Original Paper

Comparative Analysis of Prognostic Significance of Molecular Markers of Apoptosis with Clinical Stage and Tumor Differentiation in Patients with Colorectal Cancer: a Single Institute Experience

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ABSTRACT
Background/Aims: The most important parameter determining the outcome of colorectal cancer (CRC) is the presence of metastases, which occur in 45-50% of all cases. The balance between proliferation and apoptosis is a key factor for tumor growth, and thus – for metastasis. Evaluation of markers for proliferation and apoptosis could therefore be helpful in predicting tumor behavior in early stage of carcinogenesis.
Methodology: Seventy-two biopsies from cases of colorectal cancer (CRC) were immunostained for the proliferation/apoptosis-related proteins Bcl-2, Bax and p53. The resected specimens were also subjected for routine pathologic assessment as part of Tumor, Node and Metastases (TNM) staging.
Results: Comparing the marker protein expression with standard prognostic factors such as clinical stage and grade of differentiation revealed a lack of correlation between markers and standard prognostic factors in cases where clinical stage favors good prognosis (I and II stage). We found lack of correlation in 52% of diagnosed patients by tumor grade and 46% in patients by clinical stage.
Conclusions: Co-expression of Bax with p53 protein is associated with poor clinical outcome, especially in cases without concomitant expression of bcl-2. The blocked apoptosis and inability of the organism to "liquidate" the neoplastic transformation of the cell (loss/mutation of p53), which we establish in our study in the half the patients with high and moderately differentiated carcinoma and separately in 46% of the patients with favorable prognosis by clinical stage is a reason for fast progression, too. The presence of a low correlation between the staging and the results of the molecular profiling suggest that the staging system needs to improve to address more precisely the issues of therapeutic options and patient survival. Using a panel of markers rather than a single marker is a step in this direction.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of death by cancer in the developed countries, comprising nearly 25% of all malignancies (1,24). Currently, the most important factor determining the outcome of CRC is considered the presence of metastases. (2,3,4,5) The incidence of lymph node and liver metastasis by CRC is 45-50% of all cases. The (TNM) staging system of International Union Against Cancer (UICC) (6,7), which is the currently used staging system for CRC, has made a major contribution to the clinical management of patients with cancer over the past 50 years, but a growing pile of evidence suggests that it needs further improvement (6) as this system is based solely on disease-related parameters such as anatomical extent of carcinoma invasion and metastasis, and does not properly address issues such as variable outcomes in patients at the same stage. (8)

Factors other than those specifically incorporated in the TNM staging system can have an impact on the patient's risk of recurrence and survival. Microscopic venous or lymphatic invasion within the specimen worsens the prognosis for any stage (9,21,22). Histologic grade, histologic type, serum carcinoembryonic antigen, and cytokine levels are all independent prognostic factors. (10,11) Additional tissue-based prognostic indicators have been sought on a molecular level, such as analysis of DNA for genotypic alterations or expression of genes involved in proliferation, apoptosis and angiogenesis. (12,13,25)

The balance between proliferation and apoptosis is a key factor for tumor growth, and thus – for metastasis. Therefore, evaluation of markers for proliferation and apoptosis could be helpful in predicting tumor behavior in early stage of carcinogenesis. Among the proteins closely associated with

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ORIGINAL ARTICLE

Factors influencing infectious complications after pancreatoduodenectomy

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Abstract
Background/purpose Rates of postoperative morbidity, particularly infectious complications, remain high after pancreatoduodenectomy.
Methods Subjects comprised 101 patients who had undergone pancreatoduodenectomy, analyzed according to presence or absence of infectious postoperative complications. Nineteen perioperative variables were analyzed to identify risk factors associated with postoperative infectious complications.
Results Postoperative infectious complications occurred in 56 patients (55%); among them 29 had serious infectious morbidity, including bacteremia (13%), intra-abdominal infection (18%) and pneumonia (12%). One patient (1%) died of multiple organ failure subsequent to a severe septic attack. Only body mass index (BMI) differed significantly between patients with and without serious infection. Logistic regression analysis identified BMI >25 as an independent factor for occurrence of serious postoperative infectious complications. BMI >25 was a common risk factor for individual infection, including bacteremia, intra-abdominal infection, and pneumonia. As for the influence of BMI on perioperative parameters, the high BMI significantly affected the operation time. Meanwhile preoperative biliary drainage had no influence on overall and individual infectious morbidities.
Conclusions This study demonstrates the need for careful postoperative monitoring in the patient with high BMI.

Keywords Pancreatoduodenectomy · Infectious complications · Body mass index · Biliary drainage

Background

In the past, pancreatoduodenectomy has been associated with high rates of complications (40–60%) and mortality (up to 20%) [1, 2]. With improvements in surgical techniques and perioperative care, mortality rates have decreased significantly, with operative mortality rates of <5% in high-volume centers, and indications for pancreatoduodenectomy have been extended. However, despite such trends toward decreasing rates of postoperative morbidity, most large studies still report postoperative morbidity rates in the range of 30–65% [3, 4]. Common postoperative complications include delayed gastric emptying, pancreatic leakage, abdominal abscess and hemorrhage. The exact contribution of specific pre- and intraoperative factors to the development of postoperative complications remains uncertain. Many researchers have indicated that preoperative instrumentation and drainage procedures of the biliary tract are associated with infectious complications [5–13]. However, relatively little information is available in the literature regarding specific evaluation of pre- and intraoperative factors associated with postoperative infectious complications. The purpose of the present study was to determine factors associated with

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postoperative infectious complications in a series of consecutive pancreatoduodenectomies performed by the same group of surgeons in our hospital.

Patients and methods

Pancreatoduodenectomy was performed for 101 consecutive patients (67 men, 34 women; mean age, 64 years; range 26–90 years) between March 2005 and July 2007. All data from patients were prospectively collected in a database. By chart review, preoperative factors [age, sex, body mass index (BMI), history of diabetes mellitus, hemoglobin (Hb)A1c level, hemoglobin level, white blood cell and lymphocyte counts of peripheral blood, serum albumin level, total bilirubin and blood urea nitrogen (BUN), preoperative biliary drainage and associated procedures, and results of bile cultures] and intraoperative factors (operation time, operative blood loss, red blood cell transfusion) were recorded. History of diabetes mellitus was present in 26 of 101 patients (26%). Malignant tumors were identified in 95 patients (94%), including 55 pancreatic adenocarcinoma, 17 ampullary cancers, 10 common bile duct cancers, 4 duodenal cancers, 1 intraductal papillary mucinous neoplasm, 1 duodenal gastrointestinal stromal tumor, 1 retroperitoneal liposarcoma invading the duodenum, 1 gallbladder cancer, 2 colonic cancers, 2 gastric cancers, and 1 metastasis of renal cancer in the pancreas. Benign diseases were seen in 6 cases (pancreaticolithiasis, $n = 1$; choledocholithiasis, $n = 1$; cystic pancreatic tumor, $n = 1$; autoimmune pancreatitis, $n = 2$; solid pseudopapillary tumor, $n = 1$). The portal vein or superior mesenteric vein was segmentally (or wedge) resected and anastomosed in 27 patients (27%). Combined resection was performed in various, for the right colon ($n = 5$), liver ($n = 3$), spleen ($n = 1$), appendix ($n = 1$) and right kidney ($n = 1$).

As for practice of the treatment for the patients undergoing pancreatoduodenectomy, preoperative biliary drainage was performed routinely in all jaundiced patients by percutaneous transhepatic cholangiodrainage, endobiliary stent placement through an endoscopic route. Our standard procedure is subtotal stomach-preserving pancreatoduodenectomy [14]. When patients already had gastrectomy, standard pancreatoduodenectomy was done. Eighty-four patients (83%) underwent subtotal stomach-preserving pancreatoduodenectomy and 17 (17%) had standard pancreatoduodenectomy. Cefazolin sodium hydrate (1 g, Cefamezine®; Astellas Pharma, Tokyo, Japan) was injected intravenously as a prophylactic antibiotic 30 min before induction and at 3-h intervals during the operation, then continued twice daily for 48 h postoperatively. Patients with unexplained postoperative fever, leukocytosis or worrisome clinical findings on physical examination underwent computed tomography. When necessary, intra-abdominal fluid collections were obtained by percutaneous puncture and aspirated fluid was sent for culturing and amylase assay. The amylase and culture study of drain discharge was done on postoperative days 1, 3, 5, and 7 (except for culture study on day 1). The surgically placed drains were routinely removed on postoperative day 7 or 9 with negative culture result and no evidence of pancreatic fistula. As for postoperative nutrition, enteral feeding was routinely started on postoperative day 3 with 200 Cal/day and advanced up to a goal of 1000 Cal/day as tolerated by the patient. The feedings were continued at this rate until oral intake was resumed with a target of 1000 ml of fluid per day. Parenteral nutrition via central venous catheter was also advanced and maintained with 800–1000 Cal/day.

