were not different among genotypes. In summary, in vivo fluid secretion under physiological stimulation with secretin was reduced in the pancreas of PCK rats despite of enhanced fluid secretion from isolated ducts.

Poster 24 Others 2

P-151

CT Volumetric Analysis of Visceral Organs in Autoimmune Pancreatitis

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Background & Aim: Pancreas is diffusely or focally enlarged during the active phase of autoimmune pancreatitis (AIP). In ~40% of patients with AIP lymphoplasmacytic infiltration is also seen in many extra-pancreatic sites including bile ducts, liver, gallbladder, kidney, and salivary glands. It is well known that pancreas volume normalizes or even shows atrophy after remission. However, little is known about volume change of extra-pancreatic visceral organs. Using CT volumetry we determined change in visceral organ volume over the course of AIP.

Methods: In 16 patients with AIP (age 58.6+/-18.9 yr, 87.5% male) we measured the volumes of the pancreas, liver, spleen, and both kidneys using CT volumetry. Organ volume was calculated as a sum of areas containing the organ of interest on multiple transverse CT images adjusted for slice thickness (Hepatobiliary Pancreat Dis Int 2004). Volumes were measured during active phase and in remission phase after steroid therapy or spontaneous improvement. Volume change of each organ was compared by paired t test. Least squares method was applied where necessary.

Results: Pancreatic volume decreased significantly following remission of AIP (99.0+/-11.1 vs. 48.4+/-8.7; mean +/- SD mm3; p=0.002). Significant decrease in size of spleen was also observed (191.0+/- 21.0, vs. 156.8+/-21, P=0.0002). The volume decline between pancreas and spleen had a weak correlation (r2=0.24, P=0.055). Volume of liver and kidneys did not change significantly after remission.

Conclusions: Pancreatic and splenic volumes decreased significantly after the remission of AIP, but not that of liver or kidney.

P-152

The Incidence of Circumportal Pancreas Shown on Multi-detector-row Computed Tomography

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Purpose: Circumportal pancreas is a pancreatic anomaly, showing complete pancreatic encasement of the portal vein above the spleno-portal junction. This anomaly has been believed to be extremely rare; there have been only seven cases reported in the previous literatures. The purpose of this study was to evaluate the incidence of circumportal pancreas shown on multi-detector-row computed tomography (MDCT).

Materials and Methods: The study group consisted of 317 consecutive liver transplant donor candidates who had undergone MDCT studies for the evaluation of vascular anatomy. There were 180 male and 137 female patients. None had history of pancreatic surgery. The age ranged from 19 to 64 years old (mean±standard deviation [SD]: 37±12 years old). Multiplanar reformation (MPR) images obtained from the portal venous phase of MDCT studies were retrospectively reviewed. The presence or absence of circumportal pancreas was assessed. If circumportal pancreas was present, the transverse diameter of an accessory pancreatic parenchyma was measured on axial images. In addition, the incidence of variant hepatic arterial anatomy was compared between patients with and without circumportal pancreas.

Results: There were eight of 317 (2.5%) patients who had circumportal pancreas. The transverse diameter of the an accessory pancreatic parenchyma ranged from 5 mm to 18 mm (mean±SD: 10±4 mm). In one patient, encasement of the common hepatic artery and retroportal main pancreatic duct were observed. The variant hepatic artery was noted in two of eight (25%) patients, which were similar to those without circumportal pancreas (72 of 309, 23%).

Conclusion: MPR images obtained from MDCT are useful to evaluate the presence of circumportal pancreas. The incidence of circumportal pancreas was 2.5% (one of 40 in normal population), which is not extremely rare.

P-153

An Influence of Obesity on Pancreaticoduodenectomy

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Background: It is still controversial whether obesity influences postoperative complications after gastroenterological surgery. In this study, we investigated an influence of obesity on pancreaticoduodenectomy.

Methods: We enrolled in this study thirty-four patients undergoing pancreaticoduodenectomy from July 2007 through March 2009. Body Mass Index (BMI) and Visceral Fat Area (VFA) were used as indicators of obesity. These indicators were measured by body composition analysis equipment InBody 720. We inquired a correlation between intraoperative blood loss, operative time, postoperative complications and BMI, VFA.

Results: Six patients were judged obesity by BMI (BMI OB group), and fifteen patients were diagnosed as visceral obesity by VFA (VFA OB group). Median blood loss was 1070ml in VFA OB group, and it was much more than that of non obesity patients ($p=0.049$). Also, median operative time was 584 minute in VFA OB group, and it was significantly longer than that of non obesity patients ($p=0.039$). While, median blood loss and operative time of BMI OB group were not different from those of non obesity patients. In VFA OB group, pancreatic fistula was observed in 3 cases, delayed gastric empting in 3 cases and SSI in 1 case. The incidence rates of these complications were not significantly different from those of non obesity cases. The result was the same when the indicator was BMI.

