as well as metachronous diseases in the remnant pancreas during surveillance after resection of IPMNs.

Recent advances in molecular biology have provided many insights into biological behaviors of IPMNs as well as PDACs,[22–26] however, molecular analyses regarding genetic changes in multiple occurrences of IPMNs and PDACs in the same pancreas have not been used to date. Others recently have shown that patients with IPMNs often have extrapancreatic tumors[1,21] and therefore patients with IPMNs might have some systemic genetic abnormalities causing carcinogenesis. Those types of investigations would provide some hints for the early detection of PDACs during management of IPMNs.

In conclusion, intense long-term, follow-up evaluation is necessary for the early detection of metachronous occurrence of IPMNs as well as distinct PDACs after resection of IPMNs.

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Prognostic Implications of Lymph Node Metastases in Carcinoma of the Body and Tail of the Pancreas

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Objective: The current classification of pancreatic cancer is based only on anatomic location of metastatic lymph nodes (LNs). On the other hand, the number of metastatic LNs has been used in staging of colorectal, esophageal, and gastric cancers. The aim of this study was to assess the prognostic impact of the number or ratio of the metastatic LNs in pancreatic body and tail carcinoma.

Methods: Eighty-five patients with pancreatic body and tail adenocarcinoma who underwent pancreatectomy were included. Location, number, ratio of metastatic LNs, and the survival of patients were analyzed.

Results: Forty patients with LN metastasis had poor prognosis ($P = 0.007$). The prognoses of patients with 5 or more metastatic LNs were poorer than those with less than 5 metastatic LNs ($P = 0.046$), and patients with a metastatic LN ratio of 0.2 or more had the worst prognosis. Multivariate analysis revealed that 5 or more metastatic LNs and metastatic LN ratio of 0.2 or more were independent prognostic factors for survival ($P = 0.0015$ and $P = 0.014$, respectively).

Conclusion: These results indicate that the number and the ratio of metastatic LNs can be used to predict poor patient survival and as a staging strategy.

Key Words: lymph node metastasis, metastatic lymph node ratio, left-sided pancreatic cancer, distal pancreatectomy

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Pancreatic cancer continues to be the gastrointestinal malignancy with the worst prognosis, with only 3% of the patients surviving 5 years after diagnosis.[1] In particular, carcinoma of the body and tail of the pancreas has dismal prognosis because it often develops without symptoms leading to inability to resect the carcinoma at the time of diagnosis.[2–4] Nevertheless, extended pancreatectomy with lymph node dissection remains the only chance for cure of the disease.

Many prognostic markers such as lymph node metastasis, resection margin, and residual tumor have been identified.[5] Pancreatic cancer frequently spreads to lymph nodes and surrounding tissues such as nerve plexi and vessels.[6] Several factors have been reported to be relevant for survival of patients with pancreatic cancer,[7–9] and many studies identified that lymph node metastasis results in a dismal prognosis in pancreatic cancer.[10–14] In this study, the prognostic influence of lymph node metastasis focusing on left-sided pancreatic cancer is anticipated owing to the fact that previous reports of lymph node metastasis focused primarily on pancreatic head cancer. It is believed that there is a difference in clinical characteristics between pancreatic head cancer and left-sided cancer owing to the anatomic location and lymph stream. Therefore, they must be considered separately.

In staging of pancreatic cancer, the classifications of the Union Internationale Contra le Cancer (UICC) and the Japan Pancreas Society consider only anatomic location of metastatic lymph nodes.[15,16] On the other hand, the number of metastatic lymph nodes has been used in staging of colorectal, esophageal, and gastric cancers.[16–20] Furthermore, current data in various gastrointestinal system cancers have emphasized the importance of the ratio of metastatic to examined lymph nodes on patients' prognosis.[21–23] There are similar studies of pancreatic head cancer that also concluded that metastatic lymph node ratio is an independent risk factor for poor survival[24]; however, there is no study evaluating the detailed influence of lymph node metastasis focused on carcinoma of the body and tail of the pancreas. Therefore, the aim of this study was to assess the impact of lymph node metastasis on patients' survival in left-sided pancreatic cancer.

MATERIALS AND METHODS

Patients and Operative Procedure

A total of 553 patients with pancreatic cancer who underwent surgery between October 1991 and November 2010 were retrieved from the prospective database of the Department of Surgery II, Nagoya University. Among these patients, 132 had carcinoma mainly at the pancreatic body and tail. Forty-seven of 132 cases were excluded because they were not resectable owing to distant metastasis or locally advanced disease, and 85 patients who underwent radical pancreatectomy with lymph node dissection were selected for analyses. Lymph node dissection including lymph nodes along the common hepatic artery (lymph node No. 8), the splenic artery (lymph node No. 11), inferior edge of the pancreas (lymph node No. 18), and lymph nodes at the splenic hilum (lymph node No. 10) during distal pancreatectomy was routinely performed (Fig. 1).[25] Para-aortic lymph node dissection was not routinely performed unless it was needed to obtain a negative retroperitoneal margin. During surgery, resection margins were carefully evaluated pathologically including the remnant pancreas and retroperitoneal region. To obtain a clear margin, resection of the portal vein or the superior mesenteric vein was aggressively performed when invasion was determined.[26] Spleen-preserving surgery, laparoscopic surgery, and neoadjuvant radiotherapy or chemotherapy were not performed in our institution. This study covered almost

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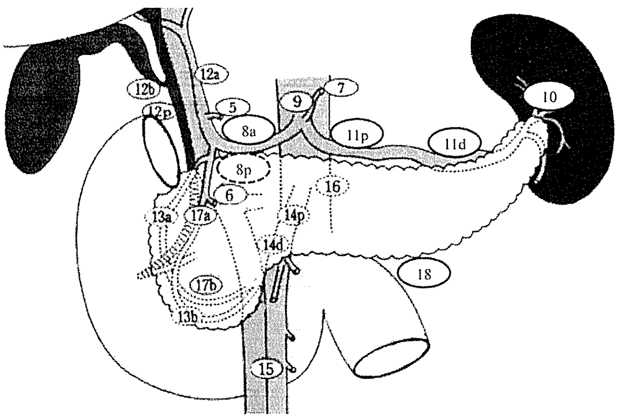

FIGURE 1. Summary of the lymph node stations according to the classification of pancreatic carcinoma proposed by the Japan Pancreas Society. Regional lymph nodes are as follows: No. 8a, lymph nodes in the anterosuperior group along the common hepatic artery; No. 8p, lymph nodes in the posterior group along the common hepatic artery; No. 10, lymph nodes at the splenic hilum; No. 11p, lymph nodes along the proximal splenic artery; No. 11d, lymph nodes along the distal splenic artery; No. 18, lymph nodes along the inferior margin of the pancreas.

19 years; however, principles in the surgical approaches have remained consistent.

In the present study, the adjacent lymph nodes were assigned to the regional lymph nodes according to the classification of Japanese Pancreatic Society (lymph node nos. 8, 10, 11, and 18; Fig. 1),[15] because the Japanese Pancreatic Society classified the localization of the lymph nodes in more detail than the UICC. The lymph nodes were microscopically analyzed using standard hematoxylin-and-eosin staining technique. Tumors were graded according to the UICC *TNM Classification of Malignant Tumors*.[16] The total number of lymph nodes excised and the number of positive nodes were also analyzed. The ratio of metastatic lymph node to examined metastatic lymph node was determined by dividing the total number of metastatic lymph nodes by the total number of examined nodes. In the analysis of the prognostic value of metastatic lymph node ratio, patients with less than 5 examined nodes were excluded from this analysis because there is a possibility that the metastatic lymph node ratio in these patients is underestimated or overestimated.

Statistical Analysis

The χ^2 test was used to analyze the correlation between lymph node metastasis and clinicopathological parameters and the differences among the numerical data between the 2 groups. Overall survival rates were estimated using the Kaplan-Meier method, and the differences in the survival curves were analyzed using a log-rank test. A multivariate analysis was performed using a Cox regression model including variables that have a $P < 0.05$ by a log-rank test, as covariates of the final model. Two multivariate analyses were performed: one with the number of metastatic lymph nodes and another with metastatic lymph node ratio as one of the covariates. Statistical analysis was performed using SPSS Statistics 17.0 software (SPSS Inc, Chicago, Ill).

RESULTS

Among the patients, 57 were men and 28 were women, with a mean age of 63.5 years (38–79 years). Most tumors (70 patients) were located at the pancreatic body. The most frequently performed operative procedure was distal pancreatectomy (76 patients [89%]). Resections of the portal vein system and the major arteries were performed in 20 and 2 patients, respectively. There were no operative deaths, and median survival time was 12.8 months. The overall survival rates were 54.8% at 1 year, 20.7% at 2 years, and 8.3% at 3 years. Patients' demographic and pathologic data including the histopathological type and stages of the patients' disease are summarized in Table 1.

The mean number of dissected lymph nodes was 18.1 (2–67), and 40 patients (47.1%) had lymph node metastasis. The anatomic localizations of the metastatic lymph nodes are summarized in Table 2. The most frequently observed site was along the splenic artery (lymph node No. 11 in the Classification of Japanese Pancreas Society) and was present in 19 patients (27.1%). Prognosis of the patients with lymph node metastasis was significantly worse than those without lymph node involvement (median survival time, 11.4 and 15.8 months, respectively; $P = 0.007$; Fig. 2A). However, interestingly, no significant difference was found in the prognosis between the patients with metastasis only to adjacent lymph nodes and those with involvement of the distant lymph nodes (median survival time, 12.8 and 10.7

TABLE 1. Demographics and Clinical Characteristics of 85 Patients

	Value
Age, yrs*	63 (38–79)
Sex (male/female)	57/28
Tumor Location	
Body	70
Tail	15
Operation	
Distal pancreatectomy	76
Total pancreatectomy	9
Vascular Resection	
Portal vein resection	20
Major artery resection†	2
Combined Resection of Other Organs‡	10
Intraoperative Radiation Therapy	53
Histopathologic Type	
Well	8
Moderate	58
Poor	11
Papillary	5
Adenosquamous	3
UICC (7th) Stage	
IA	2
IB	2
IIA	28
IIB	35
III	2
IV	16
Median Survival Time, months	12.8

*Value is median (range).

