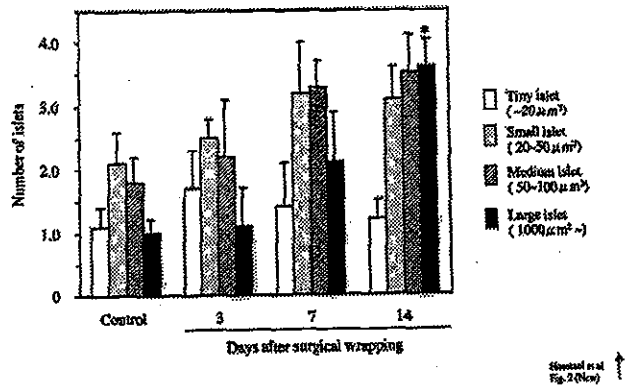

Fig 2. The number of islets after surgical wrapping. Tiny islets increased during the relatively early phase, small and medium islet increased continuously, and large islets increased during the later stages. The number of islets was counted per low power field. Mean ± SD (5 rats, each count for triplicate fields); $*P < .05$ vs control (ANOVA).

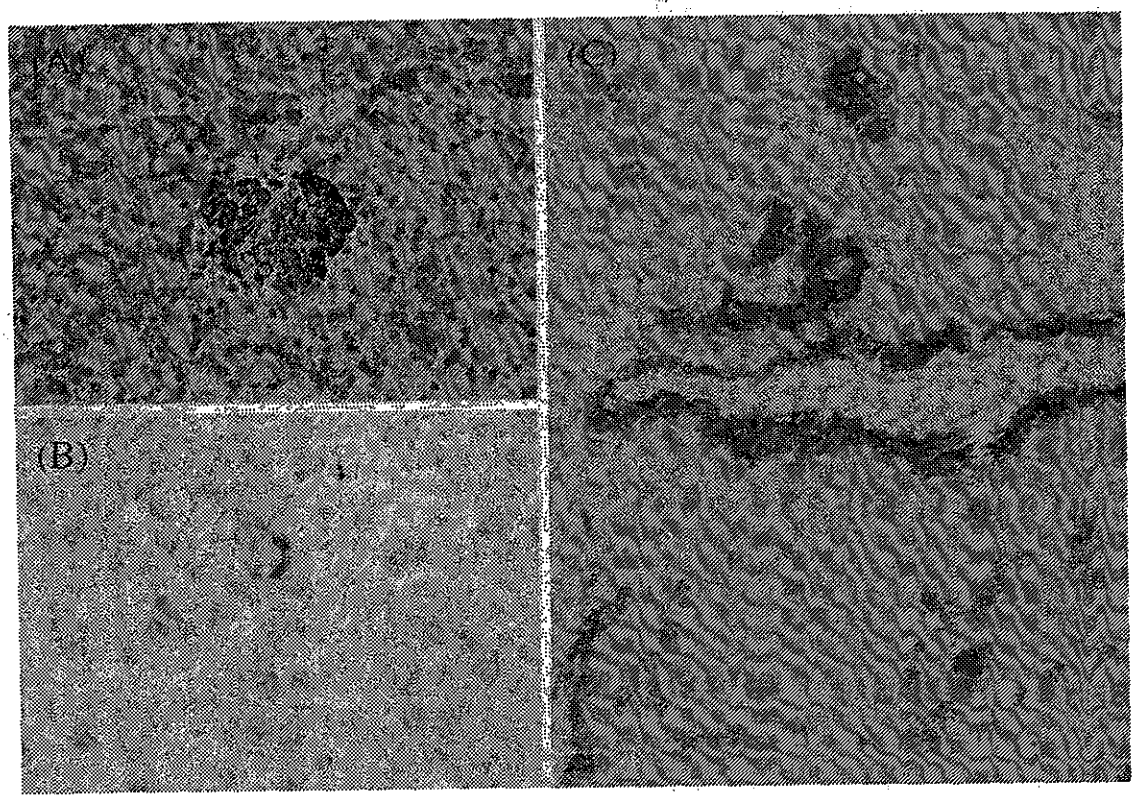

Fig 3. Double staining of insulin and cytokeratin: **A**, Control (original magnifaction ×200); **B** and **C**, 3 days after surgical wrapping (original magnification ×400). Insulin immunoreactivity was detected with DAB brown and cytokeratin immunoreactivity with Fuchsin red violet. After surgical wrapping, cells positive for both insulin and cytokeratin were detected inside the acini and in ductal structures.

increased to approximately triple that of the control 14 days after SW.

Extraislet insulin-positive cells. Insulin IR was also detected in single cells outside the islets. Extraislet insulin-positive cells were scattered in control pancreata. The cells dramatically increased in number, especially 3 days after SW. To clarify the origin of the insulin-positive cells in the exocrine area, we performed double staining of insulin and cytokeratin, a ductal cell marker. In control

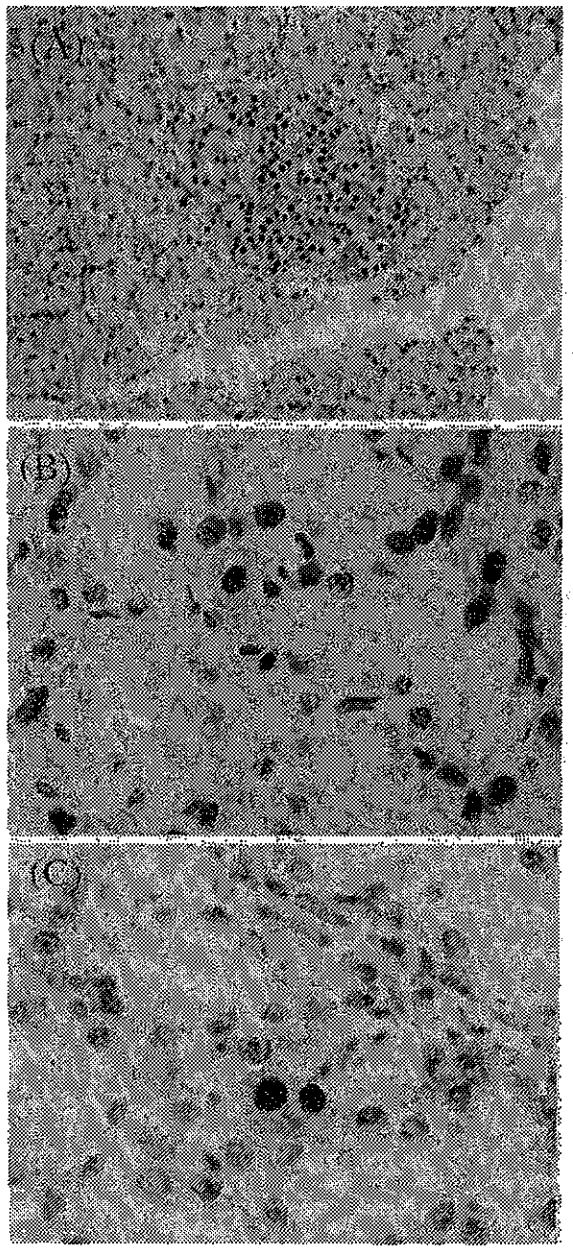

Fig 4. Immunohistochemical staining of PDX-1. **A**, 1 day after surgical wrapping (original magnification ×100). **B**, 1 day after surgical wrapping (original magnification ×400). **C**, 3 days after surgical wrapping (original magnification ×400). PDX-1–positive cells were seen inside the islets. After surgical wrapping, PDX-1 immunoreactivity was also detected as a single cell in the exocrine area.

pancreata, cytokeratin IR was observed in the epithelial cells of intracanalicular or smaller ducts and in cells composing the acinar structure, supposedly centroacinar cells (Fig 3, *A*). Three days after SW, cells positive for both insulin and cytokeratin were detected inside acini (Fig 3, *B*) and in the ductal structures (Fig 3, *C*). Immunoreactivities of both DAB brown and Fuchsin red violet were seen in cytoplasm of the cells. However, it was noted that insulin-positive cells were observed in centroacinar cells, as well as in epithelial lining or just outside the lining of ductal structure.

PDX-1–positive cells. To examine the expression of PDX-1, we performed immunohistochemistry with a specific antibody. PDX-1 IR was mainly observed in the nuclei of islet cells (Fig 4, *A*). PDX-1–positive cells were detected in both normal islets and surgically wrapped islets, with the number of intraislet cells showing no apparent increase after SW. However, PDX-1–positive cells were detected in extraislet single cells only after SW (Fig 4, *B, C*).