Postoperative infectious complications included (1) bacteremia, (2) intra-abdominal infection, (3) abdominal drain infection, (4) wound infection, and (5) pneumonia. Bacteremia was defined as positive blood cultures with a setting of high grade fever. Intra-abdominal infection was defined as high grade fever of $\geq$38°C with positive culture results from fluid obtained from surgically placed drains or ultrasound- or computed tomography-guided intervention. Abdominal drain infection was defined as purulent exudates showing positive cultures from the surgically placed drain without clinical symptoms. Wound infection was defined as culture-positive purulent drainage from the operative wound, requiring open packing. Pneumonia was defined as clinical or radiographically significant lung injury associated with pulmonary infiltrate with positive sputum cultures. Postoperative death was defined as in-hospital death after surgery. Pancreatojejunal anastomotic insufficiency was defined as drain amylase level >3 times the upper limit of normal serum amylase level on postoperative day 3, according to the definitions of the International Study Group of Pancreatic Fistula [15–17].

Continuous variables were expressed as mean ± standard deviation, and means were compared between groups using Student's t test. Univariate comparisons for all categorical variables were performed using the Pearson χ^2 test. A logistic regression model for multivariate analysis was used to determine independent risk factors. Values of $p \leq 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS for Windows version 10.0 software (SPSS, Chicago, IL, USA).

Results

Among a total of 101 patients who underwent pancreatoduodenectomy, postoperative infectious complication occurred in 57 (56%) patients. As shown in Table 1,

Table 1 Type of infectious complications

Type of infection	Cases (%)
Bacteremia	13 (13)
Intra-abdominal infection*	18 (18)
Abdominal drain infection	26 (26)
Wound infection	8 (8)
Pneumonia	12 (12)
Urinary tract infection	1 (1)
Colitis	3 (3)
Liver abscess	1 (1)
Cholangitis	2 (2)

Including 12 cases without clinical symptoms, but with purulent exudate showing positive cultures from the drain

bacteremia was observed in 13 (13%) patients, intra-abdominal infection in 18 (18%), abdominal drain infection in 26 (26%), wound infection in 8 (8%), pneumonia in 12 (12%), and other infectious sequelae in 7. Among the 18 patients who were categorized into intra-abdominal infection, only 1 patient underwent a percutaneous drainage after removing the drain; the remaining 17 showed the positive drain discharge with higher than moderate grade of fever. One patient died of aggressive septic episode with multiple organ failure on postoperative day 19 (mortality rate, 1%) due to numerous subcutaneous abscesses from comorbid autoimmune dermatitis. The intra-abdominal infection had a positive relationship with bacteremia ($p = 0.01$) and pneumonia ($p = 0.007$), and bacteremia was also related with pneumonia ($p = 0.008$) by chi-square test. The abdominal drain infection and wound infection did not have any relationship with all these factors.

Patients were divided into two groups according to clinical significance, with 29 (29%) showing serious infectious complications, including bacteremia, intra-abdominal infection, and pneumonia, and the remaining 72 (71%) experiencing no such sequelae. Various factors were compared between these groups (Table 2). BMI and preoperative serum level of BUN showed significant difference between patients with and without infection. Only 1 patient showed a BMI >30. Other preoperative variables were comparable between these groups. No differences were observed in operation time or intraoperative blood loss between the two groups.

Preoperative biliary drainage was implemented in 54 patients, and bile cultures were positive in 35 of these patients (65%). Significant infectious complications occurred in 16 patients (30%) with biliary drainage. Thirteen of the 47 patients without drainage (28%) developed serious infectious complications. No significant differences were seen between drainage vs. non-drainage, or between percutaneous vs. endoscopic approaches. Likewise, results of pre- and intraoperative bile culture showed no significant differences between groups (Table 2).

Logistic regression analysis including all possible risk factors (age <70 vs. ≥70; BMI <25 vs. ≥25; history of diabetes mellitus; serum level of BUN <12 vs. ≥12 mg/dl; preoperative biliary drainage: performed vs. not performed; pancreatic fistula: present vs. absent; red blood cell transfusion: performed vs. not performed; combined resection of other organs: performed vs. not performed) showed only BMI ≥25 as an independent factor associated with high incidence of serious postoperative infectious complications (odds ratio [95% confidence interval], p value 6.5 [1.8–23.7], 0.005). High BMI also independently influenced the occurrence of intra-abdominal infection (9.9 [2.7–36.8], 0.001). As for bacteremia, BMI ≥25 (4.6 [1.1–19.0], 0.04) and red blood cell transfusion (3.2 [0.9–12.9], 0.06) were identified as independent risk factors. No factors were found to independently influence the occurrence of wound infection.

Regarding the influence of BMI on perioperative parameters, high BMI significantly affected the operation time (Table 3). The other perioperative factors, including operative blood loss and transfusion, resection of other organs, and occurrence of pancreatic fistula had no relationship with BMI.

As for the causative bacteria of infectious complications, positive blood cultures from septicemia were almost monomicrobial (12 of 13; 92%). In our series, *Staphylococcus epidermidis* was the most frequent pathogen (6 of 13; 46%). Among 6 patients showing positive blood culture results for these bacteria, 3 patients (50%) showed positive findings for the central venous catheter and 2 for abdominal drain culture. Preoperative bile culture was not at all predictive of the cause of septicemia. Intra-abdominal infection was oligomicrobial, including intestinal coliform bacteria, pathogenic Gram-negative rods such as *Pseudomonas*, and *Staphylococcus* species. Among the 37 patients with positive bile cultures, 20 patients had intra-abdominal infection; bile culture was predictive of causative bacteria in 8 of 20 (40%). Almost all pneumonia was caused by normally colonized microorganisms in the upper respiratory tract.

Discussion

Despite the trend toward a decreasing rate of postoperative mortality, the morbidity rates associated with pancreatoduodenectomy are reportedly still high [3–9, 18, 19]. Even high-volume centers with vast experience in pancreatic surgeries have reported rates of major complications of approximately 20% for patients undergoing pancreatoduodenectomy [3]. Among the various morbidities seen after pancreatoduodenectomy, infectious complications remain a

Table 2 Comparison of pre- and perioperative factors between two groups

Variables	No serious infection ($n = 72$)	Serious infection ($n = 29$)	p
Age (years)[a]	64.7 ± 9.8	63.9 ± 13.6	0.74
<70 ($n = 68$)	48	20	0.51
≥70 ($n = 33$)	24	9	
Sex			
Male ($n = 67$)	46	21	0.28
Female ($n = 34$)	26	8	
BMI[a]			
≥25 ($n = 12$)	4	8	**0.002**
<25 ($n = 89$)	68	21	
History of diabetes mellitus			
Yes ($n = 26$)	21	5	0.22
No ($n = 75$)	51	24	
Hb (g/dl)[a]	12.3 ± 1.8	12.9 ± 1.2	0.16
HbA1c (%)[a]	6.0 ± 1.8	5.8 ± 1.7	0.59
WBC ($\times 10^3/mm^3$)[a]	6.1 ± 1.7	5.7 ± 1.4	0.27
Lymphocytes ($\times 10^3/mm^3$)[a]	1.6 ± 0.6	1.6 ± 0.6	0.83
Albumin (g/dl)[a]	4.0 ± 1.1	3.9 ± 0.4	0.56
Total bilirubin (mg/dl)[a]	1.6 ± 1.8	1.3 ± 1.2	0.47
BUN (mg/dl)[a]	12.8 ± 4.0	14.2 ± 4.0	0.06
Preoperative biliary drainage			
No ($n = 47$)	34	13	0.63
Percutaneous ($n = 32$)	21	11	
Endoscopic ($n = 22$)	17	5	
Bile culture[b]			
Positive ($n = 37$)	24	13	0.36
Negative ($n = 10$)	8	2	
Pancreatic fistula			
Yes ($n = 21$)	16	5	0.58
No ($n = 80$)	56	24	
Operation time (min)[a]	523 ± 86	528 ± 144	0.83
Blood loss (g)[a]	709 ± 478	811 ± 652	0.39
Red blood cell transfusion			
Yes ($n = 15$)	10	5	0.67
No ($n = 86$)	62	24	
Benign or malignant			
Benign ($n = 6$)	5	1	0.26
Malignant ($n = 95$)	67	28	
Combined resection			
Yes ($n = 35$)	9	2	0.41
No ($n = 66$)	63	27	

Statistically significant analysis results are indicated in bold values

[a] Values represent mean ± standard deviation

[b] Results of bile culture were unavailable for 54 patients

significant issue, despite technical and pharmacological efforts to address them. The present study revealed overall infectious complications in 56% of patients, more frequent than reported in other large studies (34–41%) [5–7]. This result indicates that, if meticulously monitored, a colonization of pathogenic organisms can very frequently be found after pancreatoduodenectomy. Among these complications, we focused on the clinically significant events, including bacteremia, intra-abdominal infection, and pneumonia, which would threaten a patient's life or prolong hospital stay.