†Major artery indicates the celiac artery and the common hepatic artery.

‡Resected organs include stomach, colon, and/or left kidney.

TABLE 2. Anatomic Localization of the Lymph Node Involvement in 85 Patients With Carcinoma of the Body and Tail of the Pancreas

Lymph Node Station*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Involvement†	0	0	2/8	0/4	0/2	0/11	0/17	5/60	6/17	2/62	19/70	1/19	3/10	9/31	1/9	5/28	3/10	5/31
Percent	0	0	25.0	0	0	0	0	8.3	35.3	3.2	27.1	5.3	30.0	29.0	11.1	17.9	30.0	16.1

*Lymph node classification is according to the classification of Japan Pancreas Society.[15]

†Lymph node involvement indicates the number of patients.

months, respectively; $P = 0.99$; Fig. 2B). Next, median survival time of the patients with less than 5 lymph node metastases was 11.5 months, whereas it was significantly reduced to 5.6 months in the patients with 5 or more metastatic lymph nodes ($P = 0.046$; Fig. 3A). When the patients' metastatic lymph node ratio was evaluated, the median survival time of the patients with a metastatic lymph node ratio of 0.2 or more was significantly shorter than patients with a metastatic lymph node ratio of less than 0.2 (median survival time, 5.6 and 12.8 months, respectively; $P = 0.007$). There was no statistically significant difference in survival between patients without lymph node metastasis and those with a metastatic lymph node ratio of less than 0.2 (Fig. 3B).

Furthermore, the correlations between overall survival and other clinicopathological parameters such as age, sex, tumor size, combined resection of other organs, tumor differentiation, pathological bile duct invasion, duodenal invasion, anterior serosal invasion, retropancreatic tissue invasion, portal venous system invasion, arterial system invasion, extrapancreatic nerve plexus invasion, dissected peripancreatic tissue margin, lymphovascular invasion, intrapancreatic nerve invasion, peritoneal washing cytology, the number of metastatic lymph nodes, and metastatic lymph node ratio were investigated. In the univariate analysis, poor tumor differentiation ($P < 0.0001$), duodenal invasion ($P = 0.0008$), arterial system invasion ($P = 0.025$), and extrapancreatic nerve plexus invasion ($P = 0.013$) were identified as statistically significant adverse prognostic factors in addition to 5 or more metastatic lymph nodes and metastatic lymph node ratio of 0.2 or more. Each of multivariate analyses identified 5 or more metastatic lymph nodes (odds ratio, 3.93; 95% confidence interval [CI], 1.69–9.15; $P = 0.0015$) and metastatic

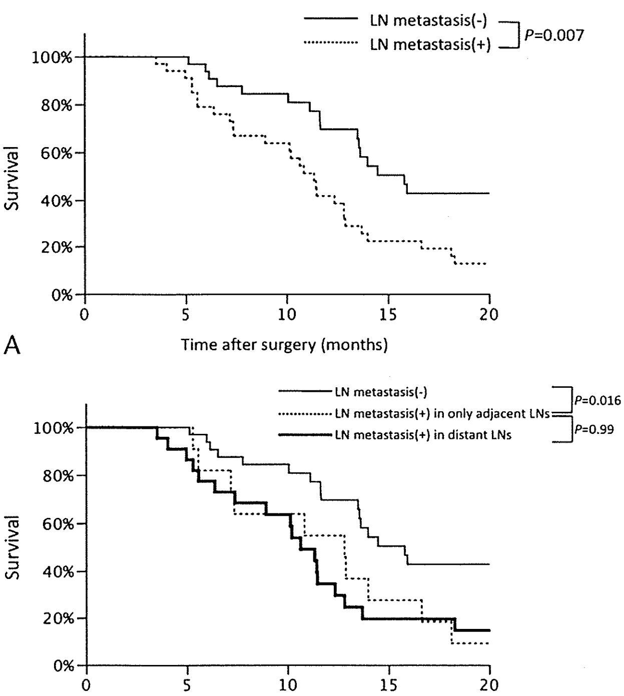

FIGURE 2. A, The overall survival rate of patients with and without lymph node metastases ($P = 0.007$). B, The overall survival of patients with metastasis only to the adjacent lymph nodes and those with involvement of the distant lymph nodes. LN indicates lymph node. No significant difference was found in the prognosis between patients with metastasis only to adjacent lymph nodes and those with involvement of the distant lymph nodes ($P = 0.99$).

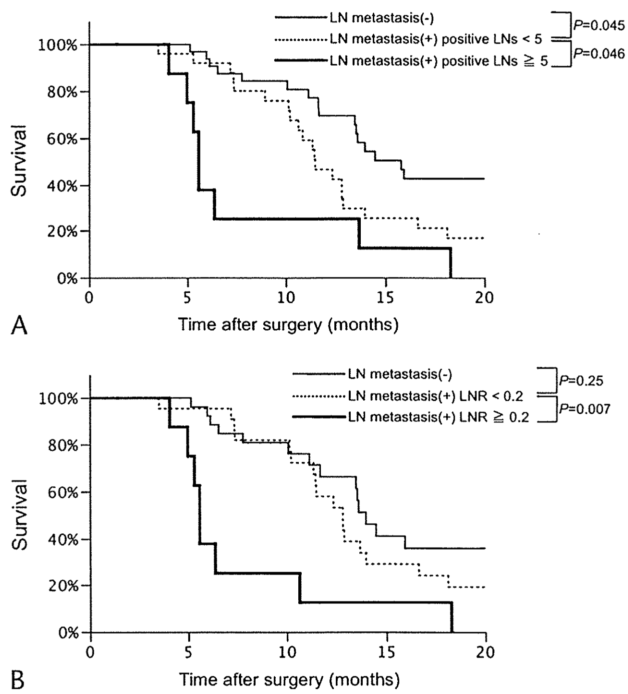

FIGURE 3. A, Association between the number of metastatic lymph nodes and the survival of patients with carcinoma of the body and tail of the pancreas. Median survival time of patients with less than 5 lymph node metastases was 11.5 months, whereas it was significantly reduced to 5.6 months in patients with 5 or more metastatic lymph nodes ($P = 0.046$). B, The impact of positive lymph node ratio on the survival of patients. Median survival time of patients with metastatic lymph node ratio of 0.2 or more was significantly shorter than that of patients with metastatic lymph node ratio of less than 0.2 (median survival time, 5.6 and 12.8 months, respectively; $P = 0.007$). LNR indicates metastatic lymph node ratio.

TABLE 3. Multivariate Analysis of 85 Patients With Carcinoma of the Body and Tail of the Pancreas

Variable	Odds Ratio	95% CI	*P*
A			
Poor tumor differentiation	4.11	1.94–8.71	0.0002*
Duodenal invasion	0.82	0.08–8.03	0.87
Arterial system invasion	1.37	0.67–2.82	0.090
Extrapancreatic nerve plexus invasion	1.67	0.86–3.24	0.13
Five or more metastatic lymph nodes	3.93	1.69–9.15	0.0015*
B			
Poor tumor differentiation	2.89	1.27–6.57	0.011*
Duodenal invasion	1.57	0.17–14.78	0.69
Arterial system invasion	7.21	0.36–3.14	0.20
Extrapancreatic nerve plexus invasion	1.43	0.70–2.92	0.33
Positive lymph node ratio of 0.2 or more	2.99	1.25–7.12	0.014*

*Statistically significant.

lymph node ratio of 0.2 or more as an independent prognostic factor for survival (odds ratio, 2.99; 95% CI, 1.25–7.12; $P = 0.014$; Table 3).

DISCUSSION

Carcinoma of the body and tail of the pancreas frequently involves the lymph nodes, and the lymph node metastasis rate is reported to range from 56% to 86.4%.[27,28] Lymph node metastasis of the pancreatic head cancer tends to show a continuous and convergent pattern toward the superior mesenteric artery and the hepatic portal region, whereas pancreatic body and tail cancers tend to show a divergent pattern toward the celiac axis.[29] Through the splenic artery route, pancreatic body and tail cancers disseminate widely to the retroperitoneal region, para-aortic regions, and to other parts of the periglandular lymph nodes.[29] In the current study, most frequent sites of lymph node metastasis were Nos. 11, 14, 8, and 9 in decreasing order, which was consistent with previous reports.[2,12,29]

Current classifications of UICC and Japanese Pancreas Society for pancreatic cancer define "N" categories only based on anatomical location of the metastatic lymph nodes. In the latest UICC staging classification, N factor is classified into the following categories in pancreatic body and tail cancer: N0, no regional lymph node metastasis; and N1, lymph node metastasis in regional lymph nodes (which is equivalent to lymph node Nos. 8, 10, 11, 14, and 18 in the classification of Japanese Pancreas Society). Metastasis to other distant lymph nodes is defined as distant metastasis (M1).[16] Likewise, the sixth edition of the *Classification of Pancreatic Carcinoma* by the Japanese Pancreas Society (2009) defines lymph node metastasis as follows: N0, no lymph node metastasis; N1, metastasis only to the regional lymph nodes (lymph node Nos. 8, 10, 11, and 18); N2, metastasis to lymph node Nos. 7, 9, 14, and 15; N3, metastasis to lymph node Nos. 5, 6, 12, 13, 16, and 17.[15] However, the number of metastatic lymph nodes has recently become a determinant of N grading of the UICC classification in other digestive system cancers, such as gastric cancer and colorectal cancer. In addition, there have been several reports of the usefulness of metastatic lymph node ratio on patient prognosis in various malignancies including pancreatic head cancer.[21–23]

In this study, no correlation was found between the anatomical location of the metastatic lymph node and the survival of the patients, whereas the number of metastatic lymph nodes and the rate of positive lymph nodes were found to be remarkably associated with survival and were each significant as independent prognostic factors. These results suggest that the N categories could be more informative if classified based on these parameters. It is assumed that carcinoma of the body and tail of the pancreas has a unique biology and intricate lymph stream, which may be the reason why the location of metastatic lymph node was not as relevant as has previously been expected. The only problem is that the classification based on the number of metastatic lymph nodes or metastatic lymph node ratio could be influenced by the extent of lymph node dissection. Limited dissection or inadequate evaluation of the resected specimens could result in an extraordinarily small number of lymph node retrieval, and this could overestimate the metastatic lymph node ratio while underestimating the number of metastatic lymph nodes. This is also emphasized by Han et al[30] who also concluded that radical resection is necessary to accurately determine lymph node status and therefore enhance the survival and cure rate of the patients undergoing resection. Thus, a large-scale study is warranted to determine the minimal requirement in the number of dissected lymph nodes.