Double staining of PDX-1 and insulin clearly demonstrated the presence of PDX-1 IR in the nucleus, as detected with DAB brown, and of insulin IR in cytoplasm, as detected with Fuchsin red violet. One day after SW, extraislet PDX-1–positive cells were mainly observed in acini with faint or no insulin IR (Fig 5). After 3 days, PDX-1–positive cells were found in the acini in the much more clearly detected presence of insulin IR (Fig 6, *A, B*). Cells positive for both PDX-1 and insulin were detected in ductular component as well (Fig 6, *C*). To clarify these sequential changes, we counted the number of PDX-1–positive and insulin-positive cells in the exocrine area in samples at each of the time points (Fig 7). We found that the number of extraislet PDX-1–positive cells significantly increased 1 day after SW (1.0 ± 0.6 vs 28.5 ± 5.1) and gradually declined thereafter. On the other hand, the peak increase in extraislet insulin-positive cells was observed 3 days after SW.

DISCUSSION

This study demonstrated that the endocrine area of the pancreas significantly increased after SW of the rat pancreas. The study also showed that the number of tiny or small islets increased during the relatively early phase and that the number of large islets increased during the later stages of the islet hyperplasia process. Double immunostaining of cytokeratin and insulin showed that extraislet insulin-positive cells were present in or along the epithelial cell lining of ductal structures, as well as in centroacinar cells after SW. PDX-1–positive cells were detected in the islets of both control and experimental animals, but these cells were detected in the exocrine area only after SW. Double staining of PDX-1 and insulin showed that PDX-1–positive cells were found in ductal structures, first with

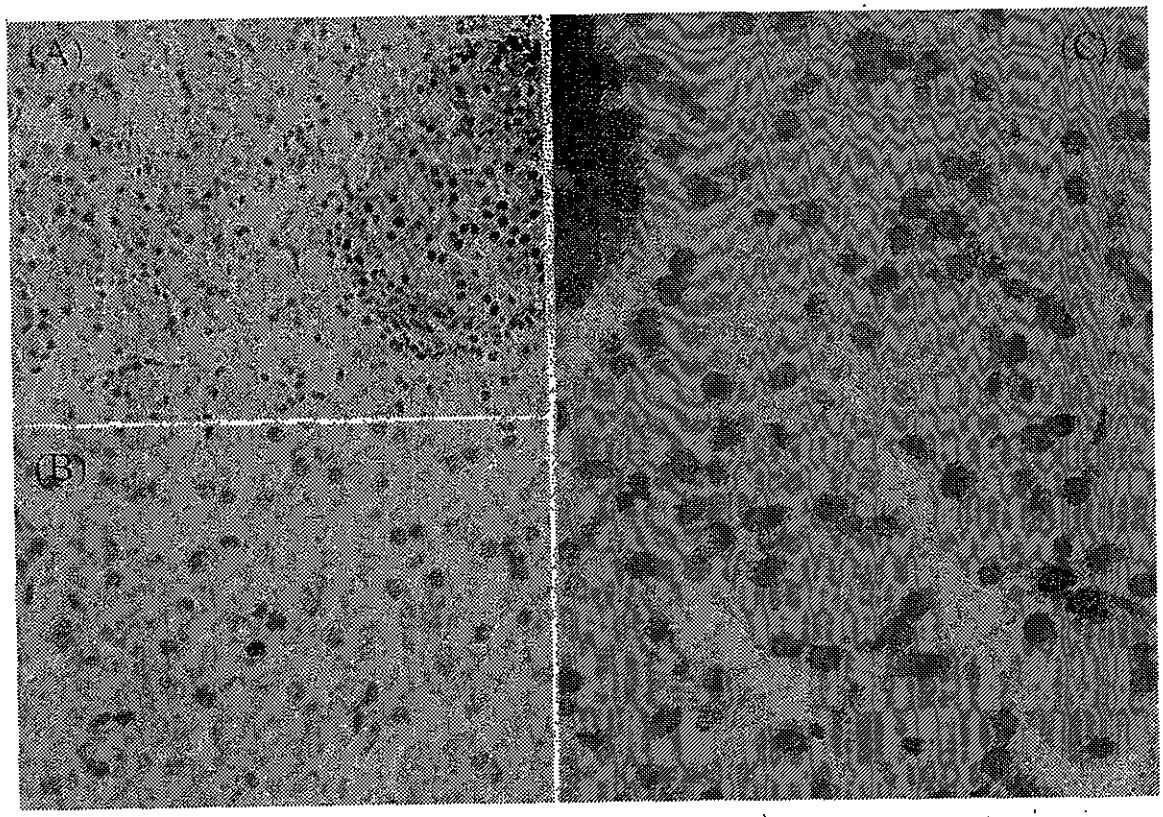

Fig 5. Double staining of PDX-1 and insulin (1 day after surgical wrapping). **A**, Original magnification ×100. **B**, Original magnification ×200. **C**, Original magnification ×400. PDX-1 immunoreactivity was detected in the nucleus with DAB brown and insulin immunoreactivity in the cytoplasm with Fuchsin red violet. One day after surgical wrapping, extraislet PDX-1–positive cells were mainly observed in acini with faint or no insulin immunoreactivity.

a faint expression of insulin but later accompanied by a much more extensive insulin production. The peak increase in the extraislet immunoreactive cell count was observed 1 day after SW for PDX-1–positive cells and 3 days after SW for insulin-positive cells. The results indicate that, in the process of adult islet neogenesis after SW, cells in the acini and ductal structures developed into PDX-1–expressing cells (supposedly progenitor cells), which in turn became insulin-producing cells and thus might be the origin of small islets.

PDX-1 appears to be a "master regulator" of pancreas development and B-cell differentiation and function,[18] which has been convincingly demonstrated in gene knockout experiments on transgenic mice. Jonsson et al[5] were the first to show that mice homozygous for PDX-1 gene mutation selectively lack a pancreas and that the mutant pups survive fetal development but die within a few days after birth. Offield et al[6] confirmed that neonatal PDX-1 −/− mice are apancreatic, but they found that the pancreas buds do form and that the dorsal bud undergoes limited proliferation and outgrowth to form a small, irregularly branched, ductal tree. Ahlgren et al[19] used the conditional gene-inactivation technique for further studies in mice with B-cell specific disruption of the PDX-1 gene and demonstrated that these mice developed diabetes with age and resembled inborn PDX-1 +/− mice. McKinonn et al[1] emphasized that there were 2 waves of PDX-1 expression in the developing pancreas. PDX-1 in the endoderm of the gut defines the region that will form the pancreas. In the absence of PDX-1, pancreatic buds will form, but PDX-1 is necessary for their growth. Neurogenin 3 expression then defines the endocrine cell linage, within which the homeodomain protein PDX-1 (during the second wave) and Nkx61 and the basic-helix-loop-helix protein NeuroD1 act as B-cell differentiation factors. Since the process of neogenesis seems to recapitulate islet ontogeny observed during embryogenesis, it is relevant for understanding

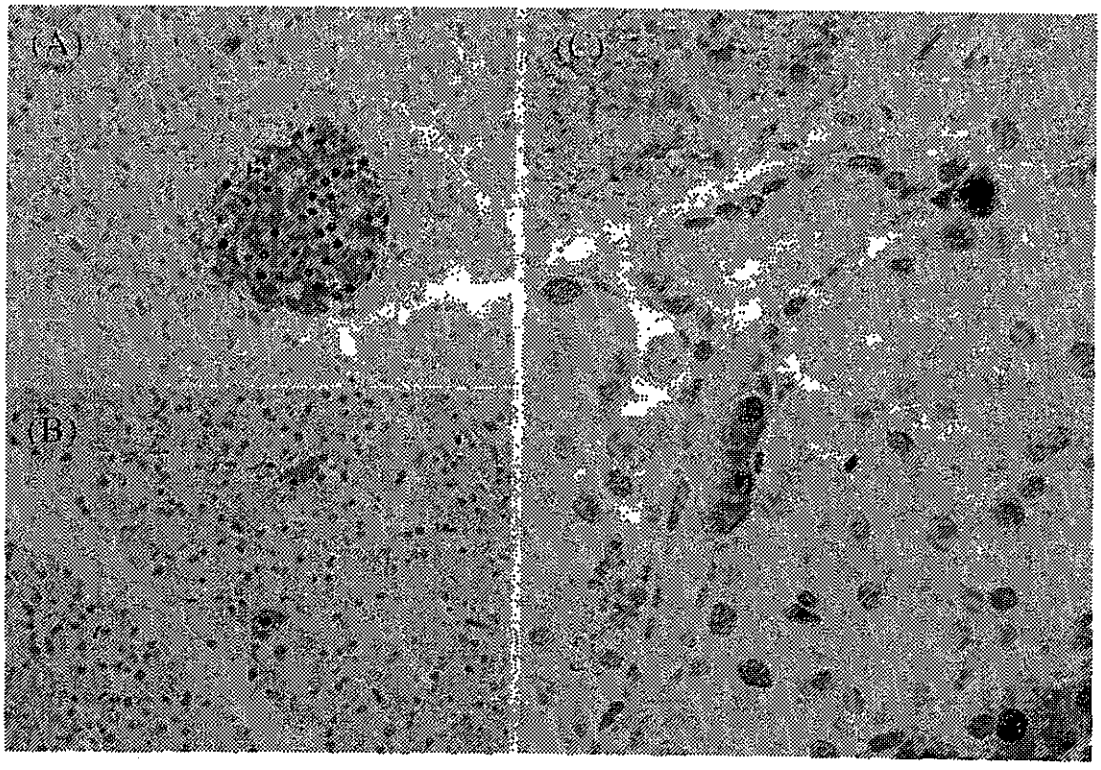

Fig 6. Double staining of PDX-1 and insulin (3 days after surgical wrapping). **A**, Original magnification ×100. **B**, Original magnification ×200. **C**, Original magnification ×400. Three days after surgical wrapping, extraislet PDX-1–positive cells were accompanied by much more evident insulin immunoreactivity.

the role of PDX-1 in islet renewal that occurs after birth.