In our study, the common risk factor found to independently influence the clinically significant infectious morbidity was BMI. While generalized obesity has long been recognized as a significant risk factor for minor and major complications after pancreatoduodenectomy [20],

Table 3 Relationship between BMI and perioperative parameter

Variables	BMI <25 ($n = 89$)	BMI ≥25 ($n = 12$)	p
Operative blood loss (g)	719 ± 494	881 ± 776	0.14
<500 ($n = 40$)	36	4	0.64
≥500 ($n = 61$)	53	8	
Blood transfusion			
No ($n = 86$)	76	10	0.85
Yes ($n = 15$)	13	2	
Operative time (min)	516 ± 90	586 ± 176	**0.009**
<600 ($n = 81$)	73	8	0.21
≥600 ($n = 20$)	16	4	
Combined resection			
No ($n = 90$)	79	11	0.76
Yes ($n = 11$)	10	1	
Pancreatic fistula			
No ($n = 80$)	70	10	0.71
Yes ($n = 21$)	19	2	

Statistically significant analysis results are indicated in bold values

many reports have been published which do not support the adverse influence of obesity on early outcomes in patients undergoing various kinds of surgery, including general abdominal surgery [21], laparoscopic surgery [22, 23], coronary artery bypass [24, 25], radical cystectomy [26], cesarean deliveries [27], and total hip replacement [28]. Some of them reported a significant increase of intraoperative blood loss [28] and more frequent incidence of infectious morbidity in obese patients [29]. However, many of them could not prove any impact of increased BMI on postoperative complications [21, 23–26, 28]. House et al. [29]. reported generalized obesity (BMI ≥30), as an independent predictor of wound infection after pancreatoduodenectomy, but not for any other complications. Recently, however, obesity has been reported as a significant indicator for increased operative blood loss, operative time [30] and increased rate of postoperative pancreatic fistula [31] in pancreatoduodenectomy. And pancreatic fistula has reportedly been associated with infectious complications, including intra-abdominal abscess [32]. Thus, obesity might increase the risk of intra-abdominal abscess. In our study, BMI had significantly positive association only with operation time. In the present study also, the increase of BMI did not lead to mortality. It was of note that although BMI of almost all patients in our study was under 30, yet we still identified this as a common risk factor for serious infectious postoperative complications, including bacteremia, intra-abdominal abscess, and pneumonia.

There have been many studies researching the effects of preoperative biliary instrumentation and biliary drainage on postoperative infectious complications after pancreatoduodenectomy [5–10, 12, 13, 29, 33]. Limongelli et al. [5] and Povoski et al. [7] demonstrated that positive intraoperative bile culture was associated with a high incidence of both intra-abdominal abscess and wound infection after pancreatic surgery. According to Cortes et al. [8] and Sohn et al. [34], preoperative interventional biliary endoscopy and percutaneous stent insertion were related to bile infection, which in turn was directly associated with an increased rate of postoperative infections. Preoperative biliary drainage introduces microorganisms into the biliary tree. When the biliary tract is transected during surgery, colonized bile can lead to contamination of both peritoneal cavity and surgical wound. They suggested that preoperative biliary drainage should be avoided in candidates for pancreatoduodenectomy [8–10]. However, many other investigations have indicated that preoperative biliary drainage shows no relationship with postoperative mortality and morbidity after pancreatoduodenectomy [11–13]. The present study did not find any significant differences in overall postoperative infection rate, or mortality, between patients showing positive and negative results for bile culture. Bacteria detected from infectious complications did not match those from bile culture in our study, except in the case of intra-abdominal abscess. This discordance might be due to the prophylactic use of antibiotics, which proved effective against bacteria detected from bile culture.

In our study, asymptomatic drain infection (defined as abdominal drain infection) was frequent (26%). It might be due to our cautious management of drains. The early removal of drains has been reported to reduce postoperative intra-abdominal infections [35]. Too much caution may do more harm than good for the management of prophylactic drains.

In a univariate analysis of our study, level of BUN was associated with postoperative serious complications with marginal significance ($p = 0.06$). Only a few articles have discussed the relationship between preoperative laboratory data and morbidity and mortality after pancreatoduodenectomy [34, 36]. In a study including 2894 patients who underwent pancreatoduodenectomy over a 25-year period, Winter et al. [33] found that significant multivariate predictors of a postoperative complication included the value of preoperative BUN (≥18 mg/dl), preoperative albumin (≤3.5 g/dl), and postoperative amylase (≥292 U/l). Thus, routine perioperative laboratory tests might help surgeons identify patients who are at increased risk for morbidity after pancreatoduodenectomy.

Patients with a high BMI undergoing pancreatoduodenectomy are at elevated risk of infectious postoperative complications. This study demonstrates the need for careful postoperative monitoring in the patient with high BMI. Adjunctive operative techniques and therapies aimed at reducing the chances of infectious complications should be considered in these patients.

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Secure placement of a peripancreatic drain after a distal pancreatectomy

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KEYWORDS:
Distal pancreatectomy;
Pancreatic fistula;
Peripancreatic drainage;
Drain fixation

Abstract

BACKGROUND: A peripancreatic drain that is placed after a distal pancreatectomy sometimes migrates and becomes ineffective postoperatively. We devised a new drainage method with fixation of the tip of a peripancreatic drain using a loose loop of an absorbable suture.

METHODS: This retrospective study was performed on 84 consecutive patients who underwent a distal pancreatectomy followed by peripancreatic drainage with (n = 31) or without (n = 53) fixation.

RESULTS: The fixed drain remained in place postoperatively and was removed easily when the drainage became unnecessary. Pancreatic fistula developed in 4 patients with and 11 patients without drain fixation, the incidence between the patients. None with and 7 patients without fixation required additional drainage (interventional or surgical) for pancreatic fistula, the difference being significant. Time to resolution of pancreatic fistula tended to be shorter after drain fixation than after nonfixation.

CONCLUSIONS: Fixation of the tip of a peripancreatic drain is a simple but useful technique for effective drainage after distal pancreatectomy.

With recent advances in surgical techniques and perioperative management, the mortality rate after distal pancreatectomy has decreased and is now less than 2% in high-volume centers.[1–3] However, the morbidity rate remains as high as 10% to 47%.[4–6] Pancreatic fistula is the most common (up to 60.9%, mostly 10%–26%)[1,3,5,7–12] and clinically relevant complication, resulting in further complications (abscess, hemorrhage, and sepsis) and prolonged hospitalization. Various surgical techniques are used for managing the pancreatic stump: hand-sewn closure, stapler closure, ultrasonic dissector, ultrasonically activated scalpel, fibrin glue sealing, seromuscular patch, and intended ligation of the main pancreatic duct.[11,13] Furthermore, somatostatin analog therapy is performed for preventing pancreatic fistula.[11,13] However, no surgical or medical method can completely prevent pancreatic fistula.

Accordingly, appropriate intraperitoneal drainage after distal pancreatectomy is important. However, recent articles rarely have addressed drainage methods. Previously, we experienced some cases that necessitated interventional or surgical drainage of peripancreatic fluid collection because the drain that had been placed near the pancreatic stump intraoperatively migrated from the stump to the left upper retroperitoneum postoperatively and became ineffective for drainage.

We devised a new technique for secure peripancreatic drainage after distal pancreatectomy. We compared the influence on the development and treatment of pancreatic

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Table 1 Indication for distal pancreatectomy and method of closing the pancreatic stump

	Fixed drain group (n = 31)	Nonfixed drain group (n = 53)	Total (n = 84)	P
Diagnosis				.694
Pancreatic tumor	22	37	59	
Nonpancreatic tumor	6	10	16	
Chronic pancreatitis	3	6	9	
Closure of pancreatic stump				.080
Hand-sewn	29	42	71	
Stapled	2	11	13	

fistula after distal pancreatectomy between our new drainage method and the conventional method.

Methods

Between 1997 and 2007, 84 consecutive patients underwent distal pancreatectomy with splenectomy electively at our institution. There were 40 men and 44 women with a mean age of 59 years (range, 26–81 y). The indication for pancreatectomy included pancreatic neoplasm (n = 59), nonpancreatic neoplasm (n = 16), and chronic pancreatitis (n = 9) (Table 1). Closure of the pancreatic stump and intraperitoneal drainage were performed at the discretion of the operating surgeon. Thirteen patients had a staple closure of the pancreatic stump. In the other 71 patients, the pancreas was transected with a scalpel or electrocautery. The main pancreatic duct was closed with ligature or suture. The pancreatic cut surface was not oversewn. Fibrin glue was not used. Octreotide was not administered prophylactically.