In summary, evaluation of metastatic lymph node ratio and the number of metastatic lymph node itself provides a reliable tool to assess the metastatic lymph node burden. An aggressive and thorough lymph node dissection should be provided in patients with pancreatic body and tail cancer to improve postoperative prognosis through accurate staging of the disease.

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Comparison of Pancreatic Head Resection With Segmental Duodenectomy and Pylorus-Preserving Pancreatoduodenectomy for Benign and Low-Grade Malignant Neoplasms of the Pancreatic Head

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Objective: The aim of this study was to investigate the clinical benefits of pancreatic head resection with segmental duodenectomy (PHRSD) with a particular emphasis on the long-term outcome.

Methods: A retrospective analysis of PHRSD (77 patients) and pylorus-preserving pancreatoduodenectomy (PPPD; 55 patients) was performed for benign and low-grade malignant neoplasms of the pancreatic head. The zintraoperative and postoperative courses and long-term nutritional statuses were compared.

Results: The mean operative time and blood loss were significantly less in the PHRSD group than in the PPPD group (351 vs 395 minutes, $P = 0.005$; and 474 vs 732 mL, $P < 0.0001$, respectively). Fewer overall postoperative complications occurred in the PHRSD group than in the PPPD group (33.8% vs 52.7%, respectively, $P = 0.03$). Postoperative weight loss and changes in the serum total protein and albumin levels were significantly milder in the PHRSD group than in the PPPD group ($P = 0.04$, $P = 0.04$, and $P = 0.046$, respectively). The overall recurrence-free survival rates in patients with noninvasive intraductal papillary mucinous neoplasms were equivalent in both groups.

Conclusions: The present results suggest that PHRSD fulfills the operative safety, long-term nutritional status, and curative goals and could be the best option for patients with benign or low-grade malignant pancreatic lesions.

Key Words: PHRSD, PPPD, IPMN, pancreas, organ-preserving, low-grade malignancy

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Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas comprise a spectrum of diseases that exhibit different degrees of malignancy, ranging from adenoma with mild atypia to invasive carcinoma.[1,2] Although some cases of invasive intraductal papillary mucinous carcinoma (IPMC) have a dismal prognosis, most IPMNs, including noninvasive IPMCs, have a more favorable prognosis than pancreatic ductal adenocarcinoma.[3–5] Recently, the development of imaging studies has facilitated the detection of IPMNs,[6,7] and consequently, the opportunity for surgical resection of benign or low-grade malignant IPMNs before they become invasive has increased. A number of less invasive techniques, such as duodenum-preserving pancreatic head resection or ventral pancreatectomy, for benign or low-grade malignant IPMNs have been reported.[8–12]

In the past, the classic Whipple procedure (pancreatoduodenectomy) was the standard technique for any lesions of the peripancreatic head.[13] However, this operation is associated with a number of possible adverse events including postoperative complications and long-term nutritional disorders with notable weight loss. Pylorus-preserving pancreatoduodenectomy (PPPD) has replaced this as the principal procedure. However, there is no evidence from prospective studies to indicate the overwhelming superiority of PPPD compared with the classic Whipple procedure. Recently, some randomized controlled trials and meta-analyses revealed that both procedures were comparable in postoperative complications, long-term results, and quality of life.[14–17] Pancreatic head resection with segmental duodenectomy (PHRSD) was reported in 1994 as an organ-preserving procedure for benign or low-grade malignant tumors of the pancreatic head.[18–21] In PHRSD, only a 3- to 4-cm segment of the duodenum is resected, and the major portion of the duodenum is preserved, in contrast to PPPD. Motilin, a polypeptide hormone released in response to alkaline conditions in the duodenum, is well known to induce phase 3 contractions of the interdigestive migrating complex and to play a pivotal role in the acceleration of gastrointestinal motility. It has been speculated that preservation of motilin exerts a favorable influence on absorption in patients who have undergone PHRSD.[22–24]

There have been few reports on the long-term benefits of these organ-preserving techniques. The original purpose of these procedures is not to preserve the organ itself but to improve the long-term nutritional status and quality of life of the patients. Therefore, the utility of these techniques needs to be evaluated. In the present study, the clinical benefits of PHRSD, with a particular emphasis on the long-term nutritional consequences, were investigated. The long-term surgical outcomes of noninvasive IPMNs were also explored to evaluate the validity of the operative procedures.

MATERIALS AND METHODS

Between July 1991 and December 2009, 660 patients underwent pancreatic resection at the Department of Surgery II, Nagoya University. Among these patients, 132 consecutive patients who underwent PHRSD or PPPD for benign or low-grade malignant neoplasms of the pancreatic head were retrieved from the

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prospective database. Preoperative computed tomography and ultrasonography were routinely performed, and endoscopic ultrasonography, magnetic resonance imaging, and endoscopic retrograde cholangiopancreatography were performed as necessary to obtain further information regarding the lesions. High-grade malignant neoplasms such as pancreatic adenocarcinomas, invasive IPMCs, malignant endocrine tumors, and advanced cancers of papilla of Vater were excluded from the analysis because of their possible influences on the general condition and nutritional status of the patients. Patients with recurrence and those who underwent adjuvant chemotherapy during the follow-up period were also excluded for the same reasons. Pancreatic head resection with segmental duodenectomy was generally considered for patients with benign or low-grade malignant lesions, whereas PPPD was indicated when a preoperative or intraoperative diagnosis of moderate or high malignancy was suspected. Pylorus-preserving pancreatoduodenectomy was also performed in patients with vascular malformations or pancreatitis of the pancreatic head region. Patients who underwent additional procedures beyond the standard PPPD technique, such as extensive lymph node dissection and vascular resection, were also excluded from the analysis. Written informed consent, as required by the Institutional Review Board of Nagoya University, was obtained from all patients.

Pancreatic head resection with segmental duodenectomy was performed as previously reported.[18,19] Briefly, the pancreatic head was completely resected with the lower bile duct and a 3- to 4-cm segment of the duodenum including the major and minor papillae. The gastroduodenal artery was preserved, and the pancreatic parenchyma was carefully exfoliated from the fusion fascia of Treitz, taking care not to damage the fascia. This attentive manipulation allowed the duodenal branches of the anterior inferior pancreatoduodenal artery to be preserved in PHRSD, in contrast to PPPD. Reconstruction of the alimentary tract was performed with pancreatogastrostomy, end-to-end duodenoduodenostomy, and end-to-side choledochoduodenostomy. In PPPD, reconstruction was performed by a Traverso method and consisted of end-to-side pancreatojejunostomy, end-to-side choledochojejunostomy, and gastroenterostomy. Oral intake was routinely started at 7 to 10 days after surgery unless postoperative complications occurred.

Postoperative complications were evaluated based on a modified Clavien grading system as follows: grade 1 indicates deviation from the normal postoperative course without need for therapy; grade 2, complication requiring pharmacologic treatment; grade 3, complication requiring surgical, endoscopic, or radiologic intervention (3a/b: without/with general anesthesia); grade 4, life-threatening complication requiring intensive care; grade 5, death.[25,26] The classification system of the International Study Group of Pancreatic Fistula[27] was used to estimate pancreatic fistulae, and grade B (fistula requiring any therapeutic intervention) or higher was regarded as significant. The diagnosis of delayed gastric emptying was based on the classification of the International Study Group of Pancreatic Surgery,[28] and grade B or higher was regarded as significant.

Computed tomography or endoscopic ultrasonography was routinely performed every 6 months as a postoperative follow-up imaging examination. A blood test was performed every 2 months. The median follow-up periods were 45.6 months in the PHRSD group and 42.5 months in the PPPD group. The serum levels of hemoglobin A1c, new-onset diabetes mellitus, and pancreatic enzyme substitution were evaluated to assess the long-term outcome of the pancreatic function. Patients with clinical suspicion of exocrine insufficiency such as a 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. The long-term nutritional status was explored by changes in the body weight of the patients and blood examinations. The following items served as candidates for nutritional immunologic factors: total lymphocyte count, hemoglobin, platelet count, total protein, albumin, total cholesterol, triglyceride, cholinesterase, and fasting blood glucose. The following formula was then applied: (postoperative numerical value − preoperative numerical value)/preoperative numerical value × 100 (%). Furthermore, the incidence of recurrence and recurrence-free survival (RFS) of noninvasive IPMNs (adenoma, borderline, and carcinoma in situ [CIS]) were also analyzed.

