Figure 2. Procedures for bypassing the portal vein. UV, umbilical vein; PV, portal vein; SV, splenic vein; SMV, superior mesenteric vein; IVC, inferior vena cava, IMV, inferior mesenteric vein; FV, femoral vein; GSV, greater saphenous vein.

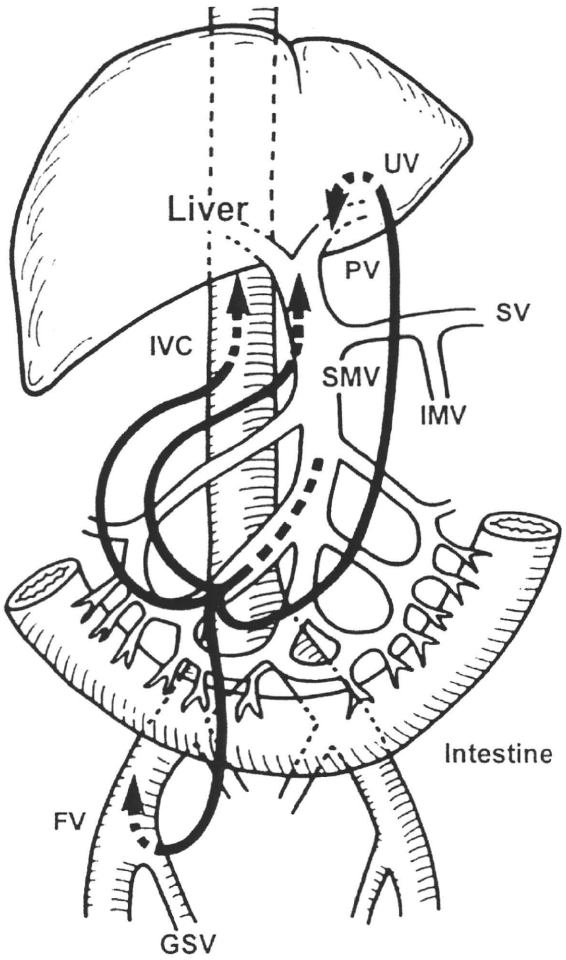


Figure 3. Photograph of catheter-bypass between the mesenteric and femoral veins. One end of the catheter is inserted in one of the branches of the superior mesenteric vein, and the other end in the femoral vein via the right greater saphenous vein. Portal venous blood flows into the femoral vein owing to the pressure differences between the portal and femoral veins.

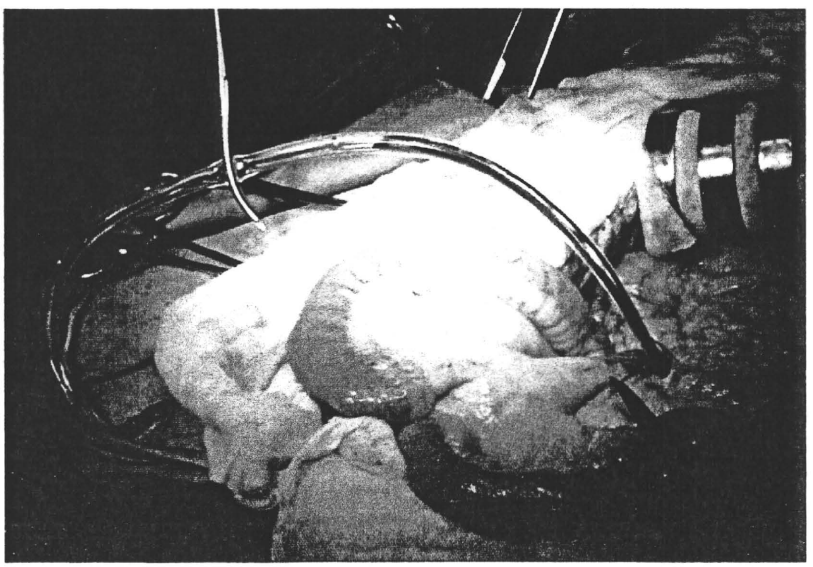
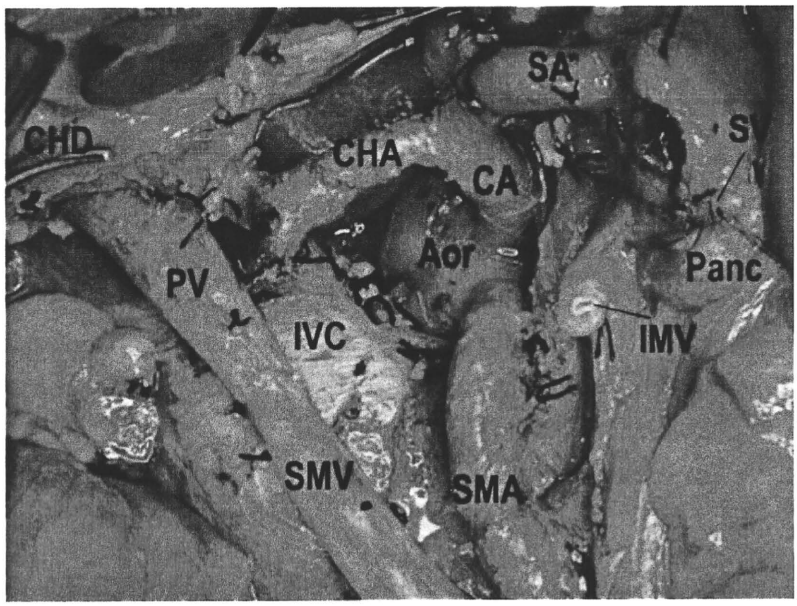


Figure 4. Isolated PD combined with portal and superior mesenteric veins resection, para-aortic lymph node dissection, and reconstruction of the portal vein by end-to-end anastomosis is done under catheter-bypass of the portal vein. PV, portal vein; SMV, superior mesenteric vein; CHA, common hepatic artery; SA, splenic artery; SV, splenic vein; CA, celiac artery; Aor, aorta; IMV, inferior mesenteric vein; Panc, pancreas; CHD, common hepatic duct; IVC, inferior vena cava; SMA, superior mesenteric artery.



3. Morbidity and Mortality

The morbidity rate of PD with portal vein resection has remained relatively high, whereas mortality rates of PD with portal vein resection have decreased. Siriwardana *et al.* have reviewed the outcome of portal vein resection during pancreatectomy for cancer [16]. They studied 52 non-duplicated papers that have provided relevant data from 1646 patients [16]. Data were available on operating time in 20 studies with a total of 616 patients. Histological evidence of portal vein invasion was detected in 668 (63.4%) of 1054 portal vein resection specimens. The rates of invasion ranged from 3% to 86% in 30 studies. Resection margins were positive in 346 (39.8%) of 870 patients with portal vein resection in 23 studies, with a range of 0–85%. Postoperative morbidity ranged from 9% to 78%, with a median per cohort of 42%. There were 73 (5.9%) reported deaths among 1235 patients in 39 studies that reported mortality after portal vein resection. The reported mortality rates in these studies ranged from 0 to 26%. The mortality rate of portal vein resection was >20% at the beginning of the era of portal vein resection 30 years ago; however, the rate has decreased to <5% in recent years.