Although it has been difficult to clearly identify the precursor population in the process of adult islet neogenesis, several studies have focused on PDX-1 expression. Fernandes et al[10] showed in STZ mice that PDX-1–positive cells appear inside the islets and that, in time, their appearance was followed by differentiation into PDX-1–positive and insulin-double–positive cells. An immunostaining study of consecutive mirror sections of alloxan-perfused pancreas demonstrated that insulin-positive cells and PDX-1–positive cells were located in the ductal structures.[11] In a regeneration model after 90% pancreatectomy, PDX-1–positive cells were found in the proliferating ductal cells.[12] PDX-1 was also strikingly expressed in the ducts of interferon-gamma transgenic mice, which exhibit new islet growth and expansion of ducts throughout their lifetime.[13] Our study of an islet hyperplasia model provides further evidence that newly formed islets arose from centroacinar and ductal cells and that significant up-regulation of PDX-1 accompanied formation of the islets. A recent in vitro study has also demonstrated that adult human cells with a typical ductal phenotype that originated from pancreatic exocrine tissue can re-express PDX-1 in culture.[20] Our double-immunostaining technique clearly demonstrated in vivo the sequential changes from PDX-1–expressing cells to insulin-containing cells. Interestingly, most animal studies, including ours, found that ductal PDX-1–positive cells were in close contact with or inside the lining of duct epithelium. PDX-1 may thus function as a transcriptional factor responsible for budding and migration of progenitor cells from the ductal structure, as well as for their differentiation into insulin-containing cells.[21]

The mechanism that up-regulates PDX-1 has not yet been clarified. Nutrients and hormones are potential regulators of PDX-1, and glucagon-like peptide-1 is the most likely hormonal candidate. This hormone and its agonist have been found to stimulate the expression of PDX-1 and increase the endocrine cell mass in vivo,[22-24] as well as to induce differentiation of PDX-1–positive pancreatic ductal cells into insulin-secreting cells in vitro.[25] Since the PDX-1 gene is associated with type 2 diabetes, a

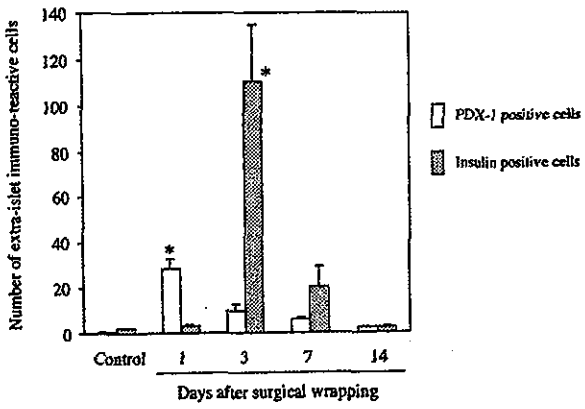

Fig 7. Number of extraislet PDX-1 and insulin immunoreactive cells after surgical wrapping. The number of extraislet PDX-1–positive cells significantly increased 1 day after surgical wrapping and gradually declined thereafter, while the peak increase in extraislet insulin-positive cells was observed 3 days after wrapping. The number of immunoreactive cells was counted per sample. Mean ± SD (5 rats, each count for triplicate samples); $*P < .05$ vs control (ANOVA).

better understanding of how PDX-1 contributes to B-cell neogenesis may have implications for the treatment of type 2 diabetes.[1] PDX-1 could also be valuable for ex vivo proliferation of insulin-secreting cells for cell therapy and a potential target for gene therapy of type 1 diabetes.[1,18] For these reasons, further studies, such as lineage tracing of PDX-1 and immunostaining of other islet hormones, are needed to clarify how PDX-1–expressing progenitor cells develop into isletlike clusters or true islets in the islet hyperplasia model.

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Treatment of Locally Advanced Pancreatic Cancer

Should We Resect When Resectable?

Masayuki Imamura, MD, and Ryuichiro Doi, MD

Abstract: While the outcome of surgery for locally advanced pancreatic cancer is still quite poor, over the past 2 decades, surgical outcomes have gradually improved in Japan. Because the advantages of surgery over radiochemotherapy have not yet been confirmed by randomized, controlled trials, it has long been discussed whether surgical resection could be indicated for locally advanced pancreatic cancer. We recently performed a multicenter, randomized, controlled trial comparing surgical resection and radiochemotherapy for locally advanced pancreatic cancer. Twenty patients were assigned to the surgery group, and 22 to the radiochemotherapy group. Although there was 1 operative death, surgery offered significantly better results than radiochemotherapy, as measured by 1-year survival (62% vs. 32%, $P = 0.05$), mean survival time (>17 vs. 11 months, $P < 0.03$), and hazard ratio (0.46, $P = 0.04$). There was no significant difference in the quality of life score or laboratory data, apart from increased diarrhea after surgery. In this article, the results of our trial are reviewed in brief, and our opinion on surgical treatment of locally advanced pancreatic cancer is discussed.

Key Words: Randomized controlled trial, treatment of pancreatic cancer, resection for pancreatic cancer, radiochemotherapy for pancreatic cancer

(*Pancreas* 2004;28:293–295)

The question of whether to perform surgery for locally advanced pancreatic cancer has long been discussed.[1,2] No consensus has arisen because no relevant randomized, controlled trial (RCT) has yet been performed. There has been a tendency for Japanese surgeons to attempt to cure this disease by resection, but in Western countries, surgery has been selected with greater discretion.[3] As we see in a number of articles, pancreatoduodenectomy has been performed safely worldwide for the past 5 years, with an operative death rate of less than a few percent.[2] So, it seems very necessary to determine whether resection is a good treatment choice for locally advanced pancreatic cancer.

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THE JAPANESE VIEW ON PANCREATIC CANCER TREATMENT BEFORE OUR STUDY

Pancreatic cancer currently kills more than 17,000 persons per year in Japan and is the fifth leading cause of cancer death.[4,5] The overall 5-year survival in patients undergoing radical curative surgery varies from 6.8% to 25%.[6–10] However, at least in Japan, there are many surgeons who have had a few patients who survived >5 years after resection for locally advanced pancreatic cancer. For the past 2 decades, improvements in operative and perioperative management have reduced operative mortality and led to a shorter hospital stays.[2,9,10]

On the other hand, pancreatic cancer is thought to be one of the most chemoresistant human malignancies.[11–13] The results of a small number of RCTs suggest that concomitant external beam radiotherapy and chemotherapy (radiochemotherapy) are preferable to chemotherapy alone, or radiation alone for patients with advanced, nonresectable pancreatic cancer with no distant metastasis.[14–16] Recently, gemcitabine has been reported to be more effective than 5-FU for prolongation of median survival time (MST) of patients with pancreatic cancer.[17] However, only a few cases have been reported of patients who survived >5 years after radiochemotherapy treatment.

RESULTS OF OUR RCT COMPARING RESECTION WITH RADIOCHEMOTHERAPY FOR PATIENTS WITH LOCALLY ADVANCED PANCREATIC CANCER

There has been no consensus on the treatment of locally advanced pancreatic cancer with no distant metastasis because no reports exist of RCTs for this stage of pancreatic cancer. We performed the first RCT comparing surgery and radiochemotherapy in patients with locally advanced pancreatic cancer extending beyond the pancreatic capsule but not invading the superior mesenteric artery or the common hepatic artery. This stage of pancreatic cancer[18] includes the largest number of patients. This results of this study are discussed briefly.

Twenty patients were assigned to the surgery group and 22 to the radiochemotherapy group. Although there was 1 operative death, surgery offered significantly better results than radiochemotherapy, as measured by 1-year survival (62% vs. 32%, $P = 0.05$), mean survival time (>17 vs. 11 months, $P < 0.03$), and hazard ratio (0.46, $P = 0.04$). There was no significant difference in the quality of life score or laboratory data, apart from increased diarrhea after surgery. We concluded that locally advanced pancreatic cancer without distant metastases and major arterial invasion should be surgically treated by experienced surgeons.