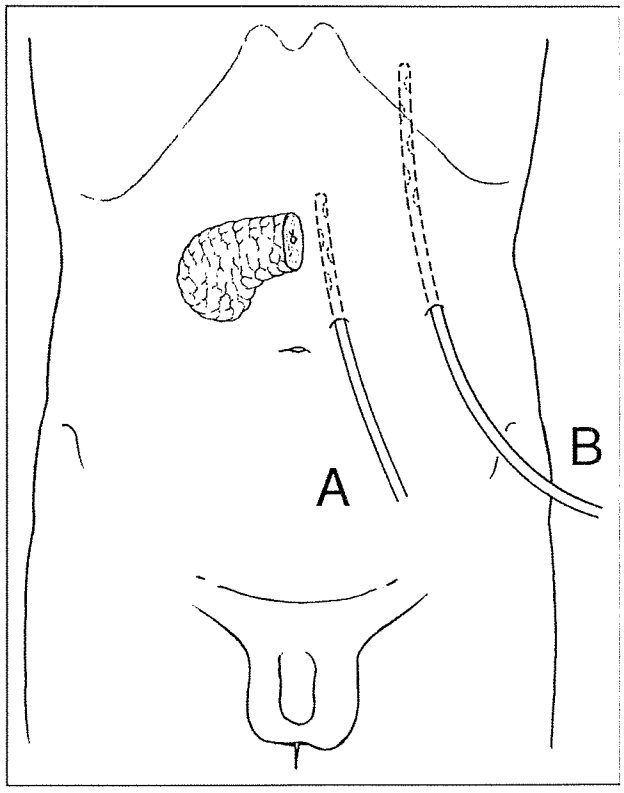

Figure 1 Intraperitoneal drainage after distal pancreatectomy. A drain (A) is placed near the pancreatic stump from the left upper abdomen and another drain (B) is placed in the left subphrenic space from the left flank.

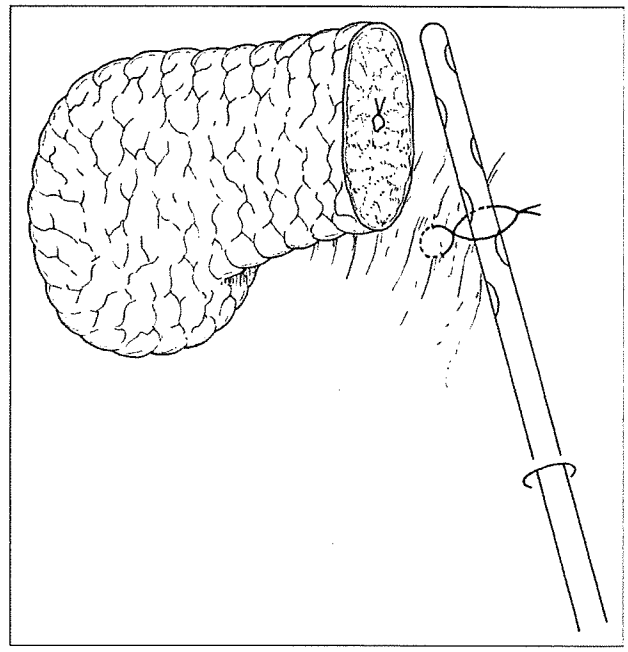

Figure 2 Fixation of the tip of a peripancreatic drain to the retroperitoneal tissue close to the pancreatic stump, with a loose loop of an absorbable suture.

Closed drainage was performed with silicone duple drains (Silascon, 525 N to 10 N; Kaneka Medix, Co., Osaka, Japan). All patients had a drain placed near the pancreatic stump from the left upper abdomen and another drain placed in the left subphrenic space from the left flank (Fig. 1). In the fixed drain group (n = 31), the tip of the peripancreatic drain was fixed to the retroperitoneal tissue close to the pancreatic stump, with a loose loop of an absorbable suture (Fig. 2). In the nonfixed drain group (n = 53), the tip of the peripancreatic drain was not fixed. This fixation was performed mostly by one (MS) of the authors after 2000. Neither sex, age, indication for pancreatectomy, nor method of pancreatic stump closure was different between both groups.

The amylase concentration of the fluid from the peripancreatic and subphrenic drains was checked on days 1, 3, and 7 after surgery. The drains were removed usually after postoperative day 3 (for the subphrenic drain) or day 7 (for the peripancreatic drain) if pancreatic fistula was denied.

Table 2 Complications after distal pancreatectomy

	Fixed drain group (n = 31)	Nonfixed drain group (n = 53)	Total (n = 84)	P
Patients with any complications	7	16	23	.251
Pancreatic fistula (ISGPF, grades B + C)	4	11	15	.342
Nonpancreatic abscess	0	2	2	.273
Intra-abdominal bleeding	0	1	1	.442
Wound infection	3	6	9	.814
Pulmonary complication	2	3	5	.882
Death	0	1	1	.442

ISGPF = International Study Group on Pancreatic Fistula.

Postoperative complications were recorded. Pancreatic fistula was diagnosed and graded according to the definition of the International Study Group on Pancreatic Fistula.[14] In the present study, pancreatic fistula of only grades B and C were included for analysis and that of grade A (transient fistula of no clinical impact) was excluded.

All values are presented as means ± standard deviation. Statistical analysis was performed using the chi-square test and the unpaired *t* test, where appropriate. Differences were considered significant at a *P* value of less than .05.

Results

Fixation of the drain tip near the pancreatic stump was feasible without any complications. The drain remained in place postoperatively and was removed easily when drainage became unnecessary.

The overall morbidity rate was 27% (23 of 84 patients), and was not different between the fixed drain group and the nonfixed drain group (Table 2). Pancreatic fistula (grades B and C) was the most common complication, occurring in 15 patients (18%). The incidence was not different between the fixed drain group (13%) and the nonfixed drain group (21%) (Table 3). Of the 15 patients with pancreatic fistula, 7 required additional drainage of amylase-rich fluid collection or abscess near the pancreatic stump postoperatively: none of the patients in the fixed drain group and 7 patients (13%) in the nonfixed drain group ($P = .035$). Additional drainage indicated grade C fistula of the International Study Group on Pancreatic Fistula,[14] although the patients were not so severely ill. These 7 patients had experienced abdominal pain and/or fever before additional drainage. Of the 7 patients, 5 underwent interventional percutaneous drainage, under guidance of ultrasonography or computed tomography. Two remaining patients underwent relaparotomy and drainage of fluid collection not accessible by percutaneous drainage. In these 7 patients, the tip of the initial drain had migrated from the pancreatic stump to the left upper retroperitoneum postoperatively. They had persistent pancreatic fistula after additional drainage. Another 2 patients with abdominal pain and fever underwent percutaneous drainage of an intra-abdominal abscess that was not caused by pancreatic fistula.

The time to resolution of pancreatic fistula after the initial surgery was shorter in the fixed drain group (20 ± 8 days) than in the nonfixed drain group (31 ± 22 days), although not statistically significant. In the nonfixed drain group, patients without additional drainage (21 ± 11 days) tended to have a shorter time to resolution of pancreatic fistula than those with additional drainage (36 ± 26 days) ($P = .299$).

There was one perioperative death in the nonfixed drain group. It was caused by intra-abdominal bleeding associated with pancreatic fistula.

Comments

In the present study, the fixed drain group had a significantly lower incidence of postoperative drainage of pancreatic fistula and tended to have a shorter period for cure of pancreatic fistula than the nonfixed drain group, although the incidence of pancreatic fistula was not different between these 2 groups.

In the present patients without staple closure, the pancreatic cut surface was left open after closure of the main pancreatic duct. The conventional technique, namely suture closure of the

Table 3 Pancreatic fistula after distal pancreatectomy

	Fixed drain group (n = 31)	Nonfixed drain group (n = 53)	Total (n = 84)	P
Pancreatic fistula (ISGPF)	25	44	69	.109
Grade A	21	33	54	
Grade B	4	3	7	
Grade C	0	8	8	
Grades B + C	4	11	15	.342
Additional drainage	0	7	7	.035
Mean time to resolution ± SD, d (range)	20 ± 8 (14–32)	31 ± 22 (12–90)	28 ± 20 (12–90)	.413

ISGPF = International Study Group on Pancreatic Fistula.

pancreatic stump parenchyma, may cause pancreatic stump ischemia via compression from the sutures, and subsequent pancreatic fistula. Recently, some surgeons have adopted the nonclosure technique to maintain blood supply at the pancreatic stump and to decrease pancreatic fistula.[15]

Pancreatic leakage after distal pancreatectomy originates from the main pancreatic duct and/or branch ducts at the pancreatic stump. Leakage from the transected branch pancreatic ducts usually is transient and stops spontaneously. On the other hand, leakage from the main pancreatic duct may develop into persistent fistula and major complications. No surgical or medical methods can completely avoid pancreatic leakage or fistula after distal pancreatectomy.[11,13]

Therefore, appropriate intraperitoneal drainage after distal pancreatectomy is important, although some investigators[16] oppose routine placement of intraperitoneal drains after pancreatic resection. A drain usually is placed to the left subphrenic space that is situated at the lowest level. Another drain should be placed near the pancreatic stump to drain transient pancreatic leakage and to treat persistent pancreatic fistula if it occurs. In general, drains should be settled via a short and straight route for effective drainage. It is recommended to insert the peripancreatic drain from the left upper abdomen.