4. Survival

Siriwardana *et al.* have studied survival after portal vein resection during pancreatectomy for pancreatic cancer [16]. The median survival was 13 months for 917 patients who underwent portal vein resection in 31 studies. The reported median survival ranged from one to 109 months [16]. The one-, three- and five-year survival rate for 1,351 patients who underwent portal vein resection in 40 studies was 50%, 16% and 7%, respectively, as shown in Figure 5 [16]. Comparative survival

curves from 23 studies of pancreatic resection with and without portal vein resection are shown in Figure 6 [16]. From 1981 to 2005, of 464 patients with pancreatic carcinoma, 305 (65.7%) underwent tumor resection in our department and vascular resection was performed in 212 (69.5%) of these. Operative mortality was 3.6% (11/305) in resected patients, 1.1% (1/93) in patients without vascular resection, 2.5% (5/197) in patients with portal vein resection without arterial resection, and 35.7% (5/14) in patients with portal plus arterial resection [17,18]. Figure 7 shows the cumulative survival rates, including operative and hospital deaths among patients with and without portal vein preservation, those with combined portal and arterial resection, and those with unresectable carcinoma of the pancreatic head. There was no significant difference in survival between unresectable patients and those who underwent combined portal and arterial resection. These data mean that carcinoma invasion to the superior mesenteric, celiac and common hepatic arteries is a contraindication for resection. Angiographic findings on portography were classified into four types: A, normal; B, unilateral narrowing; C, bilateral narrowing; and D, marked stenosis or obstruction with collateral veins [17]. Figure 8 shows that the prognosis after resection correlates with the angiographic findings in patients with pancreatic head carcinoma [17–19]. Cumulative survival rates based on histopathological portal invasion or invasion of the dissected peripancreatic tissue margin in resected pancreatic head cancer are shown in Figure 9. Histopathological carcinoma invasion of the portal vein wall was detected in 64.5% (12/186) in patients with portal vein resection for pancreatic head cancer. Survival for more than one year after resection was observed in the group with tumor-free margins, even when the portal vein wall had been invaded. In contrast, cumulative survival rates in patients with cancer-positive margins were quite low, and showed no statistically significant difference from the rate in patients with unresectable tumors.

Figure 5. Survival after pancreatic cancer with portal vein resection. The blocks represent the total numbers of known survivors at each time interval (from [16]).

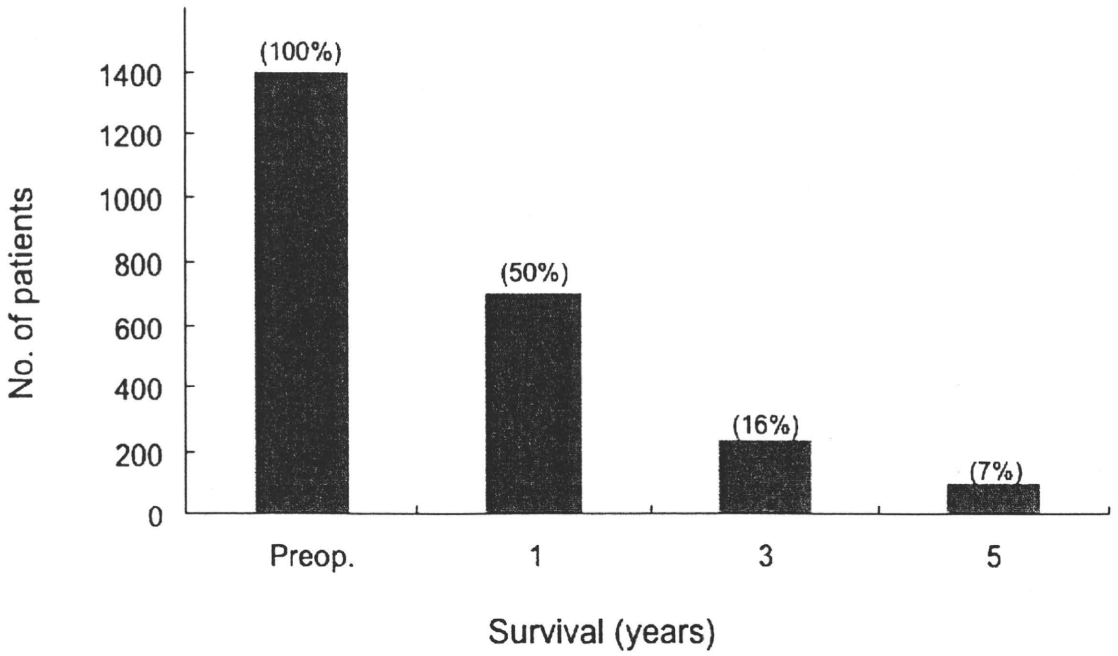


Figure 6. Comparison of survival in patients with or without portal vein resection (PVR). The blocks represent the total numbers of known survivors at each time interval. Comparisons were drawn by pooling data from 23 studies that had outcome data for pancreatectomy with portal vein resection. Note that this is not a parallel comparison of pancreatectomy with PVR in patients with tumor involvement *versus* pancreatectomy without PVR with tumor involvement, and patients without PVR are likely to have had earlier stage disease (from [16]).

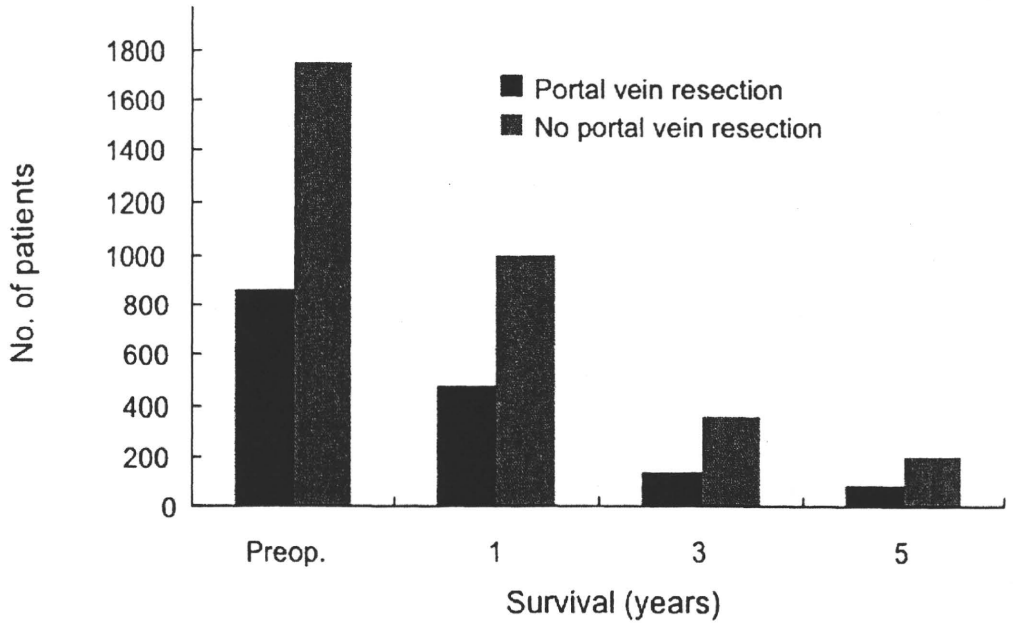


Figure 7. Comparison of cumulative survival rates in patients with no portal vein resection (PV resection(-)), portal vein resection (PV resection(+)), combined resection of portal vein and artery (PVAR; PV resection(+), A resection(+)), and unresectable pancreatic head carcinoma (from [19]).