Statistical Analysis

Differences in numerical data between the 2 groups were examined using a χ^2 test or Fisher exact test for $n < 5$. The Mann-Whitney U test was used for quantitative variables. Survival was estimated using the Kaplan-Meier method, and differences in the survival curves were analyzed using a log-rank test. All statistical analyses were performed using the software StatView Version 5.0 (Abacus Concepts, Berkeley, Calif). All continuous data are presented as the mean (SD). The presence of a statistically significant difference was denoted by $P < 0.05$.

RESULTS

Patient Characteristics and Surgical Treatments

The characteristics of the 132 patients are summarized in Table 1. The patients were followed up for a median period of 44.2 months or until death. Overall, 77 patients who underwent PHRSD, comprising 45 males and 32 females with a mean age of 61.0 years (range, 26–84 years), were compared with 55 patients who underwent PPPD, comprising 35 males and 20 females with a mean age of 62.4 years (range, 20–82 years). Among the patients, 51 of the 77 PHRSD patients and 33 of the 55 PPPD patients had IPMNs.

TABLE 1. Demographics and Clinical Characteristics of 132 Patients

	PHRSD	PPPD	*P*
No. patients	77	55	
Age, mean (range), yr	61.0 (26–84)	62.4 (20–82)	0.18
Sex (male/female)	45/32	35/20	0.59
Type of neoplasms, n (%)			
IPMN	51 (66.2)	33 (60.0)	0.12
Endocrine tumor	6 (7.8)	0	
Carcinoma of papilla of Vater	4 (5.2)	7 (12.7)	
Chronic pancreatitis	3 (3.9)	4 (7.3)	
Serous cyst neoplasm	3 (3.9)	3 (5.5)	
Duodenal carcinoid tumor	3 (3.9)	0	
Others	7 (9.1)	8 (14.5)	
Preoperative diabetes mellitus, n (%)			
Absent	65 (84.4)	44 (80.0)	0.64
Present	12 (15.6)	11 (20.0)	
Preoperative body mass index, mean (range)	21.8 (16.0–28.3)	21.7 (14.9–32.4)	0.74

TABLE 2. Comparisons of Perioperative and Short-Term Follow-Up

	PHRSD	PPPD	P
No. patients	77	55	
Perioperative variables			
Operative time, mean (SD), min	351 (61)	395 (110)	0.005*
Blood loss, mean (SD), mL	474 (192)	732 (471)	<0.001*
Blood transfusion, (%)	4 (5.2)	9 (16.4)	0.04*
Postoperative results, n (%)			
Mortality	0	0	>0.99
Overall morbidity (Clavien grade 3 or higher)	26 (33.8)	29 (52.7)	0.03*
Pancreatic fistula (ISGPF grade B or higher)	23 (29.9)	22 (40.0)	0.27
Delayed gastric emptying (ISGPS grade B or higher)	14 (18.2)	15 (27.3)	0.29
Length of the hospital stay, mean (SD), d	46.1 (15.8)	46.6 (18.8)	0.86
Days to start oral intake, mean (SD), d	12.8 (13.2)	15.2 (12.2)	0.18

*Statistically significant.

ISGPF indicates International Study Group of Pancreatic Fistula; ISGPS, International Study Group of Pancreatic Surgery.

Perioperative Results

There were no operative or hospital deaths. The mean operative time and blood loss were significantly less in the PHRSD group than in the PPPD group (351 vs 395 minutes, $P = 0.005$, and 474 vs 732 mL, $P < 0.001$, respectively; Table 2). The incidence of perioperative blood transfusion was also significantly less in the PHRSD group than in the PPPD group ($P = 0.04$). The overall postoperative complications (Clavien grade 3 or higher) were significantly decreased in the PHRSD group compared with the PPPD group ($P = 0.03$). The rate of pancreatic fistula formation (International Study Group of Pancreatic Fistula grade B or higher) tended to be lower in the PHRSD group than in the PPPD group, but there were no differences between the 2 groups ($P = 0.27$). The incidence of delayed gastric emptying, the length of hospital stay, and the number days to initiation of oral intake were equivalent between the 2 groups.

Postoperative Long-Term Results

Regarding the long-term nutritional status, there was no significant difference between the 2 groups for the incidence of new-onset diabetes mellitus, reflecting the endocrine function of the pancreas (Table 3). With respect to the exocrine function, however, there was a significant increase in the postoperative requirement for enzyme substitution in the PPPD group compared with the PHRSD group ($P = 0.04$). Postoperative body weight loss and changes in the levels of serum total protein and albumin were significantly less in the PHRSD group than in the PPPD group ($P = 0.04$, $P = 0.04$, and $P = 0.046$, respectively; Table 4). The PHRSD group was inclined to show superior outcomes to the PPPD group in all 10 parameters examined.

Incidence of IPMN Recurrence

Fifty-one patients in the PHRSD group and 33 patients in the PPPD group were analyzed to assess the recurrence rates of noninvasive IPMNs (benign IPMNs and CIS). All recurrences occurred in the remnant pancreas of the adenoma patients in both the PHRSD and PPPD groups, as well as in the CIS patients. The overall recurrence rates were comparable between the PHRSD group (2/51) and PPPD group (2/33). All recurrences occurred in the remnant pancreas and were considered to be consequences of multicentric tumorigenesis because no recurrences were observed at the true resection margin of the previous surgery. No extrapancreatic recurrences were observed. The overall RFS

TABLE 3. Comparisons of Long-Term Pancreatic Function

	PHRSD	PPPD	P
No. patients	77	55	
Median follow-up period, mo	45.6	42.5	0.81
Endocrine function			
Preoperative hemoglobin A1c, mean (SD), %	5.6 (0.8)	6.4 (1.5)	0.09
Postoperative hemoglobin A1c, mean (SD), %	6.1 (0.9)	6.6 (1.6)	0.24
New-onset diabetes mellitus, n (%)	4 (5.2)	5 (9.1)	0.49
Exocrine function, n (%)			
Enzyme substitution	22 (28.6)	26 (47.3)	0.04*

*Statistically significant.

TABLE 4. Comparisons of Long-Term Nutritional Status

	PHRSD	PPPD	P
No. patients	77	55	
Body weight loss, kg	2.1 (3.7)	5.7 (8.7)	0.04*
Total lymphocyte count change rate, %	10.2 (41.4)	11.5 (53.5)	0.90
Hemoglobin change rate, %	−1.1 (9.0)	−2.9 (14.9)	0.24
Platelet change rate, %	0.3 (25.0)	−5.9 (31.5)	0.33
Total protein change rate, %	3.6 (7.4)	−0.4 (11.5)	0.04*
Albumin change rate, %	0.2 (7.6)	−7.1 (15.0)	0.046*
Total cholesterol change rate, %	−7.9 (18.3)	−10.0 (32.5)	0.21
Triglyceride change rate, %	−10.7 (34.2)	−47.6 (36.7)	0.04*
Cholinesterase change rate, %	3.5 (26.6)	−7.4 (35.1)	0.14
Fasting blood glucose change rate, %	7.6 (32.3)	15.3 (61.3)	0.93

Values are mean (SD) as a percentage of predisease values.

*Statistically significant.

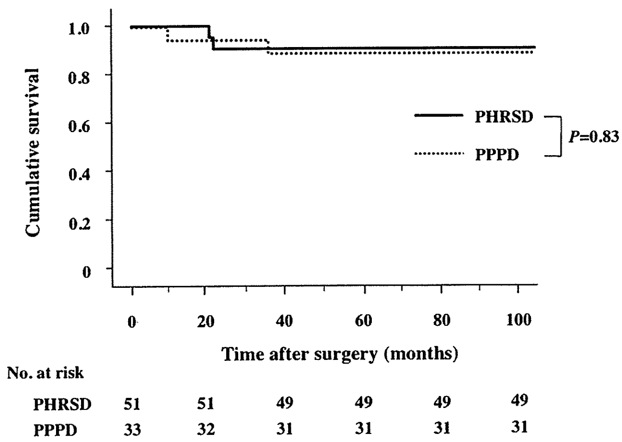

FIGURE 1. Actuarial Kaplan-Meier analysis of RFS in 84 patients with histologically confirmed noninvasive IPMNs who underwent PHRSD or PPPD. $P = 0.83$ (log-rank test).

rates were equivalent between the 2 groups (5-year RFS, 88.9% for PHRSD vs 88.4% for PPPD, $P = 0.83$; Fig. 1).

DISCUSSION

Recently, the development of imaging studies has contributed to the early detection of asymptomatic benign or low-grade malignant tumors of the pancreas, such as IPMNs and endocrine tumors.[6,29] Before, the classic Whipple procedure was performed as the standard technique, even for indolent tumors of the pancreatic head. Given the favorable prognosis and noninvasive nature of tumors with low-grade malignancy, functional preservation that leads to clinical benefits in the long-term has begun to attract more attention, and several organ-preserving limited resections of the pancreas have been proposed as alternative techniques.[18–21,30,31] However, these limited procedures have failed to achieve widespread acceptance. This situation may partly have arisen because the long-term postoperative results and safety profiles of these operations remain unknown, and the benefits of these techniques have not been robustly shown.

Local resection of the pancreas, that is, enucleation, ventral pancreatectomy, or inferior pancreatic head resection, is technically intricate and is associated with intolerable postoperative complications, especially pancreatic fistulae.[32] Moreover, complete resection of the pancreatic head is preferable for tumors, such as IPMNs, which have malignant potential and risk of recurrence. One patient with an IPMN developed peritoneal dissemination and died of recurrence at 18 months after inferior head resection.[33] Duodenum-preserving pancreatic head resection for IPMN may not be an appropriate procedure. Preservation of the lower bile ducts and their blood supply involves the risk of a residual portion of the pancreatic parenchyma, which may result in pancreatic fistula formation or tumor recurrence.[34] In contrast, complete removal of the pancreatic parenchyma can potentially lead to necrosis or perforation of the lower bile ducts.