Additional Details

Our criteria for patient enrolment were (1) age between 20 and 75 years, with a performance status (PS) of 0–2; (2) tumor invasion of either the serosal (anterior) or retroperitoneal (posterior) surface of the pancreas or extension to the intrapancreatic portal vein without complete obstruction (ie, the tumor was either S2, RP2, or PV2 according to the JCS classification system[18]); (3) no adjacent organs were involved except the transverse mesocolon, the duodenum, and the common bile duct; (4) there was no invasion of the superior mesenteric or common hepatic artery or peripancreatic nerve plexuses (A0 and PL0); (5) paraaortic lymph node metastasis was absent (N0 or N1); (6) the maximal diameter of the tumor was >2 cm but <6 cm (TS2 or TS3); and (7) there was no liver metastasis or peritoneal seeding (H0 and P0). These criteria are consistent with stage IVa cancer according to the JCS. Other exclusion criteria were (1) previous radiation therapy or chemotherapy; (2) abnormal reaction to drugs, including contrast media; (3) presence of serious cardiovascular, pulmonary, renal, or hepatic diseases; (4) coexistence of an active neoplasm; and (5) any other conditions that the physician would consider preclude participation in the trial.

Once a patient met our eligibility criteria based on preoperative examinations, including abdominal CT, angiography, ultrasonography, chest x-rays, and routine laboratory tests, informed consenting patients were registered as potential candidates at the central office of the trial not later than 1 day before a scheduled laparotomy. Eligibility was finally decided according to the operative findings of laparotomy, and the patient was randomized by telephone call to our central office. Eligible patients were categorized by tumor location (pancreatic head versus body and tail) and were assigned to either a surgery group or a radiochemotherapy group.

Patients assigned to the surgery group underwent pancreatoduodenectomy or distal pancreatectomy for resection of the main pancreatic cancer with dissection of the regional lymph nodes that belong to group 1 (or more) according to the JCS. At least a half circle of the plexus of the root of the superior mesenteric artery was resected. Patients received no postoperative adjuvant therapy unless recurrence was obvious, at which point the doctor in charge was permitted to select another therapy.

In patients assigned to the radiochemotherapy group, the abdomen was closed once a biopsy specimen had been taken to confirm diagnosis, although the surgeon in charge was free to perform anastomotic surgery, such as gastrojejunostomy or biliodigestive anastomosis. The patient received radiation therapy within 1 week. This was delivered as a single course of total radiation dose of 5040 cGy in 28 fractions at 180 cGy over 5.5 weeks, using 10–14-MV photons. The radiation fields took in the primary tumor and a margin of 1–3 cm covering the regional lymph nodes and was directed on the basis of computed tomographic images taken 1 or 2 days before treatment. During radiotherapy, there was continuous intravenous infusion of 5-fluorouracil (5-FU) at 200 mg/m^2/d. This was followed by weekly intravenous infusion of 5-FU at 500 mg/m^2, starting in most cases within 1 week and always within 4 weeks of completion of radiochemotherapy.

Figure 1 shows the survival curves for the 2 treatment groups. The surgery group displays significantly better survival than the radiochemotherapy group. The resulting statistical significance increased further when the operative death was treated as censored. Cox univariate analyses revealed that the only variable to be a significant independent predictor of survival was resection.

UNIQUE POINTS OF OUR CLINICAL TRIAL

In our trial, eligibility criteria were based on operative findings, which are more accurate than preoperative imaging, and considerable discrepancies between preoperative and operative diagnoses in the extent of the tumor and distant metastases were noted. Of 81 registered patients who were potentially eligible, 39 patients were excluded based on the opera-

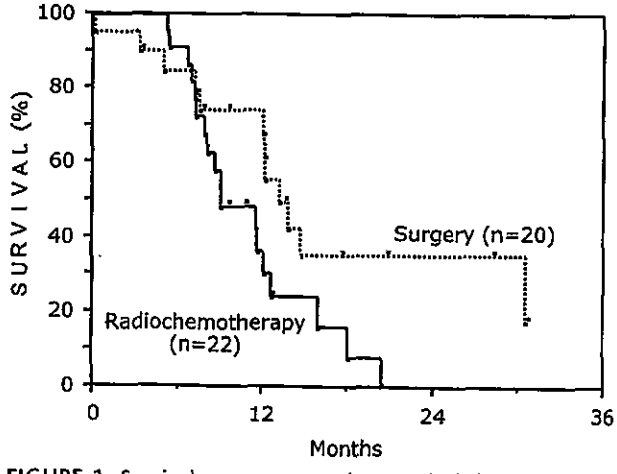

FIGURE 1. Survival curves comparing survival times and percentages in the surgery and radiochemotherapy groups.

tive findings. When we compared the preoperative evaluation by CT with the operative findings in these 81 registered patients, the diagnostic accuracy for anterior capsular invasion, retroperitoneal invasion, and portal venous system invasion was 65%, 84%, and 86%, respectively.

As a result, about half of all preregistered patients were ultimately excluded from the trial, leaving a subset of patients who were very homogeneous and expected to respond to the treatments similarly. This may explain why a statistically significant difference was detected using a smaller number of patients (42 patients) than the original estimate of the necessary sample size (150 patients). Irrespective of sample size, there remains the question of whether our results, obtained from one study of a strictly defined population, apply in a more general population.

OUR OPINION ON SURGICAL TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER

Through this study, all patients with resectable, locally advanced pancreatic cancer meeting the chosen criteria were fully apprised of the study, although 59% of them (117 patients) did not agree to be registered in the clinical trial. Ninety-one patients strongly requested surgical resection, but the remaining 26 strongly requested radiochemotherapy. Apparently, Japanese patients with pancreatic cancer still believe that surgical resection is the optimal treatment.

According to a nationwide survey by the Japanese Pancreas Society, 2005 patients with surgical stage IVa ductal cancer who are closely comparable with our study population underwent resection between 1980 and 1999. They had an average 1-year survival rate of 49%, a 5-year survival rate of 10%, and a 10-year survival rate of 5%.[4] Together with our trial, these results imply that a substantial number of patients in stage IVa still have a curatively resectable disease and would have a more favorable outcome with surgery than with other treatments. In contrast, more patients undergoing laparotomy would not benefit from surgery and may even be harmed by surgery, including those with subclinical metastases that are not detectable preoperatively or at the time of laparotomy, as well as those who die of operative complications. Efforts, therefore, should continue to avoid negative or adverse outcomes of surgery by improving imaging accuracy and other noninterventional diagnostic procedures, such as laparoscopy. Also, surgery should be performed at specialized centers with large patient numbers since there is a clear association between high patient numbers and reduced mortality rates.[2,19–22]

CONCLUSION

From this multicenter, RCT comparing surgical resection and radiochemotherapy, we conclude that locally advanced pancreatic cancer, without involvement of the common hepatic artery or superior mesenteric artery, can be successfully treated surgically by experienced surgeons at specialized centers with large patient numbers.

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Pancreatic Endocrine Tumor in Japan

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Abstract: Japanese clinicians and scientists have contributed significantly to reporting, investigating, and managing patients with pancreatic endocrine tumors and other multiple endocrine neoplasias for the past several decades. This article summarizes the latest progress in this field in Japan. Particularly, our contribution to the development of diagnostic and localization methods is reviewed. Further, the present use of somatostatin receptor scintigraphy and the application of the laparoscopic surgery for pancreatic endocrine tumor in Japan are discussed.

Key Words: selective arterial secretagogue injection test, multiple endocrine neoplasia-1, enteropancreatic tumor, ^{111}In-pentetreotide scintigraphy, calcium sensing receptor

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Pancreatic endocrine tumors constitute a wide variety of rare lesions that are named according to the hormones that they produce. Although this group of diseases is termed pancreatic endocrine tumors, this can be misleading because many of the tumors, such as gastrinoma and somatostatinoma, occur outside the pancreas. Tumors can occur in either a sporadic fashion or a hereditary fashion [multiple endocrine neoplasia-1 (MEN-1)]. These tumors continue to be challenging diagnostic and prognostic lesions in surgical pathology and clinical medicine because treatment must be directed first at the clinical syndrome caused by excess hormone production and the tumor itself and the possibility of malignancy. Gastrinoma, in particular, is recognized as a malignant tumor in nature, even if a metastatic lesion is not found at the diagnosis. Therefore, precise localization is essential for complete resection of the tumors.

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This article summarizes the latest progress in diagnosis and treatment of pancreatic endocrine tumors in Japan. In particular, our contribution to the development of diagnostic and localization methods is outlined. Furthermore, current utilization of somatostatin receptor scintigraphy and the application of the laparoscopic surgery for pancreatic endocrine tumors in Japan are discussed.

DEVELOPMENT OF SELECTIVE ARTERIAL SECRETAGOGUE INJECTION TEST

Pancreatic endocrine tumors are usually found and diagnosed by the clinical syndrome caused by excess hormone production. Localization of the tumors is determined by imaging diagnosis, such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). Intrapancreatic tumors and larger size tumors are easily found by these imaging methods. However, it is often difficult to diagnose and localize small tumors and extrapancreatic tumors, such as duodenal gastrinomas.

