

TABLE 5 Reports on the Factors Predictive of Malignant IPMN

Author	Raimond <i>et al.</i> (26) (n=45)	Sugiyama <i>et al.</i> (27) (n=62)	Wiesenauer <i>et al.</i> (28) (n=64)	Kitagawa <i>et al.</i> (25) (n=63)
Physical factors				
Alcohol history (Yes)	S	†	†	NS
Recurrent pancreatitis (Yes)	S	NS	NS	NS
Extrapancreatic malignancy (Yes)	†	S	†	†
Diabetes mellitus (Yes)	NS	NS	S	NS
Symptomatic (Yes)	NS	S	†	†
Pain (Yes)	NS	S	NS	NS
Duration of symptoms (Short)	S	†	†	S
Jaundice (Yes)	NS	NS	S	S
Laboratory examination				
Serum ALP (Elevated)	†	†	S	†
Liver function tests (Elevated)	†	†	NS	S
Serum CA19-9 (Elevated)	†	NS	NS	S
Tumoral factors				
Tumor type (Main duct or combined type)	†	S	†	S
Tumor location (Head)	†	S	†	NS
Mural nodule (Yes)	†	S	†	†
MPD diameter (≥ 7 mm)	†	S	NS	†
Patulous papilla (Yes)	†	S	NS	†
p53 staining (Positive)	†	†	†	S

S, significant predictor; NS, non-significant predictor; †, not described.

TABLE 6 Reports on the Factors Predictive of Invasive IPMC

	Maire <i>et al.</i> (29) (n=73)	Sugiyama <i>et al.</i> (27) (n=62)	Our cases (n=57)
Physical factors			
Alcohol history (Yes)	†	†	NS
Recurrent pancreatitis (Yes)	NS	NS	NS
Extrapancreatic malignancy (Yes)	†	NS	†
Diabetes mellitus (Yes)	NS	NS	S
Symptomatic (Yes)	NS	S	NS
Pain (Yes)	NS	NS	†
Jaundice (Yes)	NS	S	†
Laboratory examination			
Serum CA19-9 (Elevated)	S	NS	S
Tumoral factors			
Tumor type (Main duct or combined type)	NS	S	S
Tumor location (Head)	NS	S	NS
Mural nodule (Yes)	†	S	S
MPD diameter (≥ 7 mm)	†	S	NS
Median tumor size (Large)	S	†	NS
Patulous papilla (Yes)	†	S	†

S, significant predictor; NS, non-significant predictor; †, not described.

tors were not significant. A main duct or a combined type was significantly associated with IPMN malignancy in three studies, and no articles denied this finding. Moreover, we summarized parameters that correlated with invasive IPMC in Table 6, but only 2 articles evaluated invasion. The presence of a main duct or a combined type, a mural nodule, and an elevated serum CA 19-9 level correlated significantly in other studies.

In conclusion, pancreatic IPMN is slow growing, but has a significant malignant potential that warrants radical surgery when the tumor component in-

vades into the parenchyma or adjacent organs beyond pancreatic duct epithelium. The main duct or combined type of IPMN or IPMN with mural nodule is likely malignant or invasive. Thus, these IPMNs may require a more radical operation. These results have already been described in several previous publications and were confirmed in this comprehensive study. Further advancements in imaging along with research to identify additional clinicopathological features in order to more accurately predict malignancy or invasion are required.

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Current Medical Treatment of Pancreatic Neuroendocrine Tumors

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KEY WORDS:

Neuroendocrine Tumors; Pancreatic; Somatostatin analog; Radiolabelled; Interferon; Chemotherapy

ABBREVIATIONS:

5-Fluorouracil (5-FU); Interferon (IFN); Insulin-like Growth Factor (IGF); Long-Acting Release (LAR); Metaiodobenzylguanidine (MIBG); Neuroendocrine Tumor (NET); Somatostatin (SST); somatostatin receptor (sstr); Subcutaneous (SC); Transforming Growth Factor (TGF- α)