However, the tip of a nonfixed drain often migrates from the pancreatic stump to the left upper retroperitoneum postoperatively, which makes drainage ineffective (Fig. 3). This occurs because the pancreatic stump in the pancreatic neck-body is situated at a higher level than the left upper retroperitoneum. If peripancreatic fluid collection or pancreatic fistula develops in such cases, interventional or surgical drainage is required. Furthermore, a percutaneously placed drain often is distant from the pancreatic stump. The fistula tract may be longer and more complex, and take a longer time to cure in such cases than in cases in which the initial drain remains in place and is effective.

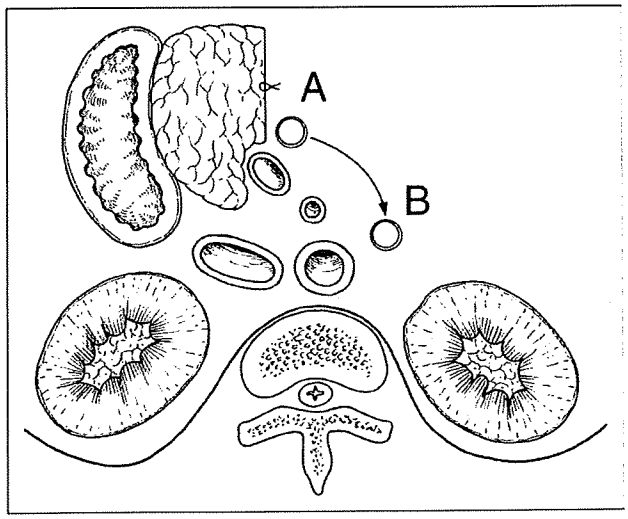

Figure 3 Axial view of the remnant pancreas and peripancreatic drain after a distal pancreatectomy. The nonfixed peripancreatic drain is apt to migrate to the left upper retroperitoneum (from A to B).

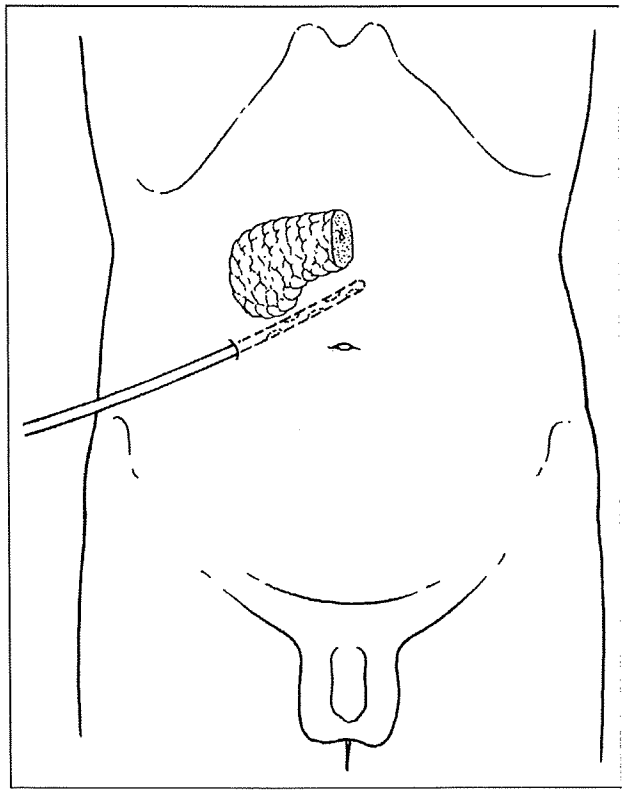

Figure 4 Placement of a drain along the inferior edge of the remnant pancreas from the right upper abdomen.

Accordingly, secure placement of a drain near the pancreatic stump is important after distal pancreatectomy. In our new method, the tip of the drain is fixed to the tissue near the pancreatic stump using a loose loop of a suture. This procedure prevents migration of the drain and allows removal of the drain when drainage has become unnecessary. This technique did not decrease the incidence of pancreatic fistula after distal pancreatectomy but eliminated the necessity for additional postoperative drainage of the pancreatic fistula. Furthermore, this technique tended to take a shorter time to cure of pancreatic fistula if it occurred.

There are other drainage methods after a distal pancreatectomy. One method is placement of a drain transversely along the inferior or superior edge of the remnant pancreas from the right upper abdomen (Fig. 4). This method may avoid drain migration. However, the tip of the drain is more distant from the pancreatic stump and may be less effective for drainage compared with a drain inserted from the left upper abdomen. Soft drains such as a Penrose drain (PHYCON; Fuji Systems, Co., Tokyo, Japan) may be placed near the pancreatic stump. This method prevents drain migration but has a risk of retrograde infection owing to open drainage. Furthermore, it may be difficult to manage high-output pancreatic fistula.

However, the present study had some drawbacks. It was a retrospective study and the fixed drain group patients were treated later during the study period. Accordingly, a prospective randomized study is required to establish the superiority of the present method of drain fixation.

In conclusion, the present technique, namely fixation of the tip of a peripancreatic drain with a loose loop, is a simple but useful technique for effective drainage after distal pancreatectomy.

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Middle pancreatectomy: Safety and long-term results

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Background. *Pancreaticoduodenectomy and distal pancreatectomy for lesions of the neck or body of the pancreas sacrifice a large amount of normal pancreatic tissue. Middle pancreatectomy (MP) is a parenchyma sparing technique that reduces the risk of postoperative endocrine and exocrine insufficiency. This study aims to evaluate the perioperative and long-term results of MP and to clarify whether MP can be performed with outcomes comparable with traditional pancreatectomies.*

Method. *Twenty-six patients who underwent MP for benign or low-grade malignant tumor of the pancreas between 1991 and 2006 at the Department of Surgery II, Nagoya University Graduate School of Medicine, were identified. Their outcomes were compared with 2 separate control groups, 35 left-side pancreatectomies (LSP) and 60 right-side pancreatectomies (RSP).*

Results. *The mean operating time of the MP group was 295 minutes, which was significantly shorter than that for RSP (P = .0001). The rate of pancreatic fistula formation was higher in the MP group than in the 2 control groups, although the differences did not reach statistical significance. After a mean follow-up of 71 months, postoperative endocrine function was equivalent to the pre-operative values in the MP group, and none of the patients developed diabetes mellitus postoperatively. Only 1 patient in the MP group required enzyme substitution postoperatively for exocrine insufficiency. The MP group was inclined to be superior to the other 2 control groups in terms of postoperative nutritional status.*

Conclusion. *Middle pancreatectomy is a reasonable technique that is indicated for selected patients with benign or low malignant tumors in the neck and body of the pancreas. Middle pancreatectomy seems to result in better preservation of exocrine and endocrine functions as well as in better nutritional status postoperatively. (Surgery 2010;147:21-9.)*

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MODERN IMAGING STUDIES have facilitated the incidental detection of cystic or endocrine neoplasms of the pancreas. This increase in detection rate has led to more pancreatic resections in recent years. Formerly, a pancreaticoduodenectomy (PD) or distal pancreatectomy (DP) was performed even for indolent lesions, although the excessive removal of normal pancreatic tissues raised concerns regarding the impairment of exocrine and endocrine functions. More recently, limited resections, such as pancreatic head resection with segmental duodenectomy (PHRSD),[1,2] duodenum-preserving pancreatic head resection,[3] pylorus-preserving pancreaticoduodenectomy (PpPD),[4] and spleen preserving distal pancreatectomy (SpDP),[5] have been proposed as alternative techniques to a radical pancreatic dissection. Data demonstrating the clinical benefits of these limited resections have been accumulating.