Angiography is one of the most widely used techniques for visualizing pancreatic endocrine tumors because they are often detected as hypervascular tumors. The sensitivity and specificity of angiography are not very high; however, in fact they are lower than 80% of trials. CT and MRI can sometimes visualize an endocrine tumor as a hypervascular tumor surrounding a pancreaticoduodenal lesion, but their specificity and sensitivity also are not high, lower than 70% in pancreatic tumors. Even endoscopic ultrasonography (EUS), which is useful for diagnosing insulinoma, is not good for visualizing gastrinomas, especially those that occur in the pancreatic uncus and tail.

In the diagnosis or localization of endocrine tumors, therefore, we emphasize the usefulness of provocative tests using secretagogues. We have devised the selective arterial secretagogue injection test using secretin (secretin-SASI test or Imamura test)[1,2] to determine localization of endocrine tumors by identifying the feeding artery for those tumors. Just as we have established a method to detect gastrinomas with the secretin-SASI test, Doppman et al and we have also developed n SASI test using calcium as a secretagogue (calcium-SASI test or SACI test) to localize insulinoma.[3,4]

We are able to determine the area and extent of the resection required, based on the SASI test, regardless of whether

any tumor has been previously visualized by preoperative imaging techniques. Since the early 1990s, these tests have been used in the diagnosis and localization of endocrine tumors because they are the most sensitive and reliable methods available. Combined with the intraoperative secretin injection test (IOS test),[5] the SASI test is indispensable for curative resection of microgastrinomas in patients with Zollinger-Ellison syndrome.

THE SECRETIN-SASI TEST

The principle of the secretin-SASI test is based on the observation that in vitro and in vivo secretin induces a prompt release of gastrin from gastrinoma cells.[6,7]

When selective arterial angiography was performed, the tip of the catheter was selectively inserted into 1 of the 3 peripancreatic arteries: the gastroduodenal artery, the superior mesenteric artery, or the splenic artery. Hepatic venous immunoreactive gastrin was measured in blood samples collected prior to and 20, 40, 60, 90, and 120 seconds after the secretin injection. When the gastrin level increased by 80 pg/mL or 20% of the basal level within 40 seconds, the artery was considered to be a feeder to the gastrinoma.[2]

THE IOS TEST

The IOS test was developed to confirm curative resection of the gastrinomas in the operating room. Before and after the resection of a gastrinoma, secretin at 3 U/kg body weight is intravenously injected, and then blood samples are collected prior to and 2, 4, and 6 minutes after the injection. Rapid radioimmunoassay of gastrin is performed by shortening the incubation time of the Gammatab gastrin assay (Baxter Healthcare Corporation, Cambridge, MA). In brief, reaction mixtures are incubated with the first antibody for 20 minutes at 37°C, followed by incubation with the second antibody for 5 minutes at room temperature. We verified a good relationship between the results of this assay and those of the standard method. Results of the IOS test are usually obtained within 60 minutes in the operating room.

KYOTO UNIVERSITY EXPERIENCE

Figure 1 shows the diagnostic and therapeutic decision tree for patients with Zollinger-Ellison syndrome at our institution. Once localization of the gastrinoma is determined by the secretin-SASI test, laparotomy is performed. With the intraoperative US and intraoperative gastrointestinal endoscopy, further localization of the tumor is anticipated. After surgical resection of the tumor, the IOS test is routinely performed. The abdomen is closed with a negative IOS test result. However, we extend the resection of the regional lymph node or modify the operative mode from excision of the duodenal tumor to pancreatoduodenectomy when the IOS test is positive.[5]

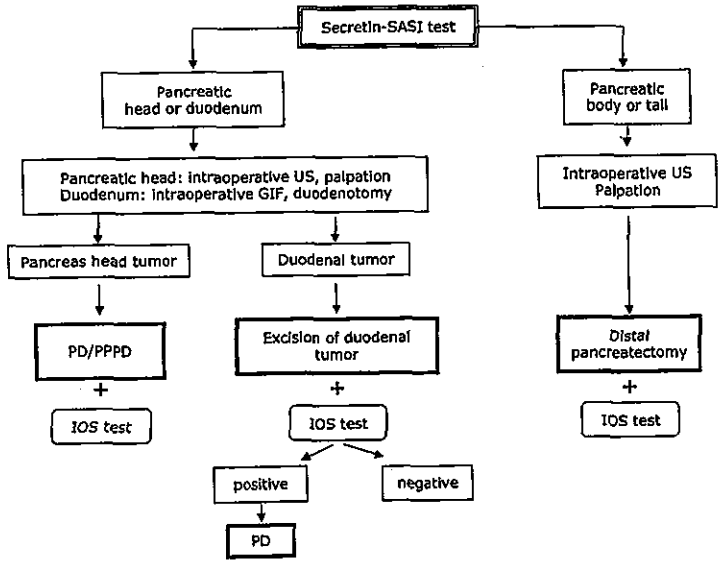

FIGURE 1. Diagnostic and therapeutic decision tree for the patients with Zollinger-Ellison syndrome at our institution. After localization of the tumor by the secretin-SASI test, laparotomy is performed. With the intraoperative US and intraoperative gastrointestinal endoscopy, further localization of the tumor is anticipated. After surgical resection of the tumor, the IOS test is routinely performed. The abdomen is closed with the negative result of the IOS test; however, we extend the resection of the regional lymph node or modify the operative mode from excision of the duodenal tumor to pancreatoduodenectomy when the IOS test is positive.

We have had 28 patients with Zollinger-Ellison syndrome. Using the secretin-SASI test, all of the gastrinomas were localized, and the feeding arteries were identified. The gastroduodenal artery was the feeder in 19 patients, the splenic artery was the feeder in 3 patients, the superior mesenteric artery was the feeder in 2 patients, 3 arteries were the feeders in 1 patient, and the proper hepatic artery was the feeder in 1 patient with metastatic hepatic gastrinomas.

Twenty patients underwent curative surgical resection of gastrinomas, including 10 pancreatoduodenectomies, 3 distal pancreatectomies, 6 excisions of duodenal tumors, 1 partial resection of hepatic tumor, and 1 resection of metastatic lymph nodes. Hepatic resection and lymph node resection were performed for the recurrent gastrinoma patients who underwent the first operation at other hospitals.

Gastrinomas were histologically diagnosed in all the resected specimens except in 1 specimen in the tail of the pancreas, although the serum gastrin level for the patient measured <80 pg/mL postoperatively. Lymph node metastases were found in 8 patients. Survival curves for those patients are shown in Figure 2.

INTRAVENOUS CALCIUM INJECTION TEST AS A NOVEL COMPLEMENTARY PROCEDURE IN THE DIFFERENTIAL DIAGNOSIS FOR GASTRINOMA

Although the secretin injection test and secretin-SASI test are powerful tools for the diagnosis of Zollinger-Ellison syndrome, we have been aware that there are patients with negative results of secretin provocative tests. Secretin injection test is the principal study in the diagnosis of Zollinger-Ellison syndrome; however, it is negative in up to 20% of patients with proven gastrinoma. Furthermore, the SASI test was negative in 11% (9 of 80) of patients with Zollinger-Ellison syndrome and positive in 92% (12 of 13) of those with a negative secretin injection test. It is important to realize that some patients have no response to secretin stimulation; therefore, a different modality has been required to detect precise localization of gastrinoma. Based on these backgrounds, we have developed a novel calcium injection test as a differential diagnosis of gastrinoma.

In calcium injection testing, calcium gluconate (Calcicol; Dainippon Co., Tokyo, Japan) 255 mg/3 mL was injected intravenously for 30 seconds. Venous blood sampling was performed before and at 2-minute intervals up to 10 minutes after calcium injection for measurement of immunoreactive gastrin. We compared the results of the intravenous calcium injection test, intravenous secretin injection test, and the SASI test in patients with Zollinger-Ellison syndrome and normal subjects.[8]

The SASI test with secretin was performed in 24 of 26 patients with hypergastrinemia, including 22 of 24 patients with Zollinger-Ellison syndrome. Accuracy in the diagnosis of tumor localization by the SASI test was 95% (21 of 22) in Zollinger-Ellison syndrome. The secretin test was negative in 3 of 21 patients (14%) with Zollinger-Ellison syndrome. Either the secretin test or the SASI test was positive in 22 of 23 patients (96%). The calcium injection test was administered to 12 patients with hypergastrinemia and 4 controls. The patients with hypergastrinemia showed significantly higher serum gastrin levels than those of the control group in the calcium injection test. Eight of 10 Zollinger-Ellison syndrome patients (80%) had a positive calcium injection test (Fig. 3). We could diagnose gastrinomas in 100% of Zollinger-Ellison syndrome patients by either the calcium injection test or the secretin test. We have thus confirmed the efficacy of the intravenous calcium injection test in the diagnosis of gastrinoma. We propose that the calcium injection test as an adjunct diagnostic test in gastrinoma, which often goes undetected with routine testing.