Pancreatic head resection with segmental duodenectomy seems to be a theoretically well-balanced and desirable procedure, with regard to postoperative complications and the risk of recurrence. However, there has only been 1 report comparing 2 different PHRSD methods for branch-duct IPMNs, comprising a comparison between the authors' institution and a specialized center in Spain.[35] In the present study, the records of a single institution were extensively reassessed, and the long-term outcomes of PHRSD were compared with those of another limited surgery, PPPD. The experience of a large single center is favorable for this type of analysis, because experienced operators perform the pancreatectomies and the postoperative courses are managed under a well-organized perioperative management protocol, thus decreasing the level of bias regarding treatments.

In this series, the mean operative time and blood loss were significantly less in the PHRSD group than in the PPPD group. Furthermore, the overall incidence of postoperative morbidity was significantly reduced in the PHRSD group compared with the PPPD group. There were fewer pancreatic fistulae in the PHRSD group, but there were no differences between the 2 groups. No operative or hospital deaths were observed, and PHRSD was identified to be safe in the perioperative period. Moreover, the long-term nutritional status in body weight and several serum biochemistry values, which further reflect the duodenal function as well as the pancreatic exocrine function, were significantly superior in the PHRSD group compared with the PPPD group. The resected volume of the pancreatic parenchyma in PHRSD is comparable to that in PPPD, and PHRSD is not actually a "limited pancreatectomy." However, small branches of the anterior inferior pancreatoduodenal artery that feed the remnant pancreas are preserved in the fusion fascia of Treitz together with the gastroduodenal artery, and therefore, the blood supply of the remnant pancreatic parenchyma around the cut margin could be better than that of PPPD and possibly result in a better function of the remnant pancreas. Moreover, it is speculated that the preservation of the major portion of the duodenum serves to preserve motilin and finally contribute a better long-term nutritional status in patients who undergo PHRSD.[22–24]

The pancreatic remnant was anastomosed to the stomach in PHRSD compared with the jejunum in PPPD. Although the present results may be affected by the differences between pancreatogastrostomy and pancreatojejunostomy, some large randomized controlled trials recently found no significant differences in the postoperative courses of the 2 procedures.[36–39] Other previous studies showed similar results or lower superiority for pancreatogastrostomy as well.[40,41] Thus, PHRSD may comprehensively exert a more favorable influence on the patients' outcome, although it includes pancreatogastrostomy.

In the length of hospital stay, no significant differences were found between the PHRSD and PPPD groups. However, these hospital stays were much longer than those in Western countries. The Japanese health insurance system differs considerably from the systems in other countries, and many patients desire to stay in the hospital after surgery because the hospital fees are not expensive. However, the length of hospital stay after PHRSD could be decreased because of fewer postoperative complications in Western countries.

One critical factor to consider when selecting the surgical procedure for IPMNs is tumor clearance because IPMNs may recur in the remnant pancreas. In the current analysis of noninvasive IPMNs, the overall RFS rates were equivalent in the PHRSD and PPPD groups. As mentioned previously, the resected volume of the pancreatic parenchyma in PHRSD is comparable to that in PPPD, and therefore, the sufficient RFS rates are reasonable. The present results may reinforce the notion that the Whipple procedure and PPPD are not necessary for IPMNs and can be excessive from the aspects of both the validity of treatment and the long-term outcomes. However, organ-preserving procedures render the operation noncurative for patients with high-grade malignant tumors owing to the limited extent of the resection and the lack of sufficient lymph node dissection. Therefore, careful preoperative and intraoperative evaluation of disease by imaging studies and frozen-section examinations are crucial.

This study had some limitations. It covered almost 18 years, during which time the perioperative diagnostic approaches and modalities improved considerably. However, the principles for the therapeutic approaches and operative techniques remained consistent, and this could be a strength of the study. Subtle differences in the disease backgrounds or patient selections for either of the 2 surgical procedures may have biased the results. A well-designed randomized controlled trial may be warranted to convincingly prove the benefits of PHRSD.

The findings of the present study offer valuable insights into the perioperative and long-term utility of PHRSD. Pancreatic head resection with segmental duodenectomy can be indicated in patients with benign or low-grade malignant lesions, such as IPMNs, other cystic neoplasms, endocrine tumors, and chronic pancreatitis of the pancreatic head, regardless of the lesion size. Patients with severe pancreatitis should be avoided because inflammation of the pancreatic head region may make the surgery difficult and result in failure to preserve the gastroduodenal artery and small branches of the anterior inferior pancreatoduodenal artery. However, this surgical procedure fulfilled the operative safety, long-term nutritional status, and curative goals, and it is most desirable for patients with benign or low-grade malignant lesions. The results suggest that PHRSD may be the best surgical option for patients with benign or low-grade malignant pancreatic lesions and should be advocated more often.

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Correlation Between Radiographic Classification and Pathological Grade of Portal Vein Wall Invasion in Pancreatic Head Cancer

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Objectives: A retrospective study was performed to clarify the correlation between radiographic type of portal vein (PV) invasion and pathological grade of PV wall invasion, and their correlation with postoperative prognosis.
Background: In many patients with pancreatic cancer, PV resection is necessary to increase resectability and obtain cancer-free margins.
Methods: We analyzed 671 patients who had undergone surgery for invasive adenocarcinoma of the pancreas between July 1981 and June 2010. Radiographic types of PV invasion of pancreatic head cancer were classified into A (normal), B (unilateral narrowing), C (bilateral narrowing), or D (complete obstruction with collateral veins), by portography or computed tomography. Pathological grades of PV wall invasion were classified as 0 (no invasion), 1 (tunica adventitia), 2 (tunica media), or 3 (tunica intima).
Results: Four hundred and sixty-three patients underwent resection, and PV resection was performed in 297. Combined arterial vessel resection was performed in 16 cases. No significant difference in operative mortality was observed between PV preservation (0.6%) and PV-only resection (2.1%), and no operative deaths occurred after 1999. Radiographic classification of PV invasion correlated with incidence of pathological PV wall invasion. In pancreatic head carcinoma, no pathological PV wall invasion was observed in type A ($n = 111$). Pathological PV invasion was observed in 51% of type B (42/82), 74% of type C (72/97), and 93% of type D (63/68). Long-term survival (>5 years) was observed in types A and B, and grades 0 and 1 subgroups.
Conclusions: Pancreatectomy with PV resection can be performed safely. Even in radiographic classification type B, pathological PV wall invasion was observed in 51% of patients. Long-term survival was observed in types A and B, and grades 0 and 1.

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Early diagnosis of pancreatic cancer remains difficult despite developments in imaging techniques, specific tumor markers and molecular biology. Surgical resection provides the only chance for cure or long-term survival, but unfortunately, pancreatic head carcinoma often invades the portal vein (PV) system, which makes surgery difficult and even impossible. The survival rate of inoperable pancreatic adenocarcinoma remains very poor, even after the development of anticancer drugs, including new chemotherapeutic agents.[1–4]

In 1973, Fortner proposed "regional pancreatectomy" as a means of increasing resectability and radicality to improve the outcome for pancreatic cancer patients,[5] and this report has greatly influenced Japanese surgeons. Vascular resection for pancreatic cancer has been safely performed in our department since 1981, when Nakao developed the concept of isolated pancreatectomy with catheter-bypass of the PV using an antithrombogenic bypass-catheter.[6–8] Isolated pancreatectomy means non-touch isolation pancreatectomy.[8,9] In pancreatoduodenectomy, the first step uses the mesenteric approach, and the inferior pancreaticoduodenal artery is ligated and divided. The gastroduodenal artery is ligated and divided after clearance of the hepatoduodenal ligament. Before manipulation of the pancreatic head region, all arteries that flow into the region and all drainage veins from the region are ligated and divided.[8,9] A cancer-positive margin is known to result in dismal prognosis, therefore, we aggressively perform PV resection whenever invasion to the PV wall is suspected.[10,11] However, there has been little comprehensive analysis of pancreatic cancer that has invaded the PV, due to a lack of cumulative data: the number of pancreatectomies with synchronous PV/superior mesenteric vein (SMV) resection was <90 in previous studies.[12]

In this study, we analyzed our experience over the past 29 years of pancreatic cancer surgery with PV resection. Our aim was to clarify the correlation between radiographic classification and pathological grade of PV wall invasion, and their prognostic association.

METHODS

There were 671 surgical patients with invasive pancreatic ductal carcinoma at the Department of Surgery II, Nagoya University, between October 1981 and June 2010. Of these, 463 patients (69.0%) underwent curative resection and 208 had unresectable tumors because of local advancement, liver metastasis, or peritoneal dissemination. Surgery was indicated in patients with borderline or locally advanced disease if we felt that cancer-free margins could be achieved by aggressive surgery with vascular resection. We performed extensive radical resection (D2) for all patients in the absence of peritoneal dissemination or distant metastases. Seventy total pancreatectomies (TPs), 9 pylorus-preserving total pancreatectomies (PpTps), 252 pancreaticoduodenectomies (PDs), 52 pylorus-preserving pancreaticoduodenectomies (PpPDs), and 79 distal pancreatectomies (DPs) were performed (Table 1). Of these, 297 cases (64.1%) required resection of the PV or SMV, and combined arterial vessel resection was performed in 16 cases (5.4%; celiac artery in 2, hepatic artery in 11, and superior mesenteric artery in 3; Fig. 1). Radiographic findings of PV invasion in pancreatic head cancer were classified into type A (absent), B (unilateral narrowing), C (bilateral narrowing), or D (stenosis or obstruction with collaterals) by portography (Fig. 2A),[13] or by computed tomography (CT; Fig. 2B). Portal venography by superior mesenteric arteriography or intraoperative portal venography by the cut down of 1 branch of the SMV was performed routinely from 1981 to 2002. CT portography has been performed

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TABLE 1. Resectability Rate and Operative Procedure for Carcinoma of the Pancreas (July 1981–June 2010)

Tumor Location	Operation	Resection	PV Resection	Resectability	Operative Deaths	Operative Procedure TP	PpTP	PD	PpPD	DP	PHRSD
Head	497	358	262	72.0%	9	51 (50)	3 (2)	250 (184)	52 (26)	1 (0)	1 (0)
Body, tail	146	93	25	63.7%	1	8 (8)	5 (2)	2 (0)		78 (15)	
Entire gland	28	12	10	42.9%	1	11 (10)	1 (0)				
Total	671	463	297 (64.1%)	69.0%	11 (2.4%)	70 (68)	9 (4)	252 (184)	52 (26)	79 (15)	1 (0)

TP indicates total pancreatectomy; PpTP, pylorus-preserving total pancreatectomy; PD, pancreatoduodenectomy; PpPD, pylorus-preserving pancreatoduodenectomy; DP, distal pancreatectomy; PHRSD, pancreatic head resection with segmental duodenectomy. Numbers in parentheses indicate the number of PV resections that accompanied each type of pancreatectomy.