SUMMARY

Pancreatic neuroendocrine tumors (NETs) consist of a wide group of neoplasms, with different biological behaviors in terms of aggressiveness and hormone production. In the last two decades, significant progress has been observed in our understanding of their biology, diagnosis and treatment. Surgery remains to be the only curative approach, but unfortunately the diagnosis is often delayed due to the slow growth of these tumors and the difficulty in identifying the symptoms related to the tumor-released hormones. In addition to surgery, other approaches to control the disease are biological therapy consisting of somatostatin analogs and interferon (IFN), systemic chemotherapy, radioligand therapy and local therapy with chemoembolization. Several newer cytotoxic agents, including irinotecan,

gemcitabine, taxanes, oxaliplatin, capecitabine and PS-341 have been studied in metastatic patients. Considering the high vascularity of these tumors, antiangiogenic agents like endostatin and thalidomide have also been evaluated in advanced NETs. Although these agents seem to have potential activity in NETs and may increase progression free survival, none of these currently available medical therapeutic options are curative. While more efficient novel strategies are to be developed, the rationale use of the current therapeutic options may improve quality of life, control the symptoms related to the hypersecretion of hormones and/or peptides, control tumor proliferation and prolong survival in patients suffering from NETs.

CURRENT MEDICAL TREATMENT OF PANCREATIC NEUROENDOCRINE TUMORS

Neuroendocrine tumors (NETs) constitute approximately 1% of all malignant tumors of the gastrointestinal system (1). These tumors consist of a wide group of neoplasms, each one having its own peculiar histology and biological behavior in terms of aggressiveness and hormone production. NETs are classified into four groups according to the production of biologically active substrates, cellular grade, primary tumor type and site, cell proliferation markers and local or vascular invasiveness (Table 1) (2). NETs are also classified according to the production of biologically active substrates. The characteristics of pancreatic NETs are given in Table 2. The heterogeneity of NETs makes the management difficult.

The treatment of pancreatic NETs is based on surgery. Surgery remains to be the only primary curative approach, but unfortunately the diagnosis is often delayed due to the slow growth of these tumors and due to the difficulty in correctly identifying the symptoms related to the tumor-released hormones. It is estimated that 50% to 95% of the patients with NETs develop liver metastases and that 80% of these patients with advanced liver disease will die within 5 years of

diagnosis (1,3). In addition to surgery therefore other approaches or strategies are required to alter the natural course of the disease. These therapeutic options are biological therapy consisting of somatostatin analogs and interferon (IFN), systemic chemotherapy, radioligand therapy and local therapy with chemoembolization. However since none of these currently available medical therapeutic options are curative, the goals of medical therapy are to improve quality of life, to control the symptoms related to the hypersecretion of hormones and/or peptides, to control tumor proliferation and to prolong survival. The treatment algorithm is illustrated in Figure 1.

Somatostatin (SST) Analogues

NETs differ from other solid tumors because they typically secrete several hormones and express growth

TABLE 1 World Health Organization Classification of Neuroendocrine Tumors

Well differentiated neuroendocrine tumors
Well differentiated neuroendocrine carcinomas
Poorly differentiated neuroendocrine (small cell) carcinomas
Mixed endocrine tumors

Clinical Implications of Peritoneal Cytology in Potentially Resectable Pancreatic Cancer

Positive Peritoneal Cytology May Not Confer an Adverse Prognosis

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Objectives: To determine the value of peritoneal washing cytology (CY) in determining resectability of pancreatic cancer.

Summary Background Data: CY has been used widely in the diagnosis and staging of several cancers. However, its predictive value in identifying potentially resectable pancreatic cancer is undetermined.

Methods: Peritoneal washing samples were collected from 233 patients with pancreatic cancer between June 1991 and August 2006.

Parameters with overall survival rates were analyzed.

Results: Malignant cells were identified in samples from 21 patients (13.4%) with resectable tumors and 27 patients (35.5%) with unresectable tumors. CY+ was more frequent in large tumors (≥ 2 cm) than small tumors (< 2 cm; $P = 0.034$). CY status did not correlate with any other clinicopathologic parameter. The overall survival of CY+ patients was worse than that of CY- patients ($P = 0.047$). Median survival following resection was 13.6 months for CY+ patients and 13.5 months for CY- patients. Among the patients who had unresectable lesions, median survival time was 5.9 months for CY+ and 6.1 months for CY- patients. However, among CY+ patients, those who underwent resection lived longer than those who did not ($P = 0.019$).