Conclusion: It is suggested that visceral obesity influences intraoperative blood loss and operative time by using VFA as an indicator of obesity. However, it was not clarified in this study whether obesity influences postoperative complications after pancreaticoduodenectomy.

P-154

Pancreaticoduodenectomy in Patients with the Celiac Axis Stenosis

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Background: The flow of celiac axis is important to maintain the hepatic arterial flow when pancreaticoduodenectomy (PD) is performed. We describe three cases of PD complicated with celiac axis stenosis due to the median arcuate ligament syndrome. Patients: PD was performed for 334 patients from September 2002 to April 2009 in

our hospital. Among the 334 patients, there were 3 patients (0.9%) with the celiac axis stenosis by the median arcuate ligament syndrome.

Results: The arterial flow of the celiac axis was improved by dissecting the median arcuate ligament in one of the three cases. In remaining two cases, the celiac artery was completely occluded, and its flow was not improved after cutting the ligament. One of the two cases was a patient with intraductal papillary mucinous neoplasm in the pancreatic head. Anterior superior pancreaticoduodenal artery (ASPDA) and right colic artery were anastomosed microscopically to preserve the hepatic artery flow, and PD was undergone. Another case was a patient who was diagnosed as a lower bile duct carcinoma. The hepatic artery flow was maintained by preserving the anterior arterial arcade of the pancreas, because the pancreas, ASPDA and anterior inferior pancreaticoduodenal artery were not invaded by the tumor. There was no mobidity and mortality in the three patients.

Conclusion: In patients with the median arcuate ligament syndrome, there are some cases whose flow of the celiac artery is not improved by dissecting the median arcuate ligament. Reconstructive procedures should be prepared for PD in patients with the celiac axis stenosis.

P-155

Pancreatoduodenectomy for Common Bile Duct Cancer After Coronary Artery Bypass Graft Using the Right Gastroepiploic Artery; Report of a Case

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The patient is a 71-year-old man with common bile duct cancer. He underwent coronary artery bypass graft surgery using the right gastroepiploic artery 8 years ago. The protruding tumor, measuring 1.5cm in diameter, in the common bile duct was detected on ultrasonography and computed tomography for jaundice. Endoscopic retrograde biliary drainage was performed and the cytology of the biliary juice yielded a diagnosis of adenocarcinoma. On the basis of a diagnosis of common bile duct cancer, operation was performed in January 2010. The interposition between the left hepatic artery and the right gastroepiploic artery using the saphenous vein was initially made. Then, we cut down the right gastroepiploic artery and performed pylorus preserving pancreatoduodenectomy as usual. The intraoperative state was uneventful.

P-156

A Case of Ruptured Pancreatic Pseudocyst After EUS Examination

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Background and Aim: Endoscopic ultrasound (EUS) guided transmural drainage is a well accepted treatment for symptomatic pancreatic pseudocysts, and it is recommended that timing of treatment is 6 weeks after occurrence of pancreatic pseudocyst. We presented a case of ruptures pseudocyst after EUS examination in 4 weeks after occurrence of pseudocyst. This case was successfully treated by EUS-guided transgastric drainage.

Case: A 65-year-old man who was made a diagnosis of alcoholic chronic pancreatitis admitted in our hospital because of continuous appetite loss for 4weeks. Computed tomography (CT) revealed that his stomach was compressed by large pancreatic pseudocyst, with 20cm in diameter. We performed EUS examination before cyst drainage to observe the adhesion between gastric wall and pseudocyst wall, and whether a mass which was at the root of pseudocyst existed or not. After 4 hours performing EUS, he complained severe abdominal pain, and subsequent CT showed fluid collection around the pancreas in the abdominal cavity. These findings suggested the rupture of the pseudocyst. Emergent EUS-guided transgastric drainage was performed, and was successful done. After procedure, his pain was relieved in small steps. One month later, endoscopic retrograde pancreatography (ERCP) was performed to evaluate the pancreatic duct, and ERCP showed a pancreatic branch duct communicated with the pseudocyst. The pseudocyst was disappear in 2 months after EUS-guided treatment.

Conclusion: From this case, it is considered that early phase in development of the pseudocyst has some risk due to fragility of the cyst wall. It should be considered that even EUS examination without intervention bring on the rupture of pseudocyst in the premature pseudocyst.