BASIC ASPECT OF THE SELECTIVE ARTERIAL SECRETAGOGUE INJECTION TEST

The selective arterial secretagogue injection test using calcium (calcium-SASI or SACI test) is an important tool for localizing insulinoma. Clinically, the selective arterial stimulant injection test with calcium is often used for localization of insulinoma that cannot be visualized by imaging techniques, such as CT, MRI, and US.[1,2,9] When we inject calcium into the insulinoma-feeding artery during selective arterial stimulant injection testing, the hepatic venous insulin level becomes elevated within 40 seconds.

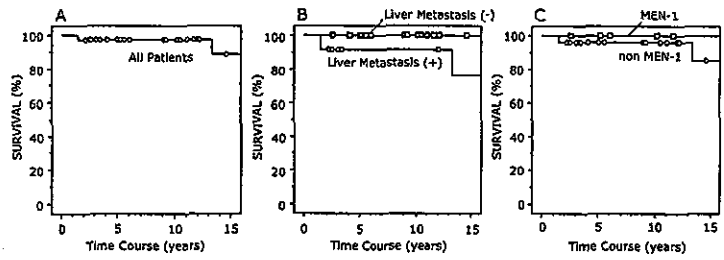

FIGURE 2. Survival curves for gastrinoma patients (A). Liver metastasis at initial diagnosis (B). Gastrinoma patients with MEN-1 versus without MEN-1.

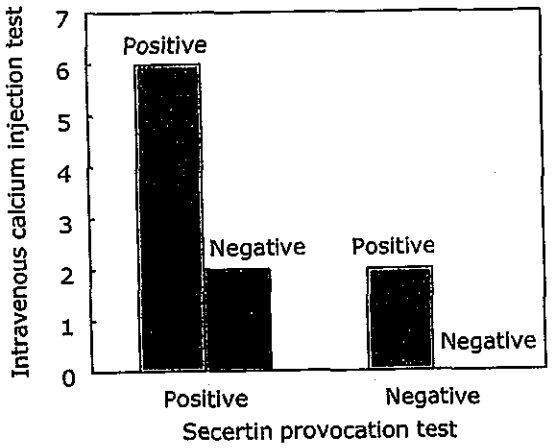

FIGURE 3. Comparison of results of the secretin test with those of the calcium injection test in Zollinger-Ellison syndrome patients. By using the secretin test in combination with the calcium test, we were able to diagnose gastrinomas in 100% of the Zollinger-Ellison syndrome patients.

We have demonstrated that human insulinoma expresses calcium-sensing receptor (CaR) and that the CaR expression of insulinoma might be related to its insulin secretion.[10] Briefly, we showed that a high $[Ca^{2+}]_o$ concentration immediately evoked a significant increase in insulin release from human insulinoma cells in vitro, which lasted 6 minutes. The $[Ca^{2+}]_i$ level in the insulinoma cells rose immediately after the $[Ca^{2+}]_o$ concentration was increased. This elevated $[Ca^{2+}]_i$ level was mediated by CaR. Interestingly, we also showed that human gastrinoma expresses CaR.[11]

However, we had no data on whether normal pancreatic islets express CaR, although Rasschaert et al[12,13] reported that normal rat and tumor cells that secrete insulin express CaR, and Bruce et al[14] found that CaR-like molecules are expressed in rat pancreatic acinar cells, ducts, and islets.

Thus, we investigated the expression of CaR in normal human pancreas and evaluated the differences in response to extracellular calcium between normal rat islets and human insulinoma cells because it is quite difficult to obtain viable normal human islets.[15] We showed that CaR is eventually expressed in both human pancreatic islets and human insulinoma cells. Microfluorometry showed an increase in the $[Ca^{2+}]_i$ level in response to changes in the $[Ca^{2+}]_o$ concentration, with a more sensitive response in human insulinoma cells than in normal islets. When 1 μmol/L wortmannin (a selective phosphatidylinositol 3-kinase inhibitor) was added to the perfusion medium, the response disappeared in insulinoma cells but not in islets. Therefore, it could be concluded that both insulinoma cells and islets expressed CaR. However, the reactivity to changes in the $[Ca^{2+}]_o$ concentration differed between them. These findings suggest that the signaling pathways controlling the changes in $[Ca^{2+}]_i$ differ between normal rat islets and human insulinoma cells and partly explain the reason why the responses of normal islets and insulinoma cells to $[Ca^{2+}]_o$ differed in SACI test, done to diagnose microinsulinoma.

We speculate that the CaR is involved in the varying responses of normal islets and insulinoma cells, the sensitivity of which further varies among cases. Recently, we had an interesting case in which neither imaging studies nor an SACI test with a conventional dose of calcium (0.025 mEq/kg) indicated the tumor.[16] The SACI test with high-dose calcium injection (0.05 mEq/kg) evoked insulin secretion when injected into the superior mesenteric artery. In this case, a solitary tumor in the head of the pancreas was resected, and plasma glucose returned to normal. Postoperatively, intravenous injection of secretin resulted in a normal response of insulin that was not found preoperatively. This case suggests the usefulness of the SACI test with a high-dose of calcium in the case of insulinoma, when the standard dose fails to detect such a tumor.

SOMATOSTATIN RECEPTOR SCINTIGRAPHY IN JAPAN

In the diagnostic approach to neuroendocrine tumors, nuclear medicine procedures are currently gaining interest.[17] This is due to the introduction of new tracers and to the technological improvement of radiation detection instruments. The most widely used radiopharmaceutical at present is a somatostatin analogue, octreotide, radiolabeled with indium-111. This peptide can be chelated with diethylene triamine pentaacetic acid (DTPA) and labeled with ^{111}In to obtain ^{111}In-pentetreotide. This radiopharmaceutical is used to image somatostatin receptors types 2 and 5, usually expressed on enteropancreatic endocrine tumors. Somatostatin receptor imaging has been successfully employed to visualize somatostatin receptor–bearing tumors.[18,19]

In terms of the clinical impact, Lebtahi et al[20] compared somatostatin receptor imaging with conventional imaging in 160 patients affected by enteropancreatic endocrine tumors. The overall sensitivity was 78%. Somatostatin receptor imaging was positive in 61% of 46 patients having tumors previously undetected with conventional imaging, and was negative in only 15% of the known tumor sites. Somatostatin receptor imaging provided additional detection sites compared with conventional imaging, even if the detection rates were comparable (78% vs. 71%). The classification of tumors was modified in 24% of the patients, and the surgical approach was changed in 25%. The authors proposed somatostatin receptor imaging as a first-line procedure in patients with enteropancreatic endocrine tumors, selecting eligible patients for curative surgery from those with extrahepatic metastases.

Although several studies have reported the usefulness of somatostatin receptor scintigraphy in the diagnosis and localization of pancreatic endocrine tumor, applying this sophisticated method is now underway in Japan. The recently com-

pleted phase III multicenter clinical study in Japan investigated the efficacy, safety, and usefulness of somatostatin receptor scintigraphy using ^{111}In-pentetreotide.[21] Forty patients were included in the study. There were 18 patients with previously detected tumors viewed by conventional imaging modalities, and 22 patients with previously undetected tumors in spite of their high serum hormone levels. By comparing the results of the octreotide suppression test, 75% of patients with previously detected tumors and 57.9% of patients with previously undetected tumors were assessed as "effective." By comparing the results of immunohistological examination, 55.6% of patients having previously detected tumors and 50% of patients having previously undetected tumors were assessed as "effective." ^{111}In-pentetreotide was judged to be clinically useful in 68.8% of patients having tumors previously detected and 26.3% of patients having tumors previously undetected. These results suggest that ^{111}In-pentetreotide scintigraphy is very useful for the diagnosis and decision on a therapeutic strategy for enteropancreatic hormone–producing tumors in Japan.

APPLICATION OF LAPAROSCOPIC SURGERY

Laparoscopic pancreatic surgery is currently used for staging malignant pancreatic tumors, occasional management of inflammatory disorders of the pancreas, and resection of benign pancreatic tumors.[22–27] Pancreatic endocrine tumors are slowly growing neoplasms and are of a relatively benign nature in 70%–80% of individuals.[28–30] With the exception of gastrinomas and somatostatinomas, which are found in the pancreatic head in 60%–70% of cases, other endocrine tumors such as insulinoma and VIPoma are located predominantly (65%–80%) in the body and tail of the pancreas.[28–30] This localization makes pancreatic endocrine tumors suitable for the laparoscopic approach. However, these tumors are rare neoplasms with an annual incidence of 0.1/100,000 to 0.4/100,000, and the evaluation of laparoscopic surgery is difficult to establish for an individual surgeon.

Analysis of the reported cases from Japanese institutes reveals a small collective experience with the laparoscopic approach.[31–35] These reported cases were successfully treated with laparoscopic approaches, although the conversion rate of the laparoscopic surgery in the large series of Gagner et al[36] was 33%. Similarly, Berends et al[37] reported 5 successful enucleations and 1 laparoscopic distal pancreatectomy for treatment of 10 patients with organic hyperinsulinism; the conversion rate was 40%. The high rate of conversion is presumably dependent on the surgical experience with the procedure.