From the viewpoint of functional preservation, benign lesions or tumors with low-grade malignancy in the neck or the proximal body of the pancreas that cannot be dealt with by enucleation are particularly challenging for surgeons, if an extended left or right pancreatectomy is to be avoided. For such cases, a middle pancreatectomy (MP), in which the pancreas is transected medial and lateral to a lesion could be an option.[6] The first MP as described by Finney in 1910 was one in which the 2 ends of the pancreas were directly anastomosed together after resecting a large benign cystic neoplasm from the midportion of the gland.[7] The procedure was largely forgotten until the late 1950s, when the first MP with 2 pancreaticoenteric anastomoses was described by Guillemin and Bessot in 1957 in a patient with chronic pancreatitis.[8] Two years later, Letton and Wilson

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performed an MP instead of a distal pancreatectomy with splenectomy in 2 cases of severe traumatic injury to the pancreatic body.[9] After the dissection, they performed a Roux-en-Y jejunal loop anastomosis to the tail of the pancreas and a blind closure of the pancreatic head remnant. Since the 1980s, MP has been more frequently performed, and other case series of MP using this mode of reconstruction were reported for benign tumors or those with low-grade malignancy.[10-29] Most of the series have either been associated with an intolerably high incidence of postoperative complications or have been reported after only limited periods of follow-up, thus lacking sufficient information regarding long-term functional or oncological outcomes. Recently, some reports have compared morbidity, quality-of-life, and other alternative measures of outcome between MP and other surgical procedures.[23,26,29]

We report here a study to compare not only the peri-operative, long-term functional, but also nutritional outcomes of patients who underwent an MP, with the control group treated by left-side pancreatectomy (LSP) and right-side pancreatectomy (RSP). Cases of benign or borderline disease that were treated either with MP, LSP, or RSP during the same time period were found using a computer database. The profiles of postoperative complications and long-term oncologic and functional consequences were compared among the groups treated with the 3 different procedures.

PATIENTS AND METHODS

Patient eligibility and characteristics. Between January 1991 (the year we performed our first MP) and December 2006, 465 patients underwent pancreatic resection; of these, 26 patients who underwent MP were identified from a database of patients treated for pancreatic tumors treated at the Department of Surgery II, Nagoya University Graduate School of Medicine. The indication for MP had been a localized lesion in the neck or proximal body of the pancreas with no evidence of high-grade malignancy. To select candidates for this procedure, computed tomography and ultrasonography were routinely performed. Additionally, magnetic resonance imaging, endoscopic ultrasonography, or endoscopic retrograde pancreatography were employed at the discretion of the gastroenterologists to obtain a pre-operative diagnosis and detailed information about local extension of the tumor and their association with the main pancreatic duct. This included the assessment of the proximal and distal margin of the pancreatic duct. In some cases, intraoperative histopathologic diagnosis with a frozen section of the primary tumor was mandated to ensure that the tumor resected by MP was not an adenocarcinoma. For comparison, patients who suffered from a similarly benign or borderline pancreatic tumor and underwent an RSP that included standard PD, PpPD, and PHRSD or a LSP that included DP and SpDP during the same period as MP (from January 1991 to December 2006) were also retrieved from the database. Follow-up was based on clinical, radiologic, and laboratory assessments. Specific aims of long-term follow-up were to evaluate tumor recurrence and long-term endocrine and exocrine function. For this latter purpose, patients underwent clinical and laboratory evaluation every 6–12 months. Observations and examinations evaluating the exocrine and endocrine functions were performed postperatively in all patients. Among patients with clinical suspicion of diabetes mellitus (HbA1c >6.0% and/or fasting blood glucose >126 mg/dL), those who were found not to recover after dietary and exercise therapy were found to have clinically diabetes mellitus and were treated with oral antihyperglycemic drugs or insulin replacement therapy. Patients with clinical suspicion of exocrine insufficiency such as presence of steatorrhea and overt weight loss received enzyme supplementation. Pancreatic exocrine insufficiency was defined as diarrhea and steatorrhea, which improved with pancreatic enzyme replacement.

Data on the pre-operative, intraoperative, and postoperative status were retrospectively reviewed and analyzed. A comparison of the nutritional status (total protein, albumin, total cholesterol, cholinesterase, and hemoglobin) before and after operation was calculated using the following formula: (postoperative numerical value—pre-operative numerical value)/pre-operative numerical value × 100 (%). As for the presence of a pancreatic fistula, the medical records were reviewed and reanalyzed based on the International Study Group on Pancreatic Fistula recommendations.[30]

Surgical procedures. Operation was initiated by a midline upper abdominal incision, the lesser sac was then opened, and the anterior aspect of the pancreas was exposed by dividing the adhesions between the posterior surface of the stomach and the pancreas. From 1995 onward, intraoperative ultrasonography of the pancreas was carried out to identify the neoplasm, to determine the transaction point, and to define its relationship with the portal vein and superior mesenteric vein.[31] The pancreatic dissection was initiated inferiorly along the superior mesenteric vein and pancreatic body.

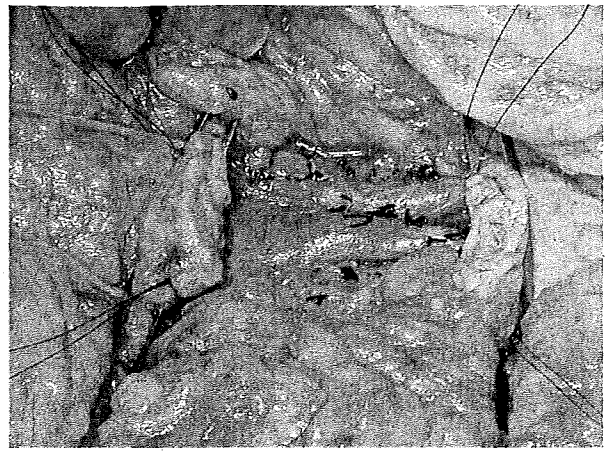

Figure. A view of the pancreas with a benign cystic lesion in the neck of the pancreas. The middle pancreatic segment containing the tumor has been separated from the splenoportal junction, and small splenic arterial and venous branches have been divided. Both sides were divided by the knife on the cut line. These procedures completed a middle pancreatectomy.

The superior mesenteric, portal, and splenic veins were dissected free from the pancreas. Then both sides were divided using a scalpel on the cut line, which was previously determined. These procedures completed the middle pancreatectomy (Figure). In the cases of intraductal papillary mucinous neoplasms, the remnant pancreatic ducts were examined by pancreatoscopy with an ultrathin pancreatoscope to be certain there were no nodular or villous lesions.[32] Both of the resected margins of the pancreas were submitted for intraoperative frozen section analysis. The main pancreatic duct and vessels in the cephalic portion were identified and selectively suture ligated, whereas the cephalic pancreatic cut surface was not routinely oversewn. As for the distal pancreas, pancreaticogastrostomy (PG) with a single-layer anastomosis was created in an interrupted fashion. A temporary pancreatic stent was placed into the main pancreatic duct of the distal remnant. Drains were left close to the sutured cephalic stump and the region of the pancreaticogastrostomy for 7–10 days when the amount of drainage fluid was less than 10 mL/day, except for these patients in whom a pancreatic fistula developed. A temporary pancreatic stent was removed 3 weeks after operation. Somatostatin analogue octreotide was not used routinely during the peri-operative period.

Clinical data analysis. All results are presented as mean ± SD. Since a comparison between RSP and LSP is not within the scope of this study, we compared differences in the various parameters between either the RSP and MP or the LSP and MP. Distributed continuous variables were compared using a 2-sample Student t test, Mann-Whitney's U test was applied to analyze nonparametric variables. Categorical variables were compared using a Pearson Chi-squared test or Fisher exact test where appropriate. A P value of less than .05 was considered statistically significant.

RESULTS

Characteristics data. The patient demographics are shown in Table I. Twenty-six patients (14 men and 12 women) with a mean age of 58 years (range, 29–73) were treated by MP. All tumors were resected with clear surgical margins, which were confirmed during operation by microscopic examination of the frozen sections, and subsequently re-evaluated by definitive histopathological examination. None of the patients who underwent MP were found to have adenocarcinoma intraoperatively or postoperatively. Final histologic examination of the resected lesions revealed a cystic tumor in 22 patients. They included 9 intraductal papillary mucinous adenomas, 8 mucinous cyst adenomas, 3 serous cyst adenomas, 2 intraductal papillary mucinous carcinomas (IPMC) of the noninvasive type, 2 endocrine tumors, 1 pancreatic metastasis of a hemangiopericytoma, and 1 carcinoid tumor of the pancreas. The splenic artery and vein as well as the spleen itself were preserved in all cases treated with MP. Twenty-four patients underwent MP with a PG, whereas the remaining 2 underwent a pancreaticojejunostomy (PJ) because they had previously had a gastrectomy. Patients treated with MP were well matched to those treated with RSP and LSP in terms of gender, age, type of neoplasms, presence of diabetes mellitus, preexisting pancreatitis, and body mass index (Table I).

Peri-operative and postoperative results. As shown in Table II, the operating time for MP (mean ± SD) was 295 ± 61 minutes (range, 210–430), which was significantly longer than that for LSP (P = .033) but shorter than that for RSP (P = .0001). The amount of blood loss for MP was 312 ± 236 mL (range, 32–896), which was significantly less than that for both RSP (P = .0004) and LSP (P = .047).