Conclusions: Cytologic status has little predictive value for survival, and patients whose pancreatic cancer would otherwise be considered resectable should not be denied curative resection solely because they are CY+.

(*Ann Surg* 2007;246: 254–258)

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ISSN: 0003-4932/07/24602-0254

DOI: 10.1097/01.sla.0000261596.43439.92

Pancreatic cancer continues to be the gastrointestinal malignancy with the worst prognosis, and only 3% of patients survive 5 years after diagnosis. Surgical resection offers the only chance for cure; and although the resection rate has increased gradually, the prognosis remains poor.¹

Peritoneal washing cytology (CY) has been used widely in the diagnosis and staging of ovarian, endometrial, and gastric cancer. Malignant cells can be identified in 7% to 30% of peritoneal washing samples from patients with pancreatic cancer.^{2–9} However, the clinical significance of their presence is yet to be determined. Prior studies have suggested that positive peritoneal cytology (CY+) may be a marker for advanced disease, predictive of early metastasis and shortened survival, and thus should be considered a contraindication for attempts at curative resection.^{4,5} On the other hand, several authors have found no correlation between CY+ and the development of peritoneal metastasis postoperatively. Consequently, these investigators claim that CY+ status in the absence of macroscopic peritoneal metastasis is not a contraindication for radical surgery.^{7–9}

In the current study, we examined peritoneal washings from 233 patients with pancreatic cancer. The purpose was to determine what, if any, whether relationship exists between cytology results and clinicopathologic parameters and peritoneal washing cytology correlates with survival.

PATIENTS AND METHODS

Patients Selection and Study Design

Peritoneal washing samples were collected from 233 pancreatic cancer patients treated at the Department of Surgery II, Nagoya University, between June 1991 and August 2006. All 233 patients were considered candidates for curative resection after a meticulous preoperative work-up. The cohort included 156 men and 77 women, with the median age of 61.9 years (range, 32–84 years). All patients were followed until death or through August 2006. The patients were followed for mean of 18.3 months or until death. Extended radical resection (D2) was performed for all cases in the absence of macroscopic liver or peritoneal metastases. A total of 157 patients had resectable lesions, while the other 76

patients had macroscopic hepatic metastases, macroscopic peritoneal metastases, or extensive local invasion. Immediately after laparotomy, 200 mL of isotonic heparinized saline was introduced into the subhepatic space and the pouch of Douglas. After gentle agitation, as much fluid was collected as possible using a syringe and quill. Smears were made from the centrifuged deposit and, after conventional Papanicolaou and Giemsa staining, examined by at least 2 experienced pathologists.⁷ All surgical specimens were examined histopathologically after being fixed and stained with hematoxylin and eosin. Pathologic findings were evaluated in accordance with the second English edition of the *Classification of Pancreatic Carcinoma* proposed by the Japan Pancreas Society,¹⁰: pT1, tumor limited to the pancreas (≤ 2 cm in the greatest dimension); pT2, tumor limited to the pancreas (> 2 cm in the greatest dimension); pT3, tumor extending directly into the bile duct, duodenum, or peripancreatic tissues; and pT4, tumor extending directly into the adjacent large vessels, plexus, stomach, colon, or spleen. This classification scheme is more detailed than the classification of the Union Internationale Contre le Cancer.¹¹ The tumor location and extension were classified according to the 6th edition of the UICC classification.

Statistical Analysis

The significance of correlations between cytologic results and clinicopathologic parameters were determined using Fisher exact test or the χ^2 test. Overall survival rates were calculated using the Kaplan-Meier method, and the difference in survival curves was analyzed using the log-rank test. Independent prognostic factors were identified by multivariate analysis using the Cox proportional hazards regression model. Data are expressed as mean \pm SD. The level of statistical significance was set at $P < 0.05$.