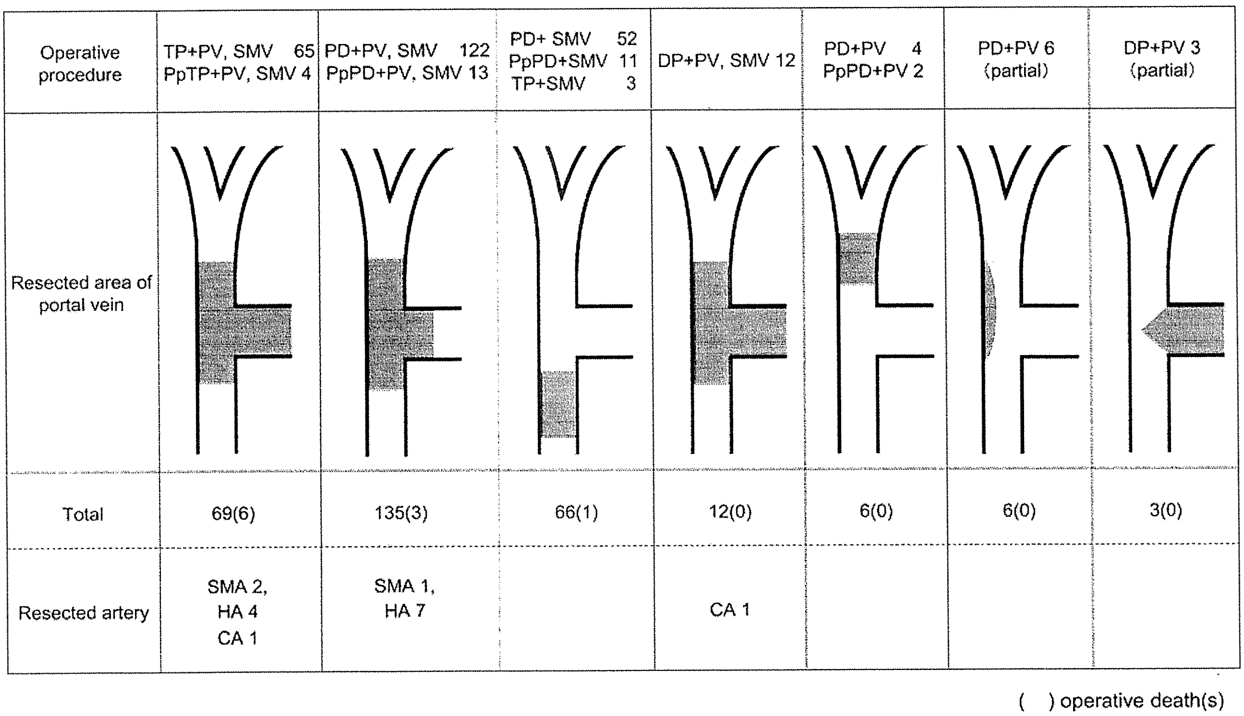

FIGURE 1. Pancreatectomy combined with PV resection, and extent of resected PV segments. Numbers in parenthesis indicate operative deaths. TP indicates total pancreatectomy; PV, portal vein; SMV, superior mesenteric vein; PpTP, pylorus-preserving total pancreatectomy; SMA, superior mesenteric artery; HA, hepatic artery; CA, celiac artery; PD, pancreaticoduodenectomy; PpPD, pylorus-preserving pancreaticoduodenectomy; DP, distal pancreatectomy.

since 2003. In addition, pathological grade of PV wall invasion was classified into: grade 0 (no invasion); 1 (tunica adventitia invasion); 2 (tunica media invasion); or 3 (tunica intima invasion) (Fig. 3). All patients were diagnosed pathologically with invasive pancreatic ductal carcinoma.

Differences in the numerical data between the 2 groups were examined using a χ^2-test or Fisher's exact test (for small numbers). Overall survival rates were estimated using the Kaplan–Meier method, and the differences in the survival curves were analyzed using a log-rank test. Statistical analysis was performed using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA). The presence of a statistically significant difference was denoted by $P < 0.05$.

RESULTS

The patients who underwent resection were aged 35 to 84 years (62.8 ± 9.2 years), and the male-to-female ratio was 297:166. Three-hundred and twenty-five patients were followed until death, and the median follow-up of the 138 patients who were still alive was 13.5 months. The tumors were located in the head of the pancreas

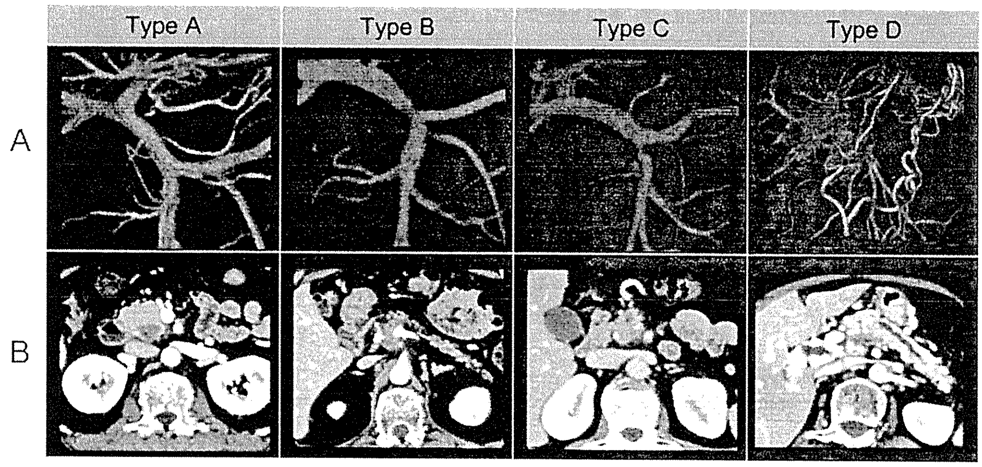

FIGURE 2. Radiographic classification of PV invasion by A, portography and B, CT.

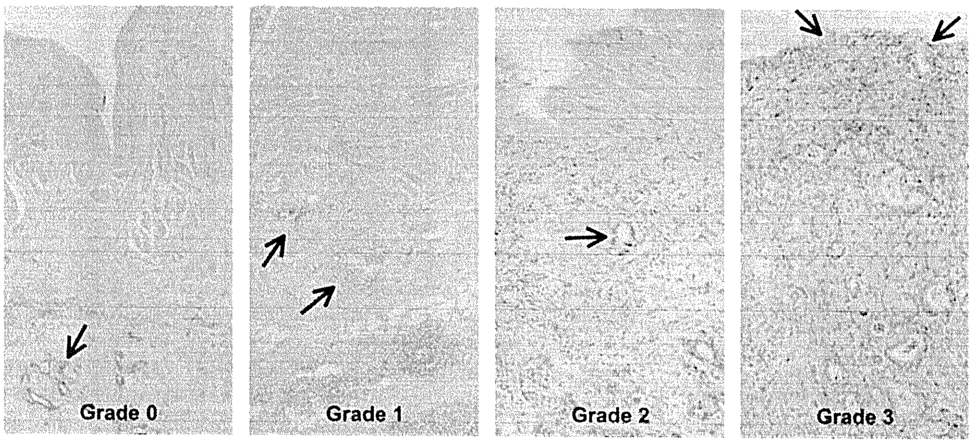

FIGURE 3. Pathological degree of carcinoma invasion into PV wall. Grade 0, no invasion; grade 1, tunica adventitia invasion; grade 2, tunica media invasion; grade 3, tunica intima invasion. Black arrow shows cancer cells.

(n = 358), the body or tail (n = 93), or the entire gland (n = 12; Table 1). Mean operation time was 471 minutes, and mean blood loss was 1275 ml. PV reconstruction was performed by end-to-end anastomosis in 293 (98.7%) of the 297 cases with PV resection. An autograft of the external iliac vein was used in 4 cases (2 TPs, 1 PD, and 1 DP). Operative death (within 30 days after surgery) occurred in 11 (2.4%) of the 463 resected cases. High mortality was observed in the patients with combined resection of the PV and arterial vessels (4/16, 25.0%), which was aggressively performed in the 1980s. No significant difference in operative mortality was observed between the PV preservation group (1/166, 0.6%) and the PV only resection group (6/281, 2.1%; $P = 0.21$). Fortunately, we have experienced no operative deaths over the past 11 years.