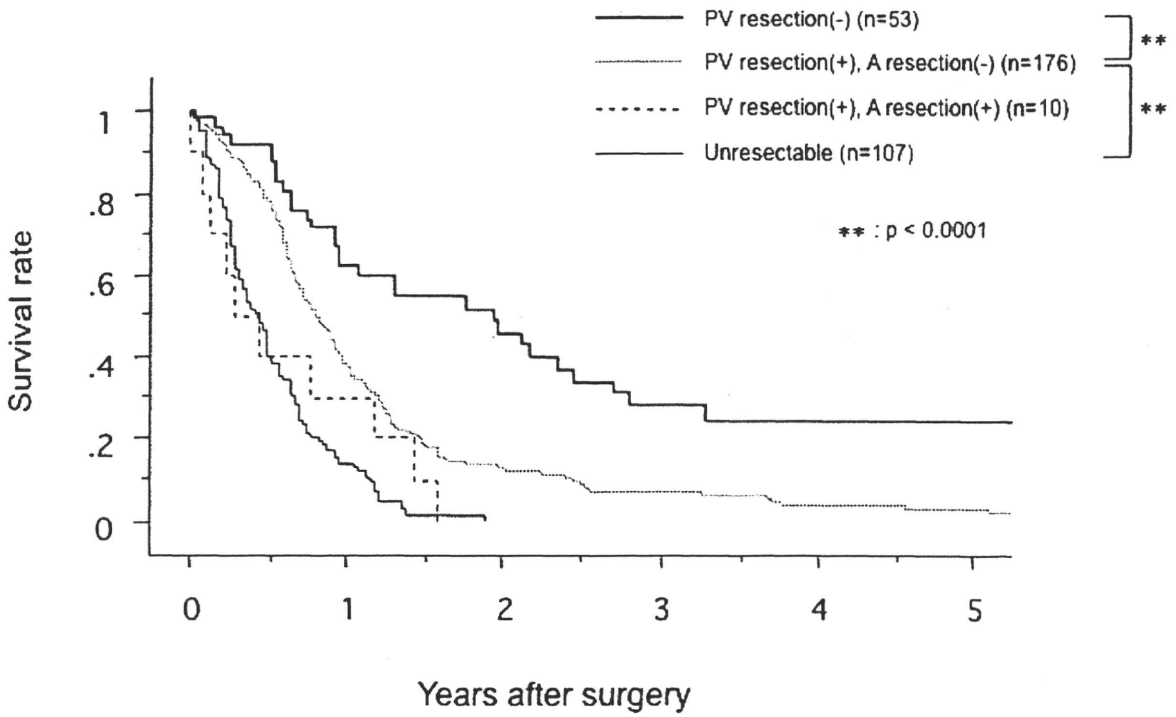


Figure 8. Comparison of cumulative survival rates according to the angiographic type of portography in patients with carcinoma of the pancreatic head. Type A, normal; type B, unilateral narrowing; type C, bilateral narrowing; type D, marked stenosis or obstruction with collateral veins (from [19]).

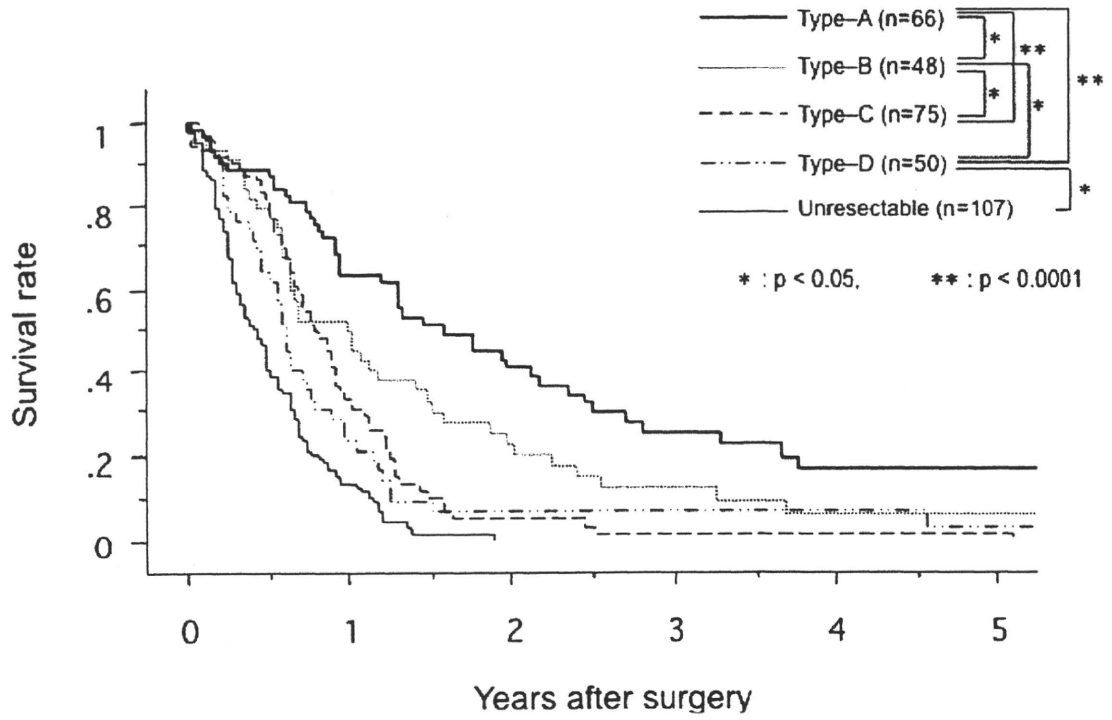
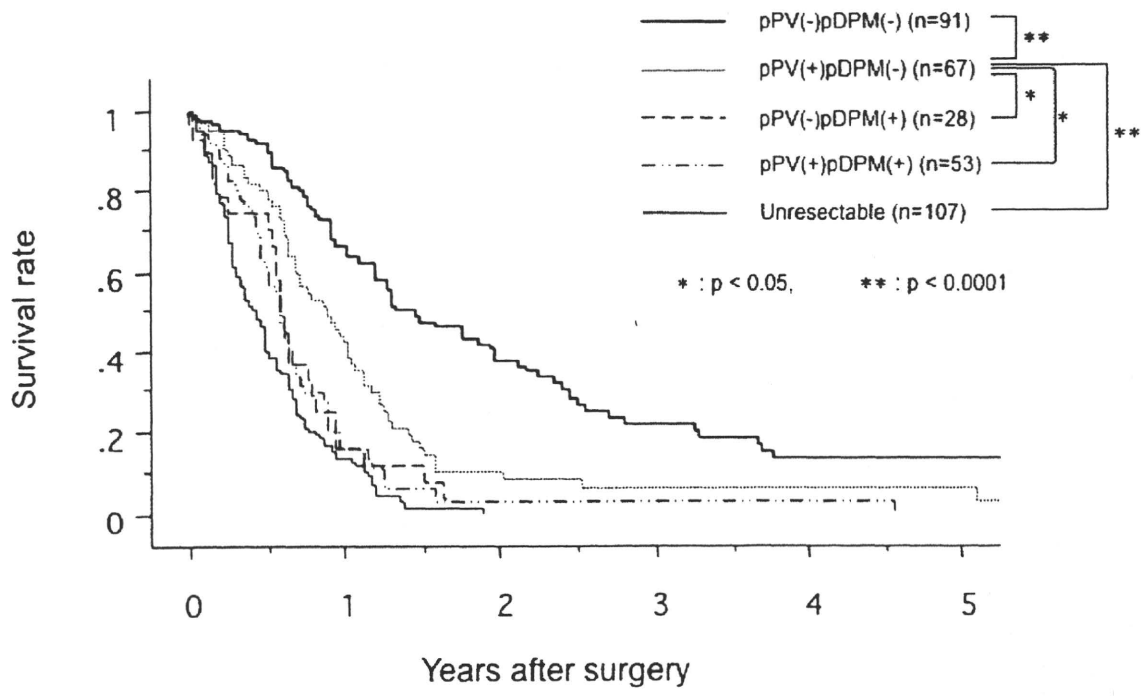


Figure 9. Comparison of cumulative survival rates in patients with and without histological invasion of a venous wall in the portal system (pPV) and invasion of the dissected peripancreatic tissue margin (pDPM) in patients with carcinoma of the pancreatic head (from [19]).