Therefore, this advanced laparoscopic surgery should be practiced on the relatively more common tumors, such as serous cystoadenomas and mucinous cystic neoplasms. Experiences with laparoscopic approaches on these tumors were reported recently,[38–42] and Japanese pancreatic surgeons can gain confidence with laparoscopic techniques, ensuring proper oncologic surgery, maximal tumor clearance, and minimal tumor recurrence.

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Effects of Preceding Gastrectomy on the Outcome of Pancreatoduodenectomy

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It is a complicated task to perform pancreatoduodenectomy for patients who previously had undergone gastrectomy. This paper reviewed our experience of eight pancreatoduodenectomies in gastrectomized patients. The indications for gastrectomy included gastric cancer in 3 patients, duodenal ulcer in 1 patient, and gastric ulcer in 4 patients. The interval between the two operations ranged from 15–254 months (average: 103 months). All patients underwent pancreatoduodenectomy, and the reconstruction after pancreatoduodenectomy was performed by the Whipple method, the Child method, or other complex Roux-en-Y type methods. All the patients recovered and were discharged without gastrointestinal disorder. The results suggest that the secondary pancreatoduodenectomy does not increase the mortality rate, although we should use the jejunal limb with less tissue damage at the anastomotic site of which circulation is well maintained for choledochojejunostomy and pancreaticojejunostomy. Furthermore, the jejunal limb should be lined carefully to avoid intestinal kinking and excess tension to the anastomosis.
(J GASTROINTEST SURG 2004;8:575–579)

KEY WORDS: Pancreatoduodenectomy, gastrectomy

INTRODUCTION

Pancreatoduodenectomy (PD) involves various complex operative procedures. The principle of the surgical technique for one-stage pancreatoduodenectomy was established by Whipple and associates.[1] There have been two types of reconstruction procedure for the remnant alimentary tract after pancreatoduodenectomy: Billroth I type reconstruction method (Imanaga method) with gastrojejunostomy; pancreatojejunostomy, and choledochojejunostomy in that order[2,3]; and Billroth II–type reconstruction with choledochojejunostomy, pancreatojejunostomy, and gastrojejunostomy (Whipple method) or pancreatojejunostomy, choledochojejunostomy, and gastrojejunostomy (Child method), in that order.[1,4]

The mortality rate of pancreatoduodenectomy has declined to less than 5% for chronic pancreatitis and 3%–8% for pancreatic cancer.[5] The mortality rate is reported to be less than 1% at specialized centers with large patient numbers and experienced surgeons.[6] In contrast, overall morbidity rates remain high, ranging between 20%–70%.[5]

It is a complicated task to perform pancreatoduodenectomy for patients who previously had undergone gastrectomy. The adhesion and the modified anatomy of the remnant organs can be obstacles for pancreatoduodenectomy. Furthermore, it is easy to speculate that the reconstruction procedure requires experience because the adhesion of the intestine and the shortened mesentery frustrate the mobilization of the small intestine. We recently performed eight pancreatoduodenectomies in gastrectomized patients. This study retrospectively reviews such pancreatoduodenectomies undertaken in gastrectomized patients and explores the lessons learned from pancreatoduodenectomy in gastrectomized patients.

MATERIALS AND METHODS

We conducted a retrospective, descriptive analysis of pancreatoduodenectomy in patients who previously underwent gastrectomy for various indications. Among 156 patients who underwent pancreatoduodenectomy at the Department of Surgery and Surgical

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Basic Science (Kyoto University) from 1991–2000, 8 patients had undergone distal or total gastrectomy before the pancreatoduodenectomy (Table 1). Those 8 patients (7 men and 1 woman) ranged in age from 39–77 years (average: 55 years). The modes of reconstruction after pancreatoduodenectomy are listed and illustrated (Figs. 1–3).

RESULTS

The indications for preceding gastrectomy and the mode of the gastric resection are summarized in Table 1. The indications for gastrectomy included gastric cancer in 3 patients, duodenal ulcer in 1 patient, and gastric ulcer in 4 patients (Table 1). Distal gastrectomy was performed in 6 patients, where Billroth I anastomosis in 3 patients and Billroth II anastomosis in 3 patients were performed, respectively. Roux-en-Y anastomosis was performed for both total gastrectomies.

All patients underwent pancreatoduodenectomy. The indications for pancreatoduodenectomy are summarized in Table 1. The interval between the two operations ranged from 15–254 months (average: 103 months). Those patients who had undergone distal gastrectomy with Billroth I anastomosis had pancreatic ductal cell carcinoma, intraductal papillary mucinous tumors (IPMT), and duodenal gastrinoma. The reconstruction after pancreatoduodenectomy was made by the Whipple method in 2 patients and by the Child method in 1 patient (Fig. 1). Patients who had undergone gastrectomy with Billroth II anastomosis had bile duct cancer, islet cell tumor, and islet cell carcinoma. While preserving the existing gastrojejunostomy, the reconstruction after pancreatoduodenectomy was performed by the Whipple method in 1 patient and by the Roux-en-Y method in 2 patients. The pancreatojejunostomy was performed at the elevated jejunum limb and at the origin of the jejunum for each type, respectively (Fig. 2).

Patients who had previously undergone total gastrectomy with Roux-en-Y anastomosis had pancreatic ductal carcinoma and pancreatic gastrinoma. After the second pancreatoduodenectomy, the previous esophagojejunostomy was preserved and the reconstruction was made by the Roux-en-Y type method using the origin of the jejunum or a new Roux limb (Fig. 3).

The operative time for the secondary pancreatoduodenectomy ranged from 8 hours and 20 minutes to 10 hours and 40 minutes (average: 9 hours and 6 minutes). The estimated blood loss ranged from

Table 1. List of the patients who underwent pancreatoduodenectomy after gastrectomy

	Gastrectomy				Pancreatoduodenectomy					
#	Age; gender	Indication	Mode of gastrectomy	Anastomosis	Age	Interval (months)	Indication	Reconstruction	Operative time	Complication
1	48; male	gastric cancer	distal	Billroth I	58	116	Pancreatic cancer	Whipple	10′ 40″	none
2	50; male	gastric cancer	distal	Billroth I	53	39	IPMT	Whipple	8′ 20″	none
3	28; female	gastric ulcer	distal	Billroth I	39	129	duodenal gastrinoma	Child	9′ 05″	none
4	31; male	duodenal ulcer	distal	Billroth II	52	245	bile duct cancer	Roux-en-Y type	9′ 39″	increased amylase in drainage
5	40; male	gastric ulcer	distal	Billroth II	44	46	islet cell tumor	Whipple	8′ 30″	afferent loop syndrome
6	62; male	gastric ulcer	distal	Billroth II	77	187	islet cell carcinoma	Roux-en-Y type	8′ 36″	none
7	65; male	gastric cancer	total	Roux-en-Y	69	43	pancreatic cancer	Roux-en-Y type	9′ 50″	afferent loop syndrome
8	45; male	gastric ulcer	total	Roux-en-Y	46	15	pancreatic gastrinoma	Roux-en-Y type	8′ 23″	none

IPMT = intraductal papillary mucinous tumors.

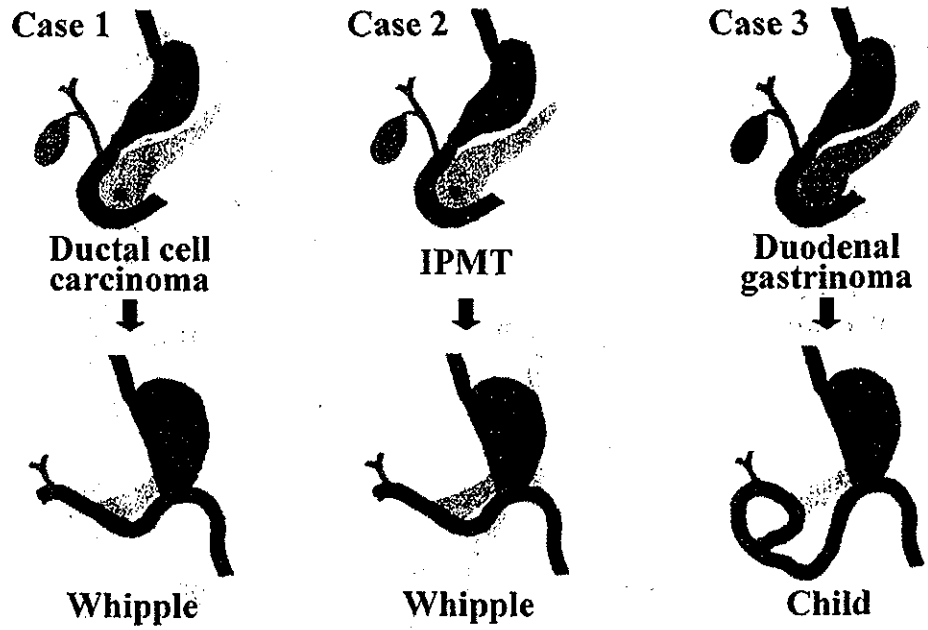

Fig. 1. Reconstruction methods after pancreatoduodenectomy for patients who previously underwent gastrectomy with Billroth I anastomosis.