A total of 358 patients with pancreatic head cancer underwent resection, and PV resection was performed in 262 (73.2%). These 262 patients consisted of 161 men and 101 women with a mean age of 62.2 (37–83) years. The length of resected PV ranged from 7 to 80 mm with a mean length of 30.1 mm. During PV occlusion, catheter bypass of the PV was used to decrease portal congestion in 215 (82.1%) of the 262 cases. The duration of PV occlusion ranged from 10 to 240 minutes with a median duration of 55 minutes, and the duration of catheter-bypass of the PV ranged from 20 to 600 minutes, with a median of 180 minutes. A total of 358 patients with resected pancreatic head cancer were classified into radiographic type A (n = 111), B (n = 82), C (n = 97), and D (n = 68). PV resection was performed in 21 of 111 type A, 77 of 82 type B, 96 of 97 type C, and all 68 type D patients. Correlation between radiographic type and pathological grade of PV wall invasion is shown in Figure 4. No pathological PV wall invasion was seen in the 21 patients that underwent venous resection and were classified radiographically as type A. However, the incidence of pathological PV wall invasion in type B, C and D was 51%, 74%, and 93%, respectively. The incidence and grade of pathological PV wall invasion increased according to the radiographic type of PV invasion.

Cumulative survival rates of patients with pancreatic head cancer in the PV preservation, PV resection, combined resection of the PV and arteries such as celiac, superior mesenteric or hepatic arteries, and unresectable groups are shown in Figure 5. The PV preservation group had a significantly higher survival rate than the PV resection group ($P < 0.0001$). The PV resection group had significantly better prognosis than the unresectable group ($P < 0.0001$), whereas no significant difference in survival was observed between the combined resection and unresectable groups.

Cumulative survival rates of pancreatic head cancer according to radiographic type are shown in Figure 6. Type A had a significantly higher survival rate than type B ($P = 0.011$), type C ($P < 0.0001$),

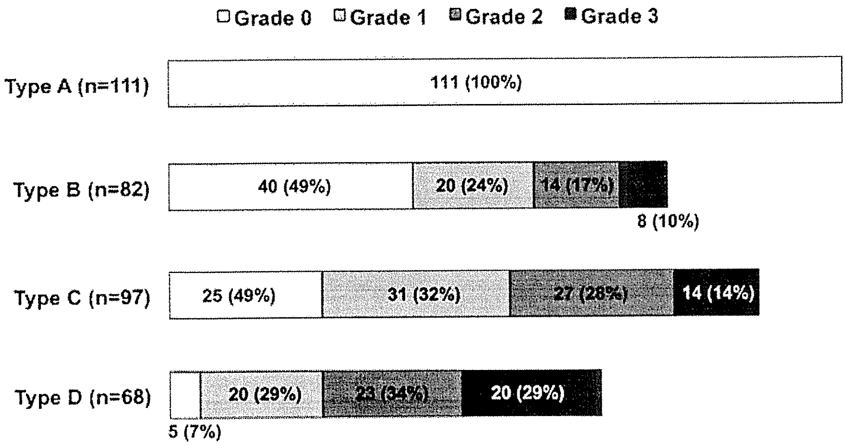

FIGURE 4. Correlation between radiographic type and pathological grade of PV wall invasion.

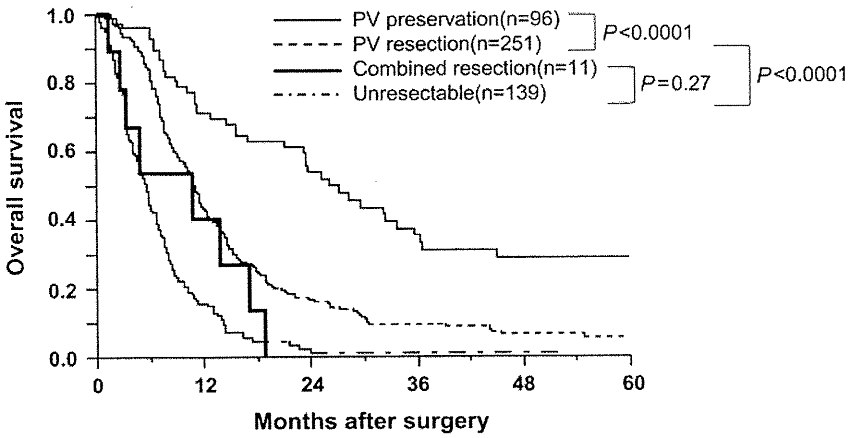

FIGURE 5. Cumulative survival rates of the PV preservation and resection groups.

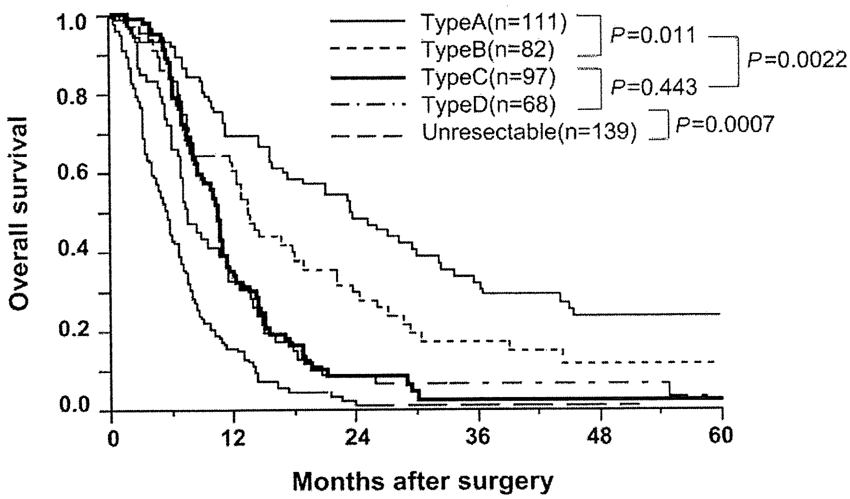

FIGURE 6. Cumulative survival rates according to radiographic type of PV invasion.

type D ($P < 0.0001$), and the unresectable group ($P < 0.0001$). Type B had a significantly better prognosis than the type C ($P = 0.0022$), type D ($P < 0.05$), and the unresectable group ($P < 0.0001$). No significant difference in survival rates was observed between types C and D, although type D had a higher survival rate than the unresectable group ($P = 0.0007$). Long-term survival (>5 years) was observed in the type A and B subgroups. Pathological PV invasion was observed in 174 (66.4%) of 262 patients with PV resection for pancreatic head cancer. Cumulative survival rates for pancreatic cancer according to the pathological depth of PV wall invasion are shown in Figure 7. Grade 0 had a significantly higher survival rate than grade 1 ($P = 0.0005$), grade 2 ($P < 0.0001$), grade 3 ($P < 0.0001$), and the

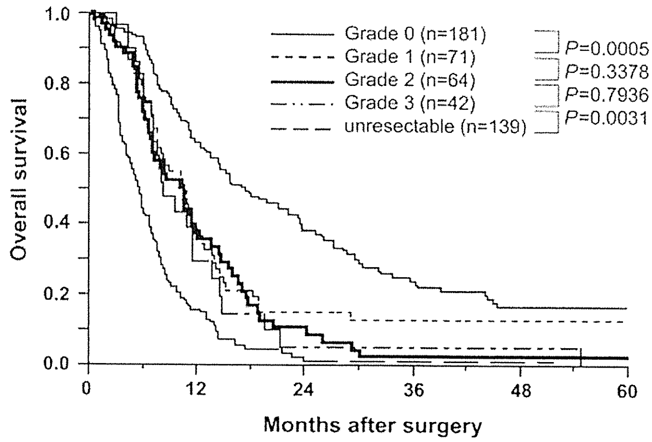

FIGURE 7. Cumulative survival rates according to pathological depth of PV wall invasion.

unresectable group ($P < 0.0001$). No significant difference in survival was noted between grades 1, 2, and 3. Grades 1, 2, and 3 had much higher survival rates than the unresectable group ($P < 0.0001$, $P < 0.0001$, $P = 0.0031$, respectively). Long-term survival (>5 years) was observed in the grade 0 and 1 subgroups.

DISCUSSION

Since 1981, we have performed isolated pancreatectomy for pancreatic cancer.[8] PV resection has been performed aggressively for cases with PV invasion without distant metastasis. The number of PV resections relative to total resection is higher than in other surgical studies because we aggressively resected type C and type D portal invasion. Also, we aggressively resected the PV when invasion was suspected. During occlusion for resection and reconstruction of the PV, antithrombogenic catheter-bypass has usually been used to prevent portal congestion or hepatic ischemia.[7] We experienced 11 operative deaths within 30 days after surgery between 1981 and 1998; however, there have been no operative deaths since 1999. Many studies have demonstrated no difference in outcome between PV resection and preservation.[14–16] Long-term outcome in the PV resection group was significantly worse than that in the preservation group in this study; possibly because the resection group had more advanced cancer than the preservation group.

In this study, we focused on the correlation between radiographic classification and pathological grade of PV wall invasion. When we perform PD for type B invasion, PV resection is necessary in >51% of cases. There is a report that patients with tunica adventitia invasion have better prognosis than those with tunica media or tunica intima invasion.[17] On the contrary, our data revealed no significant difference in postoperative survival according to the degree of histological invasion of the PV wall. Also, no significant difference was observed in the subgroup analysis of patients with potentially curative resection (R0) only. Patients without PV invasion apparently had better prognosis than those with invasion. The prognosis of patients with histologically positive PV wall invasion is very poor; however, we experienced some patients who survived for >5 years postoperatively in the group with cancer-free dissected peripancreatic margins.[18] The aim of PV resection is to increase resectability and obtain cancer-free surgical margins. In patients in whom the surgical margin is cancer-positive despite extended surgery with PV resection, the postoperative prognosis is much worse than in those with a negative surgical margin.[19–21] The main cause of a cancer-positive surgical margin is extrapancreatic invasion of the pancreatic head nerve plexus or plexuses around the arteries, such as the superior mesenteric, common hepatic or celiac arteries.[22,23] If the cancer invades these areas, it is difficult to obtain a cancer-free surgical margin even if PV resection is performed.[24] In our series, cancer-free surgical margin was obtained in 80.2% of type A, 73.2% of type B, 56.7% of type C, and 39.7% of type D patients. The main cause of cancer-positive surgical margins was extrapancreatic nerve plexus invasion.