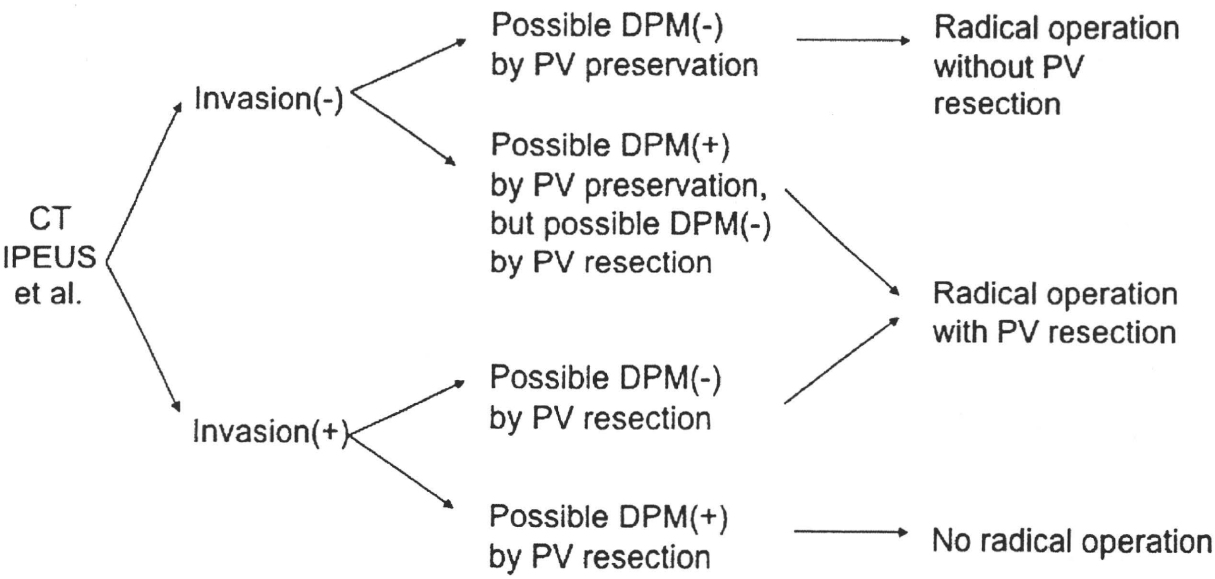
5. Indications for Portal Vein Resection

Indications for portal vein resection in pancreatic cancer and criteria for resectability of pancreatic cancer are shown in Table 1. Preoperative staging, including portal vein invasion, for pancreatic cancer is usually performed with dynamic-phase spiral computed tomography, and intraportal endovascular ultrasonography also provides important information during surgery [20,21]. The algorithm for the indications for portal vein resection for pancreatic cancer is shown in Figure 10. Portal vein resection is indicated when carcinoma-free surgical margins are obtained by portal vein resection. There is no indication for portal vein resection in patients in whom surgical margins would become cancer-positive if such an operation were done. The safe operative procedure without intraoperative or postoperative complications is essential, and postoperative quality of life and social activity must be guaranteed.

Table 1. Criteria for resectability (from [19]).

Resectable
No distant metastases (liver, peritoneal, *etc.*)
No superior mesenteric, celiac or hepatic artery encasement
Normal portography
Locally advanced resectable (Borderline resectable)
Abnormal portography, but possibility of reconstruction
Tumor abutment on celiac or superior mesenteric artery
Invasion of stomach, colon or mesocolon
Unresectable
Distant metastases (liver, peritoneal, *etc.*)
Superior mesenteric, celiac, or hepatic artery encasement
Lymph–node metastases outside the dissection field
Portal or superior mesenteric venous invasion with obstruction indicating impossibility of reconstruction
Severe concomitant disease

Figure 10. Indications for portal vein resection for pancreatic carcinoma.



6. Effect of Clinical Volume

For PD, several studies have reported the effect of institutional volume on patient outcomes. In 1993, Edge *et al.* [22] assessed 223 PD procedures from 26 university hospitals in the United States. The operative mortality was 6% (13/223) and the rate of severe complications was 21%, but they found that the caseload did not correlate with mortality. However, surgeons who performed fewer than four resections per year had more complications than those who performed more than four. In 1995, Lieberman *et al.* [23] assessed 1972 pancreatectomies including total pancreatectomies in 184 institutions in New York State. High-volume centers with more than 40 cases per year had significantly less mortality than low-volume centers (4% *vs.* 12.3%). Several other studies have also reported decreased mortality, length of hospital stay, and overall cost at high-volume centers compared with low-volume centers [24–26]. The definition of high and low volume varied among all these studies. Birkmeyer *et al.* [27] have reported a marked difference in mortality rates of PD in very low-volume (0 or 1 per year) and low-volume (1 or 2 per year) hospitals compared with higher-volume hospitals (>5 per year). In-hospital mortality rates at very low- and low-volume hospitals were significantly higher than those at high-volume hospitals (16% and 12%, respectively, *vs.* 4%; $p < 0.001$). These data strongly suggest that pancreatic resections should be done at institutions that perform a large number of them annually. In pancreatectomy combined with portal vein resection, more skillful technique, abundant experience and special postoperative care are necessary compared with PD without portal vein resection. Therefore, these types of operations should be done at large-volume centers.

Over the past 30 years, the operative mortality rate of pancreatectomy combined with portal vein resection has greatly decreased, and portal vein resection in pancreatic surgery has become a well-tolerated operative procedure in large-volume centers. The resectability rate of pancreatic cancer has increased by aggressive surgery combined with portal vein resection; however, the five-year survival rate is still low. Portal vein resection has been done in locally advanced cases of pancreatic cancer; therefore, a high incidence of cancer-positive surgical margins has been observed. Some patients with portal invasion who survive for more than years after surgery have been observed, and they are restricted within the state of cancer-free surgical margins. These findings show that portal vein resection is indicated when carcinoma-free surgical margins are possible. Therefore, preoperative and intraoperative diagnosis of cancer development is very important to decide the indications for resection of pancreatic cancer. These types of operation must be performed at large-volume centers.

7. Conclusions

Portal vein resection will be performed more often, safely and aggressively over the next five years if a cancer-free margin is obtained by resection. In addition to radical surgery, adjuvant therapy combined with chemotherapy, chemoradiotherapy and molecular targeting therapy might serve to improve the prognosis of pancreatic cancer.

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Pancreatic head resection with segmental duodenectomy for pancreatic neoplasms

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Abstract

Background/purpose We have experienced 67 cases of pancreatic head resection with segmental duodenectomy (PHRSD) for benign or low-grade malignant tumor of the pancreatic head region. Here we introduce our operative technique for these 67 cases.

Methods Pancreatic head resection is performed with segmental duodenectomy including minor and major papilla. By conserving the right gastric artery and the gastroduodenal artery, 5–7 cm of the first portion of the duodenum is preserved with good arterial circulation. In addition, by conserving the anterior inferior pancreatoduodenal artery, the third portion and anal side or the second portion of the duodenum are preserved with good arterial circulation. Cholecystectomy is performed. The procedure is completed by resection of the pancreatic head with 3–4 cm of segmental duodenectomy including minor and major papilla. Reconstruction of the alimentary tract is performed with pancreatogastrostomy, end-to-end duodenoduodenostomy and end-to-side choledochoduodenostomy.

Results In 67 cases with diseases of the pancreatic head region, chiefly intraductal papillary mucinous neoplasms, this procedure was successfully performed without operative or hospital death. Postoperative quality of life was quite satisfactory.

Conclusion Total resection of the pancreatic head can be performed safely and effectively by this procedure.

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Keywords Pancreatic head resection with segmental duodenectomy · Organ-preserving pancreatectomy · Pancreatogastrostomy · Intraductal papillary mucinous neoplasms of pancreatic head

Introduction

Organ-preserving pancreatic resections are reasonable surgical options for benign or low-grade malignant tumors of the pancreas. Pylorus-preserving pancreatoduodenectomy (PpPD) [1] has now been recognized as the ideal surgical method for treating benign, low-grade malignancy and malignant tumors of the pancreatic head region. Duodenum-preserving pancreatic head resection (DpPHR) [2] is also one of the options for organ-preserving pancreatic head resection. In the DpPHR, there are two types of operation: combined resection of the common bile duct and common bile duct preservation [2–4]. In DpPHR the arterial blood circulation of duodenum or common bile duct is a great problem. Ischemia of the duodenum, or common bile duct, causes necrosis of the duodenum or common bile duct and leads to perforation [3, 4]. The other major problem with DpPHR and partial resection of the pancreatic head is failure to complete extirpation of intraductal papillary mucinous neoplasms (IPMN), because IPMN tends to spread into the main or branch pancreatic ducts. To prevent these complications, we have been performing complete pancreatic head resection with segmental duodenectomy (PHRSD) [5–7], including the minor and major papilla, for mainly benign or low-grade malignant tumors of the pancreatic head region in 67 cases. Reconstruction of the alimentary tract after PHRSD has been performed with pancreatogastrostomy, end-to-end duodenoduodenostomy

and end-to-side choledochoduodenostomy. We report here the operative procedure of PHRSD and postoperative results.