There were no in-hospital deaths after operation in any of the 3 groups. The incidence of postoperative complications among those treated with MP was 38% (10/26 patients). All 3 patients who had postoperative bleeding underwent a reoperation. Bleeding from the proximal cut surface of the pancreas and from the right gastroepiploic artery, which were not associated with

Table I. Comparisons of patient characteristics and short-term follow-up among right side pancreatectomy, middle pancreatectomy, and left side pancreatectomy

	RSP		*MP*		*LSP*		P *value*	
Variable	(n = *60*)	*Range*	(n = *26*)	*Range*	(n = *35*)	*Range*	*RSP vs MP*	*MP vs LSP*
Patient characteristics								
Gender (M/F)	37/23		14/12		16/19		.498	.530
Age (yr)*	61 ± 12	20–78	58 ± 9	29–73	57 ± 15	12–79	.415	.733
Type of neoplasms								
IPMA	24		9		8			
IPMC	11		2		2			
SCA	3		3		6		.191	.635
MCA	6		8		8			
Endocrine	6		2		3			
SPT	1		0		3			
Other	9		2		5			
Presence of DM								
None	50		26		31		.086	.204
NIDDM	7		0		3			
IDDM	3		0		1			
Pre-existing pancreatitis	3		0		2		.550	.503
Body mass index (kg/m^2)*	23.5 ± 3.5	20.7–28.5	23.2 ± 3.8	21.4–28.1	23.9 ± 3.1	21.3–29.0	.331	.159

*Mean ± SD.

DM, Diabetes mellitus; *IDDM*, insulin-dependent diabetes mellitus; *IPMA*, intraductal papillary mucinous adenoma; *MCA*, mucinous cyst adenoma; *NIDDM*, non-insulin-dependent diabetes mellitus; *SCA*, serous cyst adenomas; *SPT*, solid pseudopapillary tumor.

Table II. Comparisons of peri-operative and short-term follow-up among right side pancreatectomy, middle pancreatectomy, and left side pancreatectomy

	RSP		*MP*		*LSP*		P *value*	
Variable	(n = *60*)	*Range*	(n = *26*)	*Range*	(n = *35*)	*Range*	*RSP vs MP*	*MP vs LSP*
Peri-operative results								
Operative time (min)*	394 ± 104	175–750	295 ± 61	210–430	246 ± 100	130–585	.0001	.033
Blood loss (mL)*	809 ± 671	170–3,700	312 ± 236	32–896	551 ± 555	49–2,360	.0004	.047
Blood transfused	6 (10%)		2 (8%)		2 (8%)		.699	.789
Postoperative results								
Mortality	0		0		0		.999	.999
Overall morbidity	21 (35%)		10 (38%)		7 (20%)		.759	.112
Pancreatic fistula	11 (18%)		8 (31%)		5 (14%)		.202	.205
Relaparotomy	0		3 (11%)		0		.025	.072
Bleeding	0		3 (11%)		0		.025	.072

*Mean ± SD.

pancreatic fistula, were successfully treated by ligation of the blood vessels responsible for the hemorrhage. The third case of postoperative bleeding resulted from a pancreatic anastomotic dehiscence; consequently, the residual left pancreas had to be removed to control the bleeding from the dorsal pancreatic artery. Eight patients, including the patient who underwent the residual left pancreatectomy, developed a pancreatic fistula (2 grade A, 5 grade B, and 1 grade C). Two patients with grade A fistulas were managed by slow removal of the operatively placed drains, little change from the normal clinical pathway was needed. Five patients with grade B fistulas did not require additional drainage, but all were managed by prolonged drainage and total parenteral nutrition. All patients treated with MP were discharged after drains were removed; none of the patients required readmission for medical complications. The rate of overall morbidity and pancreatic fistula formation were consistently higher in the MP group compared with the other 2 groups, although the differences did not reach statistical significance (Table II).

Table III. Comparison between middle pancreatectomies performed early (before May 1999) and late (after June 1999)

Variable	*MP early term* (n = *13*)	*Range*	*MP late term* (n = *13*)	*Range*	P *value*
Operative time (min)*	302 ± 65	210–420	289 ± 58	230–430	.605
Blood loss (mL)*	405 ± 255	32–1,028	221 ± 182	38–624	.045
Complication	7		3		.226
Pancreatic fistula	6		2		.202
Relaparotomy	2		1		.999
Bleeding	2		1		.999

*Mean ± SD.

Difference in outcome of MP according to period of operation. Patients treated with MP were divided into 2 groups at the halfway point; 13 patients were treated before May 1999, and 13 were treated after June 1999 (Table III). Blood loss was significantly less in the more recently treated group ($P = .045$). Although no significant difference was observed, there was a tendency toward decreased operating time, decreased incidence of pancreatic fistula formation, and fewer incidences of relaparotomy in the more recently treated group.

Postoperative long-term follow-up. Follow-up was complete and updated in January 2008 in 85% of the patients in the MP group, 86% in the LSP group, and 92% in the RSP group. In addition, all the patients who were lost to follow-up had 1 clinical evaluation performed at least 24 months postoperatively.

Tumor recurrence was observed after 68 months in 1 patient who had IPMC of the noninvasive type. This recurrence was subsequently treated by resection of the proximal remnant pancreas with a segmental duodenectomy followed by a duodeno-duodeno anastomosis and choledocho-duodeno anastomosis as in the procedure of PHRSD[1,2]; no complications or recurrences were observed after operation. All other patients had excellent long-term outcomes.

Of the 26 patients who underwent MP, 1 subsequently underwent DP after the residual left pancreatectomy, and 1 subsequently underwent PD after resection of the proximal remnant pancreas due to tumor recurrence. These patients were classified into the LSP and RSP groups, respectively. Long-term follow-up was performed for 61 RSP, 24 MP, and 36 LSP patients. The results of the various laboratory findings during the postoperative surveillance period are summarized in Table IV. The mean follow-up time was similar among the 3 groups. The postoperative pancreatic endocrine function, as reflected in HbA1c concentrations, was equivalent to the pre-operative values in patients treated with MP, whereas the postoperative HbA1c values in the RSP and LSP groups were significantly elevated. None of the patients in the MP group developed diabetes mellitus postoperatively. There was a statistically significant increase in new onset diabetes mellitus in the LSP group ($P = .032$) compared with the MP group. As for pancreatic exocrine function, only 1 patient in the MP group needed enzyme substitution postoperatively, whereas a statistically significant increase in new onset exocrine insufficiency was observed in the RSP group ($P = .009$).

Four out of 5 parameters measuring nutritional status increased postoperatively in the MP group, whereas 4 out of 5 decreased in both the RSP and LSP groups. The MP group was superior to the other 2 groups in all 5 parameters tested. A statistically significant difference in the concentrations of serum total protein ($P = .006$), serum albumin ($P = .037$), serum total cholesterol ($P = .0006$, $P = .045$), and serum cholinesterase ($P = .036$) were observed between the MP and control groups.

DISCUSSION

In the past, benign tumors of the pancreas and tumors with low malignant potential have been treated with standard resection procedures such as PD or DP. These procedures, although oncologically sound, involve the resection of a considerable amount of normal parenchyma. Enucleation of these tumors has the advantage of preserving more pancreatic parenchyma as well as preservation of the spleen, without a significant increase in the morbidity, mortality, or late sequelae of an extensive resection.[33,34] Enucleation is not always feasible, because unfavorable tumor location such as a tumor involving the main pancreatic duct may make enucleation impossible. Tumors in the neck of the pancreas formerly had to be treated with a subtotal DP or an extended PD, sacrificing a considerable portion of the normal pancreatic

Table IV. Comparisons of long-term follow-up among right side pancreatectomy, middle pancreatectomy, and left side pancreatectomy

Variable	*RSP* (n = 61)	*Range*	*MP* (n = 24)	*Range*	*LSP* (n = 36)	*Range*	P*value* *RSP vs MP*	*MP vs LSP*
Follow-up (mo)*	70 ± 49	12–182	71 ± 43	13–154	63 ± 42	12–148	.664	.192
Exocrine and endocrine function								
Pre-operative HbAc1*	5.6 ± 0.8		5.2 ± 0.5		5.5 ± 0.8			
Postoperative HbAc1*	6.2 ± 0.8#		5.3 ± 0.6		6.3 ± 0.9#			
New-onset diabetes mellitus	7/51 (14%)		0/24		6/32 (19%)		.089	.032
NIDDM	5		0		3			
IDDM	2		0		3			
Enzyme substitution	19 (31%)		1 (4.2%)		1 (2.8%)		.009	.999
Nutritional status								
TP changed rate (%)*	4.4 ± 9.0		7.6 ± 7.4		1.3 ± 8.3		.195	.006
Alb changed rate (%)*	−3.4 ± 11.4		1.4 ± 8.3		−3.3 ± 13.5		.037	.087
T. Chol changed rate (%)*	−11.3 ± 17.8		6.2 ± 24.7		−6.6 ± 22.8		.0006	.045
ChE changed rate (%)*	−8.1 ± 23.2		1.0 ± 25.2		−12.8 ± 20.4		.103	.036
Hb changed rate (%)*	−2.9 ± 12.9		0.7 ± 10.0		−4.3 ± 13.9		.249	.105

*Mean ± SD.
#$P < .05$ by paired t test.
Alb, Albumin; *ChE*, cholinesterase; *Hb*, hemoglobin; *HbA1c*, glycosylated hemoglobin A1c; *IDDM*, insulin-dependent diabetes mellitus; *NIDDM*, noninsulin-dependent diabetes mellitus; *T. Chol*, total cholesterol; *TP*, total protein.

parenchyma. Under such circumstances, the recent reintroduction of MP has attracted much attention.[10-29] MP involves a limited resection of the midportion of the pancreas, thereby preserving both the spleen and most of the pancreatic parenchyma.