Compared with pathological classification, radiographic classification of PV invasion was better able to stratify patients into subgroups with different prognoses. For pathological classification, invasion-positive groups (grades 1–3) had nearly identical prognoses, although it was significantly better than that in unresectable cases. This could mean that the radiographic type of PV invasion somehow correlates with the clinical stage, whereas pathological PV wall invasion simply denotes advanced stage.

Recently, we have analyzed the factors that affect overall survival after surgery in patients with pancreatic head cancer.[11] PV system invasion, extrapancreatic nerve plexus invasion, lymph node metastasis, and macroscopically positive margins are significant indicators of poor prognosis. Recent development of diagnostic modalities such as multidetector-row CT, magnetic resonance imaging and endoscopic ultrasonography has contributed to more precise diagnosis of tumor stage, but PV wall invasion or extrapancreatic nerve plexus invasion remains difficult to assess. Intraportal endovascular ultrasonography could make it possible to diagnose precisely these types of pancreatic cancer invasion.[25,26]

In conclusion, PV-resected patients have a significantly worse prognosis than those who do not undergo resection. However, PV resection is still justified because it can be done safely, and some of the patients do well; mainly those who do not have pathological invasion, and those in whom invasion is limited to the tunica adventitia. Radiographic classification of PV invasion correlated with pathological grade of invasion. Unilateral narrowing of the PV (type B) by pancreatic head cancer resulted in pathological PV wall invasion in 51% of cases, and there was no stratified correlation between pathological degree of PV invasion and postoperative prognosis.

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ORIGINAL ARTICLE – PANCREATIC TUMORS

Preservation of the Pyloric Ring Has Little Value in Surgery for Pancreatic Head Cancer: A Comparative Study Comparing Three Surgical Procedures

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ABSTRACT

Background. Pylorus-preserving pancreatoduodenectomy (PPPD) has replaced conventional pancreatoduodenectomy with a distal gastrectomy (cPD) as the most commonly performed procedure. However, there has been no evidence from prospective studies to indicate the overwhelming superiority of PPPD over cPD. A recent report revealed that resection of the pyloric ring reduced the incidence of delayed gastric emptying (DGE) in a randomized controlled trial.

Methods. In 158 patients with pancreatic head cancer, the perioperative outcomes and long-term nutritional consequences were retrospectively compared among three types of pancreatoduodenectomy: cPD; PPPD; and subtotal stomach-preserving pancreatoduodenectomy (SSPPD), in which the pyloric ring and duodenum were removed and more than 90% of the stomach was preserved.

Results. The incidence of DGE was significantly higher in the PPPD group than in the cPD and SSPPD groups (27.3 vs. 5.8 and 5.4%, respectively; $P = 0.0012$). The serum albumin concentration and total lymphocyte count at 1 year postoperatively were significantly higher in the SSPPD group than in the PPPD group ($P = 0.0303$ and $P = 0.0203$, respectively). The patients in the SSPPD group showed longer survival times than the patients in the cPD and PPPD groups (median survival times, 21.3, 17.1, and 17.7 months, respectively), although the differences did not reach statistical significance.

Conclusions. Our results suggest that preservation of the pyloric ring without vagal innervation has little significance, and that SSPPD with better perioperative and long-term outcomes is more suitable as a standard procedure for patients with pancreatic head cancer.

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Pancreatoduodenectomy (PD) for a periampullary lesion originally included a distal gastrectomy (cPD), which was responsible for a number of adverse events including postoperative complications and long-term nutritional disorders with notable weight loss.[1–4] Pylorus-preserving PD (PPPD) was developed by Traverso and Longmire,[5] and has replaced conventional PD with a cPD as the most commonly performed procedure. However, there has been no evidence from prospective studies to indicate the overwhelming superiority of PPPD over cPD. In fact, some randomized controlled trials revealed that the two procedures were comparable in terms of postoperative complications, long-term results and quality of life.[6–9]

Subtotal stomach-preserving PD (SSPPD), in which the pyloric ring and duodenum are removed and more than 90% of the stomach is preserved, has recently been performed in surgery for pancreatic head disease.[10–12] In this procedure, the gastric outlet can be greater than that in PPPD, resulting in a lower incidence of delayed gastric emptying (DGE), which occurred among 19–31% patients undergoing PPPD.[6,7,13] The few previous reports of comparisons between SSPPD and PPPD indicated that the incidence of DGE was far lower in SSPPD than in PPPD, or comparable between the two procedures.[10–12]

Pancreatic cancer is prone to result in nutritional deficiency owing to the high-grade malignancy, highly invasive surgery including portal vein resection, and postoperative adjuvant chemotherapy, and differs from other benign or low-grade malignant lesions including intraductal papillary mucinous neoplasms or endocrine tumors.[14,15] Malnutrition in patients with pancreatic cancer could influence the prognosis because of their attenuated immune status and inability to tolerate chemotherapy.[16] Therefore, it could be desirable to select the surgical procedure for patients with pancreatic head adenocarcinoma from the viewpoint of nutritional consequences. The previous reports comparing SSPPD with PPPD have not quite addressed this issue because they were not focused on treatment of invasive ductal carcinomas but included surgery for any lesions of the peripancreatic head, Moreover, no previous studies have compared three methods of PD.[10–12]

In the present study, cPD, SSPPD, and PPPD were compared to assess the best option for PD in patients with cancer of the pancreatic head. However, preservation of the organ should not compromise radicality. Therefore, the frequencies of lymph node metastases in the peripyloric region were also investigated.

PATIENTS AND METHODS

Patient Selection

In this study, the International Union Against Cancer (UICC) staging classification of pancreatic cancer (7th edition, 2009) was applied.[17] Between July 1981 and June 2010, 463 pancreatectomies for pancreatic cancer were performed at the Department of Surgery II, Nagoya University. The resected tumors were pathologically confirmed to be invasive ductal adenocarcinomas. Other periampullary malignant neoplasms such as lower bile duct cancers, cancers of Vater's papilla, malignant endocrine tumors, and malignant cystic neoplasms including invasive intraductal papillary mucinous carcinomas were excluded from the analysis because the surgeries and postoperative courses differed from those of pancreatic cancer. Initially, 358 patients with pancreatic head cancer were retrieved from the prospective database to assess the frequencies of peripyloric lymph node metastases. Lymph node metastases were separately counted by their locations as lymph nodes along the lesser curvature of the stomach, lymph nodes along the greater curvature of the stomach, suprapyloric lymph nodes, and infrapyloric lymph nodes. In the subsequent analyses comparing the outcome stratified by the amount of the stomach preserved, 199 consecutive patients who underwent PD after 2000 were selected. Pancreatic cancers that involved the celiac axis and superior mesenteric artery (UICC stage III), and had distant metastasis (UICC stage IV) were also excluded from the analysis because of their possible influences on the general condition and nutritional status of the patients. Of these, only 158 resected patients in whom the data for immunonutritional status as evaluated by blood examination tests were available were included. Written informed consent for retrospective analysis of various outcomes, as required by the Institutional Review Board of Nagoya University, was obtained from all the patients.

Surgical Procedures

Pancreatectomy and systematic lymphadenectomy with intent for cure were performed for all patients in the absence of peritoneal dissemination or distant metastases. In cPD, the stomach was resected by 50% or more. In SSPPD, the stomach was resected at 2–3 cm proximal to the pyloric ring (Fig. 1) and the distal portion of the antrum was removed together with the entire duodenum. The procedures for cPD and PPPD were previously reported.[18] The surgical procedure was generally selected according to the surgeon's discretion, although PPPD was avoided if the tumor had invaded close to the pyloric ring or lymph node metastases around the pyloric ring were suspected. Even in PPPD, the suprapyloric and infrapyloric lymph nodes were also dissected. A portal vein resection was performed in combination with a standard pancreatectomy in patients with possible or definitive tumor invasion. Reconstruction was performed by a modified Child's method in cPD and SSPPD or by a Traverso method in PPPD, consisting of an end-to-side pancreatojejunostomy and an end-to-side choledochojejunostomy. An end-to-side antecolic gastrojejunostomy in cPD and SSPPD or a duodenojejunostomy in PPPD was

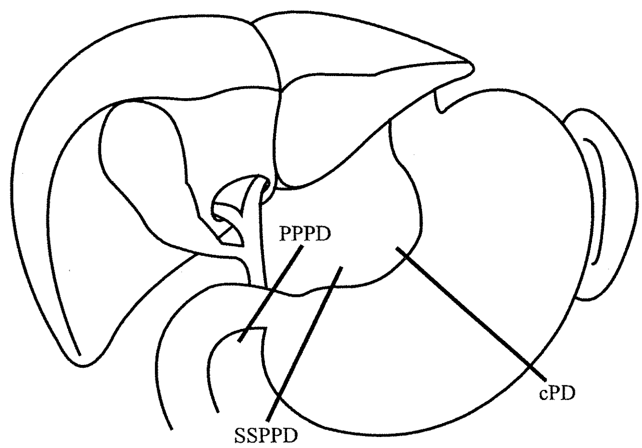

FIG. 1 Schematic illustrations of the three types of PD: conventional PD with cPD, SSPPD, and PPPD. In SSPPD, the stomach is resected at 2–3 cm proximal to the pyloric ring