Patients and methods

From 1988 to 2008, 67 patients who underwent PHRSD had 47 IPMNs, 7 non-functional endocrine tumors of the pancreatic head region, 6 papilla of Vater cancers, 2 serous cytadenomas, 1 pancreas head cancer, 1 common bile duct cancer, 1 insulinoma, 1 annular pancreas and 1 anomalous engagement of the pancreatobiliary ductal system. Laparotomy is done by upper midline skin incision. The gastrocolic and duodenocolic ligaments are divided with preservation of the right gastroepiploic artery (RGEA) and vein to explore the front of the pancreas. The right gastroepiploic vein is ligated and divided at the root. The anterior–superior pancreatoduodenal artery (ASPDA), the posterior–superior pancreatoduodenal artery (PSPDA) and a few other branches running from the gastroduodenal artery (GDA) towards the pancreas are ligated and divided. By conserving the RGEA and GDA, 5–7 cm of the first portion of the duodenum is preserved with good arterial circulation. The pancreas is divided on the line of the portal vein. The extrapancreatic nerve plexus between the uncinate process and the superior mesenteric artery is preserved, so the inferior pancreatoduodenal artery (IPDA) is preserved. The anterior–inferior pancreatoduodenal artery (AIPDA) is preserved, and the posterior–inferior pancreatoduodenal artery (PIPDA) is ligated and divided. The AIPDA is ligated and divided near the major papilla (Figs. 1, 2). Cholecystectomy is performed. The common bile duct is divided at the upper border of the pancreas. A 2–3 cm ischemic area of the duodenum, including the major and minor papilla, is observed (Fig. 3). The oral side of the duodenum is divided 5–7 cm from the pyloric ring. The anal side of the duodenum is divided at the point of AIPDA ligation. Thus, PHRSD with preservation of GDA is completed. The length of the resected duodenum ranges from 3 to 5 cm (Fig. 2). Reconstruction of the alimentary tract is performed with pancreatogastrostomy (temporary pancreatic stent in the main pancreatic duct of the remnant pancreas and drained externally), end-to-end duodenoduodenostomy, and end-to-side choledochoduodenostomy (temporary transhepatic biliary stenting) (Fig. 4).

Results

No operative or hospital death was observed in the 67 cases. Minor leakage from the anastomosis portion of alimentary tract such as pancreatogastrostomy in 19.4%, choledochoduonenostomy in 4.5% and duodenoduodenostomy in 1.5% were observed, but healed with conservative treatment. Intraabdominal bleeding was observed in two cases, but successfully treated by transarterial embolization. All patients discharged from the hospital showed extremely good postoperative quality of life (QOL).

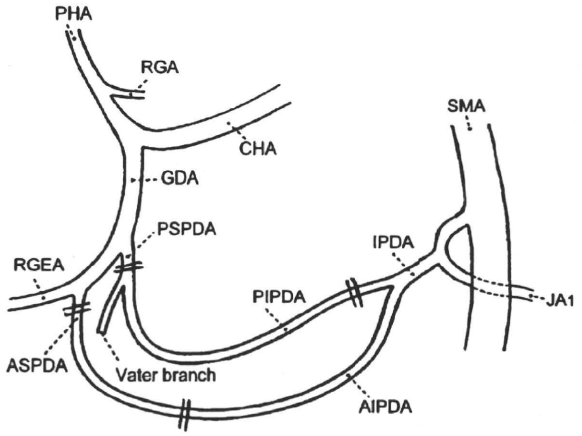

Fig. 1 Divided lines of the pancreatoduodenal arteries in pancreatic head resection with segmental duodenectomy. *PHA* proper hepatic artery, *RGA* right gastric artery, *CHA* common hepatic artery, *GDA* gastroduodenal artery, *RGEA* right gastroepiploic artery, *PSPDA* posterior–superior pancreatoduodenal artery, *ASPDA* anterior–superior pancreatoduodenal artery, *IPDA* inferior pancreatoduodenal artery, *PIPDA* posterior–inferior pancreatoduodenal artery, *AIPDA* anterior–inferior pancreatoduodenal artery, *JA1* first jejunal artery, *SMA* superior mesenteric artery

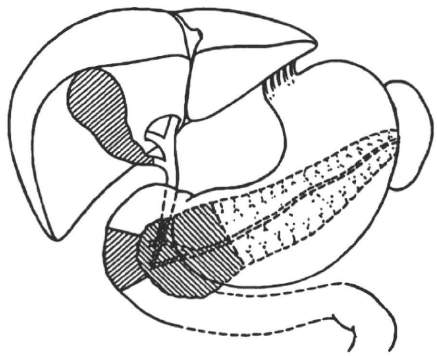

Fig. 2 Resected portion in pancreatic head resection with segmental duodenectomy

Discussion

Organ-preserving pancreatic resection for benign tumor of the pancreatic head or chronic pancreatitis such as PpPD [1] or DpPHR [2] has been recognized as the ideal surgical method. There are two types of DpPHR operation: combined resection of the common bile duct [3] and

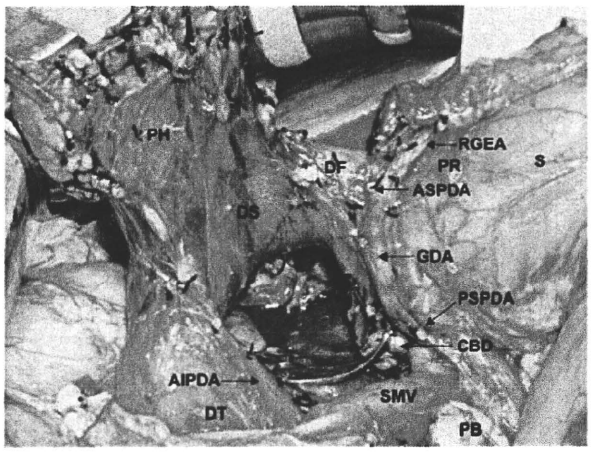

Fig. 3 Segmental duodenectomy completes the total pancreatic head resection. *PH* pancreatic head, *PB* pancreatic body, *DF* duodenal first portion, *DS* duodenal second portion, *DT* duodenal third portions, *S* stomach, *PR* pyloric ring, *CBD* common bile duct, *GDA* gastroduodenal artery, *PSPDA* posterior–superior pancreatoduodenal artery, *ASPDA* anterior–superior pancreatoduodenal artery, *RGEA* right gastroepiploic artery, *SMV* superior mesenteric vein

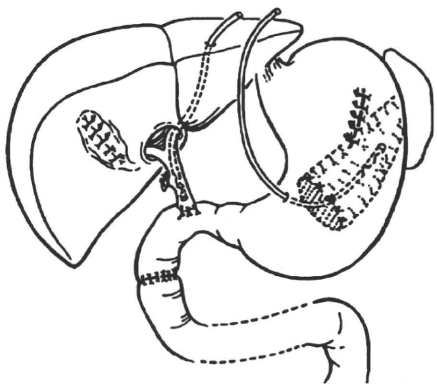

Fig. 4 Schematic of alimentary tract reconstruction after pancreatic head resection with segmental duodenectomy

preservation of the common bile duct [2, 4]. To preserve the duodenum and common bile duct, the preservation of the pancreatic head arcade of the arteries is very important. The anatomy of the arcade of the arteries of the pancreatic head has been studied [8, 9]. The branch of the PSPDA that runs along the right side of the common bile duct and toward the major papilla (Vater branch) is important to preserve the common bile duct and major papilla [8, 9], but this branch is difficult to visualize during operation. The preservation of the pancreatic parenchyma between the common bile duct and duodenum (groove area) is necessary to preserve this branch in DpPHR with the preservation of the common bile duct and sphincter function of major papilla [9]. The preservation of the anterior arcade of the arteries in the pancreatic head is technically difficult near the minor and major papilla. If these arteries cannot be preserved, postoperative ischemic necrosis or perforation of the common bile duct or duodenum may result [10, 11]. Successful complete resection of the pancreatic head with preservation of the common bile duct and duodenum has been reported [10, 11]. However, complete resection of the pancreatic head including the pancreatic parenchyma between the common bile duct and duodenum will cause ischemia of the common bile duct and major papilla. However, complete preservation of the arcade of the arteries of the pancreatic head with common bile duct preservation is technically difficult and impossible. DpPHR with incomplete resection of the pancreatic head cannot ensure complete extirpatlon of IPMN, because IPMN tends to spread into the main or branch ducts. High morbidity and mortality rates were observed in DpPHR [12]. We have already reported the advantage of PHRSD compared with PpPD in delayed gastric emptying, endocrine function, body weight decrease and postoperative enzyme substitution [7]. We recommend PHRSD for the above reasons.