630 g–2620 g (average: 1919 g). All the patients recovered and were discharged without gastrointestinal disorder. The length of hospital stay after the pancreatoduodenectomy ranged from 20–115 days (average: 56 days). During the postoperative course, afferent loop syndrome was recorded in 2 patients (cases 5 and 7), and increased amylase in the drainage was observed in 1 patient (case 4). In this case, a closed silicon drain was placed at the site of pancreaticojejunostomy. The amylase level in the drainage

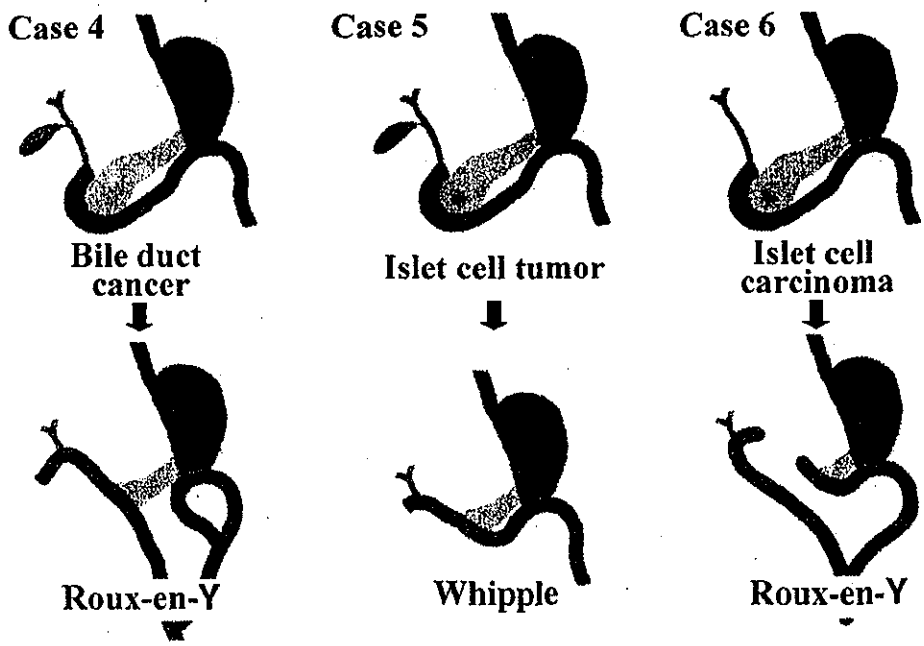

Fig. 2. Reconstruction methods after pancreatoduodenectomy for patients who previously underwent gastrectomy with Billroth II anastomosis.

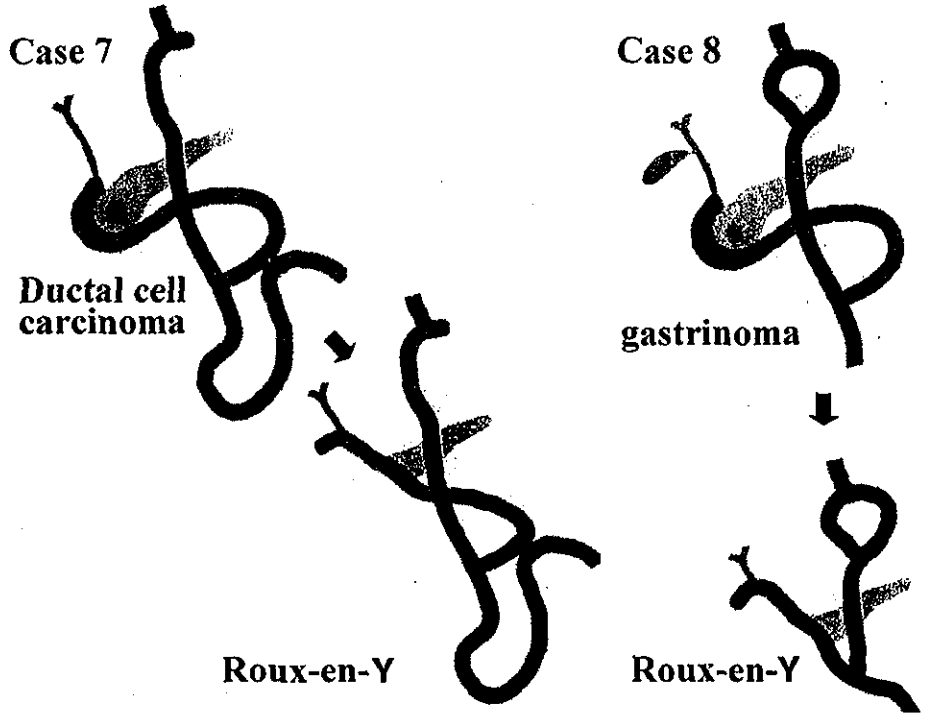

Fig. 3. Reconstruction methods after pancreatoduodenectomy for patients who previously underwent gastrectomy with Roux-en-Y anastomosis.

was normalized after 4 weeks of fasting without relaparotomy and surgical intervention.

DISCUSSION

It is a challenging task to perform a successful pancreatoduodenectomy on a patient who has a past history of major abdominal surgery. Preceding gastrectomy, in particular, affects the operative procedure of pancreatoduodenectomy because the intestinal adhesion and the modified anatomy of the upper abdomen may confound the operator and pose a risk for postoperative morbidity. We performed eight pancreatoduodenectomies for gastrectomized patients. As expected, the average operative time of 9 hours was considerably longer than the usual pancreatoduodenectomy procedure and the estimated blood loss was, to some extent, increased. An average hospital stay of 56 days for the second pancreatoduodenectomy is not significantly long as compared with those patients who underwent pancreatoduodenectomy for the first time. That is because under the Japanese insurance system, patients are generally allowed to stay in the hospital until they can live in their homes without professional support.

There was no mortality in the current series of patients, however, we observed afferent loop syndrome in 2 patients and increased amylase level in the drainage. As we have not encountered afferent loop syndrome after usual pancreatoduodenectomy, we speculate the reasons for the current patients are as follows. In case 5 (Fig. 2), the original gastrojejunostomy was preserved. The oral side of the jejunum was brought up to the hepatic hilus and choledochojejunostomy and pancreatojejunostomy were performed. Because this limb was slightly short (approximately 10 cm from the gastrojejunostomy), there the afferent loop might have been mildly kinked. In case 7 (Fig. 3), choledochojejunostomy and pancreatojejunostomy were performed in the same way. In this case, the jejunal limb associated with the choledochojejunostomy and pancreatojejunostomy was long enough and was not bent, however, the jejunal passage distal to the jejunojejunostomy was very poor because the patient experienced postoperative ileus twice after previous gastrectomy at another hospital. We have not experienced afferent loop syndrome or similar symptoms in our recent 160 consecutive pancreatoduodenectomies. Therefore, resurgery, especially under post-gastrectomized conditions, likely puts the patient at risk of developing afferent loop syndrome.

It is conceivable that patients after gastrectomy could have a relatively higher risk of anastomotic leakage at the sites of choledochojejunostomy and

pancreatojejunostomy than those who have undergone primary pancreatoduodenectomy because, in such patients, there may be higher intraluminal pressure at the site of anastomosis. One patient experienced an elevated amylase level in drainage. The amylase level in the drainage was normalized after 4 weeks of fasting without relaparotomy and surgical intervention. We have previously reported that the rate of pancreatic leakage—defined as (1) discharge from the peripancreatic drain with an amylase concentration of more than 1000 IU/ml at postoperative day 7 or (2) radiographic demonstration by fistulography or cholangiography—[7]was 10.6% for our consecutive 160 pancreatoduodenectomies. In the current series, one pancreatic leakage out of 8 patients (12.5%) was not significantly different from the previous analysis for conventional pancreaticojejunostomy ($P = 0.86$).

In a previous necropsy-based case control study where 439 autopsied individuals who had died of pancreatic carcinoma were compared with those who were matched for age at death, gender, and year of death, there was no relationship between pancreatic carcinoma and previous gastric resection,[8] although elderly patients are being referred for surgery in increasing numbers. Therefore, we will have more chance in the future to perform pancreatoduodenectomy in gastrectomized patients. In conclusion, the lesson from the current study is that secondary pancreatoduodenectomy does not increase the mortality rate, although we should use the jejunal limb with less tissue damage at the anastomotic site of which circulation is well maintained for choledochojejunostomy and pancreaticojejunostomy. Furthermore, the jejunal limb should be lined carefully to avoid intestinal kinking and excess tension to the anastomosis.

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