MP has been used by experienced pancreatic surgeons for over a decade, but it requires meticulous surgical technique. One of the major deterrents to the widespread acceptance among general surgeons is its high complication rate and, in particular, the formation of a pancreatic fistula.[35] Morbidity among 512 patients from 21 different series was 41%, ranging from 13–62% (Table V). The most frequently reported complication in the literature is the pancreatic fistula, with a frequency that varies from 0–62%, and an overall frequency of 27%. Although comparable with what has been reported in the literature, morbidity and the incidence of pancreatic fistula formation were also high in the current series, and tended to be higher than those following RSP or LSP. In fact the incidence of pancreatic fistula in RSP (18%) and LSP (14%) added up to the incidence in MP (31%) in the current series (Table II), and one could argue that the increase in the site of pancreatic resection in MP simply results in a corresponding increase in pancreatic fistula. Indeed, leakage was commonly observed both from the closed cut edge of the pancreas head and the pancreaticoenterostomy. Since the tumors targeted for resection by MP are relatively small, the main pancreatic duct is generally free from mechanical obstruction or dilation, and the pancreatic parenchyma has usually been minimally affected by pancreatitis. This could have been another reason that pancreatic fistula is commonly observed after MP. Current analysis also revealed a decrease, although not statistically significant, in various surgical complications among patients who had been treated more recently (Table III). MP, after all, is essentially a procedure that consists of a pancreaticoenteric anastomosis and the closure of the proximal cut edge of the pancreas, both of which are procedures familiar to pancreatic surgeons. Although the morbidity remains high, management of the complications in the expert institution eventually resulted in safe recovery.

Although many centers adopt PJ, we believe there is a minimal difference in outcome between these 2 techniques of pancreaticoenterostomy in the setting of MP. Randomized controlled trials have shown no significant difference between PJ and PG after PD regarding overall postoperative complications, pancreatic fistula, intra-abdominal fluid collection, and mortality.[36]

Many cases of MP are intraductal papillary mucinous neoplasms (IPMN), and there have been an increasing number of reports where either IPMN relapse or new primary lesions developed in the remnant pancreas (body or tail) after resection of IPMN.[37] There is no doubt regarding the fact that although endoscopic examination of the distal remnant pancreas is impossible for patients

Table V. Middle pancreatectomy: summary of more than 10 case series in the literature

Author	*Year*	*N*	*Median follow-up (month)*	*Reconstruction PG/PJ*	*Morbidity N (%)*	*Pancreatic fistula N (%)*	*Reoperation N (%)*	*Mortality N*	*Exocrine insufficiency N (%)*	*Endocrine insufficiency N (%)*	*Recurrence N (%)*
Rotman et al[10]	1993	14	36	–/14	4 (29%)	2 (14%)	3 (21%)	0	1 (7%)	0	0
Ikeda et al[11]	1995	24	40	–/24	3 (13%)	3 (13%)	0	0	2 (8%)	0	0
Iacono et al[12]	1998	13	68	–/13	3 (23%)	3 (23%)	0	0	0	0	0
Warshaw et al[13]	1998	12	18	–/12	3 (25%)	2 (17%)	0	0	0	0	0
Sperti et al[14]	2000	10	63	–/10	4 (40%)	3 (30%)	0	0	0	0	0
Yamaguchi et al[15]	2000	10	—	1/9	—	4 (40%)	—	0	0	0	0
Sauvanet et al[16]	2002	53	26	25/26	22 (41%)	16 (30%)	3 (6%)	1	2 (4%)	3 (6%)	4 (15%)
Balzano et al[17]	2003	32	66	–/10	20 (62%)	16 (50%)	0	0	2 (6%)	3 (9%)	0
Shibata et al[18]	2004	10	96	–/10	4 (40%)	3 (30%)	0	0	0	1 (10%)	0
Goldstein et al[19]	2004	12	18	12/–	3 (25%)	0	0	0	0	2 (17%)	0
Efron et al[20]	2004	14	12	14/–	7 (50%)	5 (36%)	2 (14%)	0	0	0	0
Iacono et al[21]	2005	20	—	–/20	7 (35%)	5 (25%)	0	0	0	0	0
Roggin et al[22]	2006	10	14	1/9	6 (60%)	3 (30%)	1 (10%)	0	0	1 (7%)	1 (7%)
Muller et al[23]	2006	40	29	–/40	11 (28%)	3 (8%)	2 (5%)	1	18 (45%)	1 (3%)	1 (3%)
Brown et al[24]	2006	10	24	4/6	6 (60%)	4 (40%)	0	0	0	0	0
Allendorf et al[25]	2007	26	33	26/-	8 (31%)	2 (8%)	0	0	0	2 (8%)	0
Crippa et al[26]	2007	100	55	5/95	58 (58%)	4 (44%)	0	0	5 (5%)	4 (4%)	2 (2%)
Shimada et al[27]	2008	13	27	3/10	6 (53%)	5 (38%)	0	0	0	0	0
Adham et al[28]	2008	50	68	44/6	18 (36%)	5 (10%)	6 (12%)	0	11 (22%)	0	2 (4%)
Ocuin et al[29]	2008	13	22	–/–	5 (38%)	8 (62%)	0	1	1 (10%)	1 (11%)	0
Our case		26	71	24/2	10 (38%)	8 (31%)	3 (12%)	0	1 (4%)	0	1 (4%)
Total		512	—	159/340	208 (41%)	136 (27%)	20 (4%)	3	43 (8%)	18 (4%)	11 (2%)

N, Number of patients.

who have undergone PJ, it remains possible for those who have undergone PG. For instance, if the gastroscope is applied to a patient who has undergone PG, the pancreatic anastomotic site is visible and a biopsy sample can easily be obtained. If the duct orifice of the remnant pancreas is patent, pancreatic duct trees can be delineated by injection of a contrast medium, and even the pancreatic juice can be sampled for cytologic examination, although identification of the remnant pancreatic duct is not always easily performed. Additionally, endoscopic ultrasonography is more effective for PG patients than for PJ patients. These examinations could be valuable in detecting a tumor originating from the pancreatic duct system.[38] Thus, for patients undergoing MP for IPMN, we consider reconstruction with PG.

Since patients who suffer from benign pancreatic tumors can expect a good long-term prognosis, the issues of postoperative pancreatic functions and nutritional status are particularly important. The strength of MP is in the preservation of the exocrine and endocrine functions of the pancreas and an improvement in nutritional status through sparing of the unaffected pancreatic parenchyma, particularly the body-tail segment where the islet cells seem to be more densely distributed. In patients with normal pancreatic parenchyma, the incidence of diabetes mellitus ranges from 10–24% after PD[39,40] and from 8–60% after DP.[22,41] In the presence of chronic pancreatitis, this ratio rises to as high as 40% after PD and to 85% after DP.[40,42] In the current series, there were no cases of new onset diabetes mellitus observed among the patients treated with MP, whereas 19% of patients became diabetic after LSP ($P = .032$). Although derived from a retrospective analysis, this finding reinforces previous data from the literature demonstrating preservation of pancreatic endocrine function after MP (Table V). A comparison in terms of the incidence of enzyme substitution between MP (4%) and RSP (32%) in the current series confirms the superiority of this organ-preserving procedure ($P = .009$). In previous reports on PD, the incidence of impaired pancreatic exocrine function ranged from 30–60% even in the absence of chronic pancreatitis,[39,40] whereas exocrine insufficiency was observed in only 8% of patients after MP.[10-29] After a mean follow-up interval of 71 months, the postoperative nutritional status in the MP group was never less than the pre-operative status in the current series, whereas several parameters remained below the pre-operative level after RSP or LSP.