Conclusions

PHRSD is a safe and reasonable technique appropriate for selected patients with benign or low-grade malignant tumor of the pancreatic head region, especially with benign or noninvasive IPMN.

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Adenosquamous Carcinoma Arising in an Intraductal Papillary Mucinous Neoplasm of the Pancreas

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Adenosquamous Carcinoma Arising in an Intraductal Papillary Mucinous Neoplasm of the Pancreas

To the Editor:

Among exocrine pancreatic tumors, adenosquamous carcinoma (ASC) is an unusual variant, with an incidence rate of 1% to 4% of all exocrine pancreatic tumors.[1,2] According to the current literature, the prognosis of ASC has been described as more deteriorated than that of common ductal cell adenocarcinoma of the pancreas.[2,3] Furthermore, intraductal papillary mucinous neoplasm (IPMN) has recently been recognized as epithelial exocrine neoplasia. In contrary to that of ASC, the prognosis of invasive adenocarcinoma derived from IPMN is more favorable than that for common ductal cell adenocarcinoma of the pancreas.[4]

To our knowledge, no case has been reported where ASC has arisen in an IPMN. Although several reports have hypothesized its origin,[5] a unified theory has not yet been determined. As mentioned previously, the prognosis for ASC is deteriorated; however, the patient in the current case study has experienced 28 months of disease-free survival. We propose that the origin of the tumor in the present case is different from that of stereotypical ASC, displaying coexisting IPMN. On the basis of the Classification of Pancreatic Carcinoma by the Japan Pancreas Society,[6] the current patient's condition was diagnosed as stage 1, which is rare even in common ductal cell adenocarcinoma. Herein, we report a case of a patient exhibiting ASC arising in an IPMN.

A 76-year-old Japanese man was admitted with epigastralgia and loss of appetite. Physical examination revealed no adverse findings, and laboratory test results were all found to be normal, with the exception of the serum amylase level (132 IU; normal range, 37–125 IU). Serum concentrations of carcinoembryonic antigen and carbohydrate antigen 19-9 were found to be within the reference range. Ultrasound and contrast-enhanced ultrasound examinations were performed and revealed a low-echoic lesion 15 mm in diameter at the head of the pancreas (Fig. 1A). The MPD was also distended by approximately 6 mm, and abdominal computed tomography discovered an irregular mass showing greater enhancement relative to nontumoral pancreatic parenchyma in the portal vein–dominant phase (90 seconds; Fig. 1B). Endoscopic retrograde pancreatography showed stenosis of the MPD at the head of the pancreas. The patient had a diagnosis of pancreatic cancer in April 2007 and underwent pancreaticoduodenectomy. The tumor filled the MPD, and small cystic lesions were identified around the cut surface of the tumor. Further examination found most of the tumor to be located in the MPD, and invasive lesions of pancreatic parenchyma were limited. The carcinomal component was found to comprise only squamous cells, with no adenocarcinomal component found (Fig. 1C). Although IPMN was detected from the MPD to the pancreatic duct branch (Fig. 1D), the stump of the MPD was found to be normal. The stage of tumor pathogenesis was determined to be stage 1, using the Classification of Pancreatic Carcinoma (fifth edition) published by the Japan Pancreas Society.[6] The patient's postoperative course was uneventful, and he has remained disease-free for 28 months.

DISCUSSION

Adenosquamous carcinoma of the pancreas is a rare and aggressive subtype of pancreatic adenocarcinoma. The exact proportion of squamous cell differentiation required to diagnose ASC is variable; however, it is required that at least 30% of the tumor tissues comprise squamous cells to diagnose ASC.[6] Madura et al[1] composed a review of 134 ASC cases, in which most patients were at least 60 years old and predominantly male. In these patients, the tumor was typically located in the head of the pancreas,[1] consistent with the current case study.

Although reports of ASC of the pancreas have recently increased, accurate preoperative diagnosis remains difficult; however, with the development of new imaging techniques, some useful descriptions for differentiating ASC from other carcinomas have been reported. For example, Nabae et al[7] described the presence of centralized necrosis in a large infiltrative pancreatic tumor that was suggestive of ASC of the pancreas. However, the tumor size in the present study was too small to detect necrosis; therefore, an exact preoperative diagnosis was not possible.

The prognosis for patients with ASC of the pancreas is less favorable than that for patients with common ductal cell carcinoma of the pancreas. The mean survival time after diagnosis of ASC is reportedly 5.7 months, with only 5 of 72 patients surviving longer than 1 year.[1] The reasons underlying the significantly poorer prognosis and severely diminished life span in patients with ASC are proposed to be that the interphase of squamous cell carcinoma is approximately eighty days, which is half

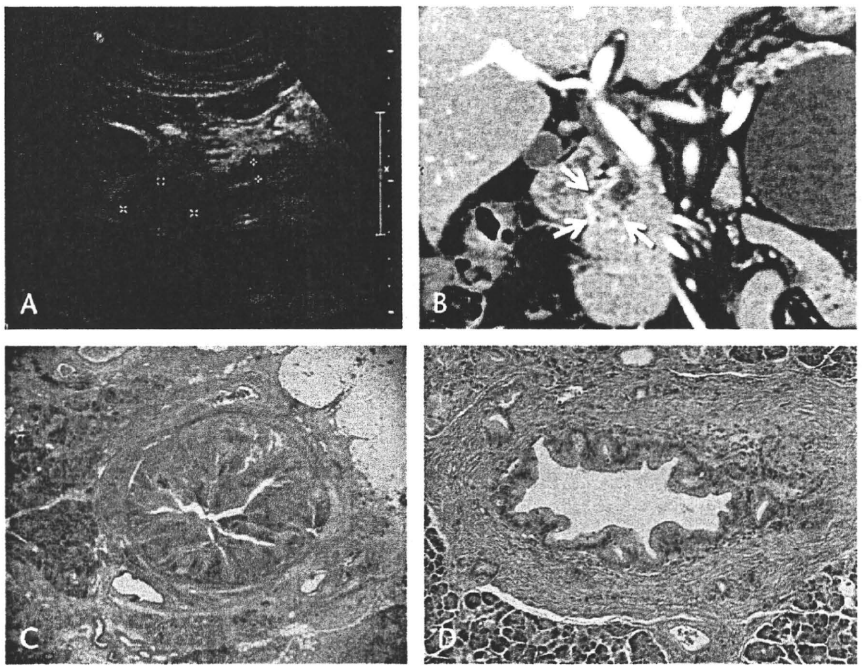

FIGURE 1. A, Abdominal ultrasound examination displays a low-echoic lesion, 15 mm in diameter, at the head of the pancreas and dilation by approximately 6 mm of the main pancreatic duct (MPD). B, Coronal imaging of abdominal computed tomography revealed the irregular mass (arrows), enhanced relative to nontumoral pancreatic parenchyma in the portal vein–dominant phase. C, The tumor was identified in the MPD and consisted of unicellular squamous cells (HE ×40). D, IPMN was identified from the MPD to the branch pancreatic duct (HE ×200).

of that of adenocarcinoma.[8] Furthermore, growth of ASC is very rapid and analogous to that of anaplastic carcinoma, with a previous study reporting squamous cell carcinomas to grow at twice the speed of adenocarcinomas.[9] The patient in the present case study has currently lived disease-free for 28 months, suggesting that the development of the tumor may differ from that of other cases reported to date.