P-157

Discrimination Between Sclerosing Cholangitis-associated Autoimmune Pancreatitis and Primary Sclerosing Cholangitis, Cancer Using Intraductal Ultrasonography

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Background: The differentiation of sclerosing cholangitis-associated autoimmune pancreatitis (SC-AIP), primary sclerosing cholangitis (PSC), and cancer of the hilar part of the bile duct (CHB) has been challenging. Objective: To evaluate characteristic intraductal

ultrasonography (IDUS) features that could be used to discriminate SC-AIP from PSC and CHB.

Patients: Six patients with SC-AIP, ten patients with PSC, and twelve patients with CHB were identified. Main outcome measurements: We reviewed the following bile duct features observed using IDUS to determine their usefulness for differentiating SC-AIP from PSC and CHB: presence of symmetrical wall thickness, wall thickness, presence of homogenous internal foci, and presence of lateral mucosal lesions continuous to the hilar.

Results: The IDUS results (SC-AIP, PSC, CHB) were as follows: wall thickness (mm), 3.7+/-0.9, 2.6+/-0.9, 2.8+/-0.6; presence of symmetrical wall thickness, 100% (6/6), 20% (2/10), 8.3% (1/12); presence of homogeneous internal foci, 100% (6/6), 10% (1/10), 8.3% (1/12); and presence of lateral mucosal lesions continuous to the hilar, 83.3% (5/6), 40% (4/10), 25% (3/12). Symmetrical wall thickness of the bile duct, homogenous internal foci, and lateral mucosal lesions continuous to the hilar were detected significantly more often among the patients with SC-PSC than among the patients with PSC or CHB ($p < 0.05$).

Conclusions: IDUS findings such as symmetrical wall thickness, presence of homogeneous internal foci, and presence of lateral mucosal lesions continuous to the hilar can facilitate the differential diagnosis of SC-AIP from PSC and CHB.

P-158

Pancreas Transaction Using a Stapling Device for a Distal Pancreatectomy

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Aim: To elucidate the usefulness of performing a staple closure after distal pancreatectomy (DP).

Patients: Twenty-four patients who underwent DP between January 2005 and December 2009 were reviewed. DP was employed for 5 patients with benign pancreatic diseases and for 2 patients with pancreatic cancer. In remaining 17 patients, DP was added to the total gastrectomy for advanced gastric cancer.

Surgical procedures: The pancreas was transected with the stapling device in 20 patients. In 10 of them, stapling of the pancreas was carried out together with the splenic vein after ligation of the splenic artery. In remaining 10 patients, pancreatic parenchyma alone was stapled after the splenic artery and the vein were ligated individually. In 4 patients, a suture method was performed to close the pancreatic stump. Fibrin glue was sprayed on the pancreatic stump in 21 patients.

Results: There was no in-hospital mortality, and 3 pancreatic fistulas (13%), which were classified in grade B according to the ISGPF definition, occurred in this series. All 3 patients underwent DP in addition to the total gastrectomy, and the pancreatic transaction was performed with stapling device followed by spray of fibrin glue. The operative times (minutes) were 218, 294, 225, and the intraoperative bleedings (g) were 70, 597, 220; these values were not different from those of other 14 gastrectomied patients (median values, 282 minutes and 570g). In one patient, pancreas and the splenic vein were stapled collectively, but no complication was noted except for the pancreatic fistula.

Conclusion: The present study suggests that the stapling closure of the pancreas is safe, and that the collective stapling of pancreas and the splenic vein is feasible for DP.

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Post-operative Pancreatic Ductal Injury Successfully Treated with Endoscopic Naso-pancreatic Drainage

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The patient was a 57-year-old woman who suffered from left-back pain. Abdominal US and EUS showed a 10-mm hypoechoic mass at the body of pancreas. Blood chemistry tests showed low level of blood sugar (54mg/dl) and high level of insulin. Of tumor markers, the level of CEA and CA19-9 were normal. MRI showed low intensity area of 10-mm in T1WI. The area has contrasted in early phase of enhanced MRI, and then diffusion was decline in DWI. MRCP showed normal image. The final diagnosis was a pancreatic insulinoma. ERP showed main pancreatic duct was adjacent to the tumor. Then, we performed partial pancreatectomy (pancreatic nucleation) in combination with pancreatic stenting to avoid the duct injury due to operation. However, she had high fever and abdominal pain 22 days later. MRI showed an effusion around pancreas. ERP showed disruption of main pancreatic duct and extravasation of the contrast meduim, suggesting pancreatic fistula. Although proximal portion of the main pancreatic duct was invisible due to disruption, we could advance a radifocus guidewire into the proximal main pancreatic duct. Eventually, endoscopic 5-Fr naso-pancreatic duct drainage (ENPD) was performed. Two weeks later, patients was doing well without pain and fever up. Then, we replaced to a 7-Fr plastic stent. Two months later, the stent was removed since ERP showed no fistula of pancreatic duct and CT showed effusion around pancreas was disappeared.