The underlying origin and mechanisms of ASC development remain unclear; several theories have been reported, but none have been well proven. The first theory suggests that ASC develops owing to malignant differentiation of pluripotential duct cells into 2 histologically distinct cell types.[4] The second theory states that ASC occurs as a result of malignant changes of an adenocarcinoma.[5] Third, ASC is hypothesized to be derived from ectopic squamous epithelium. The final theory is that ASC is a derivative from squamous metaplasia of the pancreatic ductal epithelium. Currently, the first and second theories are, in general, recognized as describing the most likely origin of ASC.

However, some reported cases of ASC have not applied the aforementioned theories owing to the presence of pancreatic tumors with a unicellular squamous appearance but without the glandular component, similarly described in the present case.[10] Because of this morphological variance, we suggest that the final theory mentioned previously best describes the most likely origin of ASC in the current study. Squamous metaplasia of the pancreatic ductal epithelium is known to occur most often in the setting of chronic pancreatitis or pancreatic obstruction.[1] Although the patient in the present case has no medical history of pancreatitis, the existence of latent pancreatitis was suspected owing to the patient's main physical complaints. In summary, we believe the squamous metaplasia discovered in the present case occurred owing to the obstruction of the MPD, filled with mucus secreted from the IPMN.

The current study reports a case of stage 1 pancreatic carcinoma, which, though rare, provides valuable insight into elucidating the development of pancreatic carcinoma from an early stage.

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Utility of 2-[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography in differential diagnosis of benign and malignant intraductal papillary-mucinous neoplasm of the pancreas

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Abstract. Intraductal papillary-mucinous neoplasm (IPMN) of the pancreas presents in various histopathological stages from benign to malignant lesions. The differentiation between benign and malignant IPMN is important in order to determine the treatment of the patients. However, preoperative differentiation remains difficult. The aim of this study was to assess the utility of 2-[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in preoperative differentiation of benign and malignant IPMN of the pancreas. In the present study we prospectively investigated 29 patients who underwent CT, FDG-PET, and surgery for IPMNs, followed by histopathological examination. The maximum standardized uptake value (SUVmax) was determined on FDG-PET, and differentiation of benign from malignant IPMN was tested using various SUVmax cut-off levels and various parameters derived from the CT. SUVmax was found to be significantly higher in malignant IPMNs (4.7±3.0) than that in benign IPMNs (1.8±0.3, P=0.0011). SUVmax values correlated with the histopathological types of IPMN (adenoma/borderline lesion/carcinoma *in situ*/invasive carcinoma) (Spearman rank correlation 0.865, P<0.0001). The specificity, sensitivity and accuracy values were best for SUVmax of 2.5 (100, 93, and 96%, respectively). The combination of mural nodule, detected on CT, and SUVmax of 2.5 offered the best diagnosis of malignant IPMN. These results suggest that FDG-PET is useful for differentiation of malignant IPMN of the pancreas, and that it should be performed in combination with other conventional imaging modalities.

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Key words: intraductal papillary-mucinous neoplasm, pancreas, positron emission tomography, standardized uptake value

Introduction

Intraductal papillary-mucinous neoplasm (IPMN) of the pancreas, which was first reported by Ohashi *et al* in 1982, originates from epithelial cells of the main pancreatic duct or its side branches and produces large amounts of mucin (1-4). IPMN presents at various histopathological stages from benign to malignant lesions, as classified by the WHO, including adenoma, borderline, carcinoma *in situ* (CIS), and invasive carcinoma (5,6). While patients with benign IPMNs can be monitored without the need for surgery, malignant IPMNs should be resected surgically according to the grade of malignancy. Moreover, the postoperative prognosis of patients with invasive IPMNs is significantly poor and similar to that of patients with pancreatic ductal adenocarcinoma (5,7,8). Therefore, preoperative differentiation between benign IPMN and malignant IPMN is important in order to determine the management of patients. To date, various features of malignant IPMN tumors using imaging techniques have been proposed, such as large lesion size, dilatation of the main pancreatic duct (MPD), and presence of mural nodules (5,9-16). However, some of these features are controversial, and their accuracy depends on the imaging modalities used. Therefore, differentiation between benign and malignant IPMN is still difficult.

2-[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is a sensitive and specific imaging protocol for the diagnosis and staging of several types of malignancies (17-20). To date, there have been few reports of FDG-PET in patients with IPMNs (21-25). Sperti *et al* (25) reported 47 cases with IPMNs confirmed histologically or cytologically, and concluded that FDG-PET was more accurate than conventional imaging techniques such as computed tomography (CT) and magnetic resonance imaging in distinguishing benign from malignant IPMN. In their report, however, the sensitivity, specificity, and accuracy of

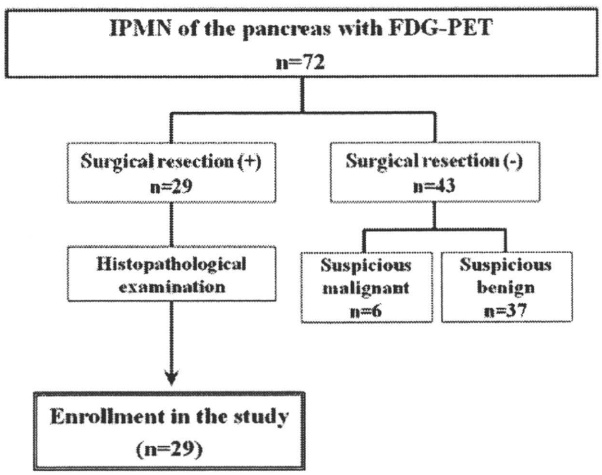

Figure 1. Distribution of the 72 patients with IPMN according to the histopathological examination. IPMN, intraductal papillary-mucinous neoplasm.

FDG-PET were evaluated only when the cut-off value of the maximum standardized uptake value (SUVmax) was set at 2.5. Moreover, although these figures were compared to those of whole CT findings, they were not compared to those of other radiological features reported to be associated with malignancy.

In the present study, by using the results of prospectively performed FDG-PET in patients with IPMN of the pancreas, we examined the correlation between the findings of FDG-PET and the histopathological type of IPMN. Furthermore, we assessed usefulness of FDG-PET in differentiation between benign and malignant IPMN using several cut-off levels of SUVmax, and the utility of FDG-PET was compared to certain CT parameters and their combinations, in the diagnosis of malignant IPMN.

Materials and methods

Patients. Between January 2006 and June 2008, FDG-PET was prospectively performed in 72 patients with IPMN at Osaka University Hospital. In 29 patients out of the 72 patients, the tumor was resected surgically and then examined histopathologically. The surgically-resected 29 patients with histopathological confirmation of the IPMN were enrolled in the present study. The remaining 43 patients were decided to be followed up without surgical resection. The distribution of IPMN patients are shown in Fig. 1.

In principle, surgical resection of IPMN was scheduled for treatment only when the clinical features suggested malignancy. The features of tumors judged to be likely malignant on CT examination were IPMN with mural nodule, main duct type and combined type IPMN with ≥7 mm dilated MPD, combined type and branch type IPMN with ≥3-cm cystic lesion, and histopathologically and/or cytologically-confirmed malignant IPMN. Among the 29 patients, 2 patients underwent surgery without fulfilling the above criterion; their clinical features were not suggestive of malignancy; one patient fervently desired resection of the IPMN and the other underwent IPMN resection at the same time as pancreatectomy for coexisting pancreatic ductal adeno-carcinoma. The type of selected surgical procedure performed was based on the location of IPMN. Pancreatico-duodenectomy was performed in 14 patients, distal pancreatectomy in 14, and central pancreatectomy in the remaining one patient.

In the 43 patients without surgical resection, 6 patients, who had clinical features suggested malignancy, did not undergo surgery for the following reasons; poor risk at surgery in three patients, refusal to surgery in two patients, and concomitant liver metastasis in one patient. The remaining 37 patients without features suggested malignancy were followed up.

For all the patients, gender, age, clinical symptoms, tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), tumor multiplicity, tumor location, IPMN type, diameter of cystic lesion, MPD dilatation, mural nodule, cytological diagnosis, histopathological diagnosis, and SUVmax of FDG-PET were prospectively investigated. Endoscopic retrograde cholangio-pancreatography (ERCP) was performed for pancreatic duct lavage cytology and/or pancreatic juice cytology in 49 patients.

FDG-PET. Whole-body FDG-PET imaging was performed as described previously (26-28). Briefly, each patient fasted for at least 4 h before intravenous administration of ~370 MBq FDG. Serum glucose levels were determined just before FDG injection. Among the 72 patients, 70 patients were normoglycemic (blood glucose <150 mg/dl), and 2 patients were hyperglycemic (blood glucose >220 mg/ml). Simultaneous emission and transmission PET scans were acquired 1 h after FDG injection. Imaging was performed with a dedicated PET scanner (Headtome/Set 2400W; Shimadzu Co., Kyoto, Japan). Fusion images combined with PET images and CT images were composed using our previously described method (28). Since April 2007, FDG-PET/CT has been introduced to clinical practice in our hospital (FDG-PET and CT performed separately; n=30, FDG-PET/CT; n=42).

For semi-quantitative analysis, regions of interest were selected semi-automatically at the most intense area of FDG accumulation in the primary tumor on the PET image, and the SUVmax was calculated using the following formula: SUVmax=PET count at most intense point x calibration factor (MBq/kg)/injection dose (MBq)/body weight (kg).

In the absence of a visible FDG uptake, on the basis of the fusion images, regions of interest were drawn exactly on the area corresponding to the primary tumor, and the SUVmax was calculated.

The afore-mentioned 2 patients who were hyperglycemic at the PET examination contained one patient in the group of the patients with surgical resection, and one in the group of the patients without surgical resection. Since the SUVmax could not be calculated in these patients for the hyperglycemic state, they were excluded from the examination related to the SUVmax in this study.

CT. CT was performed either with a LightSpeed Qxi scanner (GE Medical Systems, Wis), a LightSpeed VCT scanner (GE Medical Systems) or an Aquilion 64 scanner (Toshiba Medical Systems, Japan) scanner using a tube voltage of

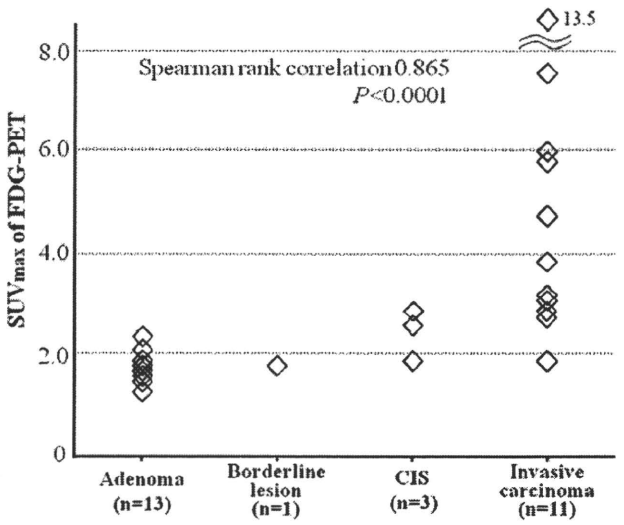

Figure 2. Correlation between histopathological type of IPMN and SUVmax of FDG-PET in 28 patients. Among the enrolled 29 patients, one patient with hyperglycemia at the FDG-PET examination was excluded. For abbreviations, see Fig. 1. SUVmax, maximum standardized uptake value; FDG-PET, 2-[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography

120 kV, a tube current of 300 mA, and a rotation period of 0.5 sec. Images of 5 mm slice thickness were used for evaluation. Contrast-enhanced multiphasic CT images were acquired at 10 sec after the peak aortic enhancement (arterial phase), followed by pancreatic phase and portal venous phase for upper abdomen. Nonionic contrast medium, 300 mg of iodine per milliliter, was administered intravenously at a rate of 4 ml/sec with a power injector. Images were interpreted especially focusing on the presence of mural nodule as well as the size of tumor and presence of dilatation of main pancreatic duct.

Histopathological diagnosis of IPMN. The diagnosis of IPMN of the pancreas in the enrolled 29 patients was confirmed on histopathological examination of the resected specimens by an experienced pathologist. The lesions were histopathologically classified into the following subtypes: adenoma, borderline lesion, CIS, and invasive carcinoma. Adenoma and borderline lesions were categorized as benign lesions, while CIS and invasive carcinoma were categorized as malignant lesions.

Statistical analysis. Receiver operating characteristic (ROC) curve analysis was performed using sensitivity and specificity at various cut-off values. The significance of differences among the groups was assessed by the χ^2, Fisher's exact test or the Mann-Whitney U test. Statistical analysis was performed using StatView (version 5.0, SAS Institute Inc, Cary, NC). A P-value <0.05 was considered statistically significant.

Ethical considerations. The study protocol was approved by the Human Ethics Review Committee of Osaka University Hospital and a signed consent form was obtained from each patient.

Results

Patient and tumor characteristics. Table I summarizes the clinical characteristics of the included 29 patients with histopathological confirmation. Among 27 patients who underwent ERCP, 9 were diagnosed as malignant IPMN based on pancreatic duct lavage cytology and/or pancreatic juice cytology. Five patients (17.2%) had multiple cystic lesions. Five patients presented with high serum levels of CEA (≥5.0 ng/ml) and 5 patients with high CA 19-9 (≥37 U/ml). The most common location of the lesion was in the head or uncinate of the pancreas (44.8%). Three patients had the main duct type (10.4%), 13 the combined type (44.8%), and 13 the branch type (44.8%). Based on the CT findings, the mean diameter of the cystic lesion was 39 mm (range, 14-75 mm) in patients with combined type and branch type, and the MPD diameter was 11.1 mm (range, 5.0-41.0 mm) in patients with main duct type and combined type. Mural nodules were identified in 13 patients (44.8%). Malignant IPMN was identified in 14 (48.3%) patients, including 11 with invasive carcinoma and 3 with CIS. The remaining 15 patients (51.7%) had benign IPMN: one borderline lesion, and 14 adenomas. The mean SUVmax of FDG-PET of the lesion for all patients was 3.3 (range, 1.3-13.5).

Correlation between histopathological type and SUVmax of FDG-PET. Fig. 2 displays the SUVmax for each histopathological type of IPMN. This analysis was performed in the 28 patients, while the remaining one patient with hyperglycemia at the FDG-PET examination was excluded from this analysis. The SUVmax correlated with the histopathological type (Spearman rank correlation 0.865, P<0.0001). In detail, there were significant differences of the SUVmax between invasive carcinoma and others (CIS, borderline lesion, and adenoma), and between malignant IPMNs and benign IPMNs. Moreover, the SUVmax in patients with CIS was significantly higher than that with benign IPMNs. The following examination focuses on the difference between malignant IPMNs and benign IPMNs.

Comparison of clinical features of patients with benign and malignant IPMN. Table I summarizes the clinical features of patients with benign IPMNs and malignant IPMNs. There was no significant difference in gender, age, the presence of symptoms, serum levels of CEA and CA19-9, multiplicity, location, IPMN type, diameter of the lesion, and MPD diameter between the two groups. On the other hand, the frequency of the presence of mural nodule in malignant IPMN (92.9%) was significantly higher than that in benign IPMN (20.0%, P=0.0001). Furthermore, the SUVmax in patients with malignant IPMNs (4.7±3.0) was significantly higher than that with benign IPMNs (1.8±0.3, P=0.0011).

Comparison of diagnosis of malignant IPMN by FDG-PET and CT. Table II lists the distribution of patients, sensitivity, specificity, and accuracy of FDG-PET and certain CT features of the tumors. Diagnosis of malignancy by FDG-PET was analyzed using various cut-off levels of SUVmax. Moreover, ROC curve was constructed by plotting sensitivity and specificity at various cut-off levels of SUVmax (Fig. 3). Such