RESULTS

Of the 233 patients, 76 had unresectable lesions due to the presence of macroscopic hepatic metastasis ($n = 38$), macroscopic peritoneal metastasis ($n = 21$), both macroscopic hepatic and peritoneal metastases ($n = 5$), or extensive local invasion ($n = 22$). The remaining 157 patients underwent pancreatoduodenectomy ($n = 81$), pylorus-preserving pancreatoduodenectomy ($n = 29$), distal pancreatectomy ($n = 30$), and total pancreatectomy ($n = 17$). The conclusive stages of the 157 patients who underwent resection according to the TNM classification¹¹ were IA in 2 cases, IB in 4 cases, IIA in 31 cases, IIB in 72 cases, III in 15 cases, and IV in 33 cases.

Malignant cells were more often present in the peritoneal washings from patients with unresectable lesions (27 cases, 35.5%) than those with resectable disease (21 cases, 13.4%; Table 1) ($P = 0.0002$). Among the 21 patients who had unresectable lesions due to the presence of macroscopic peritoneal metastasis, 15 (71.4%) were CY+.

Patients with large tumors (≥ 2 cm) were more likely to be CY+ than those with small tumors (< 2 cm; $P = 0.034$). However, no other correlation between cytologic status and clinicopathologic parameter existed (invasion of the anterior pancreatic capsule or retroperitoneal tissue, bile duct inva-

TABLE 1. Demographics and Clinical Characteristics of Patients With Resectable Pancreatic Cancer and Positive Peritoneal Washings

Characteristic	Value
Age (yr) [range (mean)]	40–76 (62.5)
Gender (M/F)	9/12
Histopathologic type	
Moderate	15
Well	1
Poor	3
Papillary	1
Adenosquamous	1
Stage	
IA	0
IB	1
IIA	3
IIB	9
III	0
IV	8
Survival time (mos) [range (mean)]	1.4–41.6 (13.6)

sion, duodenal invasion, portal vein invasion, arterial invasion, perineural invasion, lymph node metastasis, lymph vessel invasion, vascular invasion, local tumor spread, location, or residual disease status) (Table 2). Of 157 resectable cases, cancer of 6 cases involved the whole pancreas and those of 32 cases occupied the body. Prognosis of these patients were poor compared with lesions localized to the pancreatic head, but no correlation between the CY status and tumor location was found at this time, partially owing to the rarity of CY+ cases among lesions located in the pancreatic body. Median survival time of R0 patients (14.5 months) was longer than that of R1 patients (9.2 months, $P = 0.015$) even when the CY status was not reflected in the R classification. In addition, no correlation was found between the CY status and the extent of residual disease. Among patients who had unresectable lesions, patients with macroscopic peritoneal metastases had a higher incidence of CY+ than those without macroscopic peritoneal metastases ($P = 0.0001$). On the other hand, CY status did not correlate with the presence or absence of hepatic metastases.

The overall survival of CY+ patients was shorter than of CY- patients ($P = 0.047$; Fig. 1). For patients who underwent resection, however, the median survival time of CY+ patients (13.6 months) was almost identical to that of CY- patients (13.5 months, $P = 0.269$; Fig. 2). This unexpected lack of a difference in survival was seen among patients with unresectable lesions as well (5.9 months for CY+ and 6.1 months for CY-, $P = 0.977$; Fig. 2). Furthermore, no difference in survival according to CY+ status was observed among patients with stages III and IV disease. There was a marked difference in survival between CY+ patients who underwent resection and those who did not ($P = 0.019$; Fig. 2).

To evaluate the value of peritoneal washing cytology as an independent prognostic determinant, multivariate analysis was performed with prognostic factors that had been found to

TABLE 2. Demographics and Clinical Characteristics of Patients With Pancreatic Cancer Subjected to Cytologic Examination of Peritoneal Washings

Clinicopathologic Parameter	No. Cases	CY-	CY+	P
Tumor size				
<2 cm	24	24	0	0.034*
≥2 cm	130	109	21	
Invasion of anterior pancreatic capsule				
Neg.	76	68	8	0.355
Pos.	81	68	13	
Invasion of retroperitoneal tissue				
Neg.	58	52	6	0.472
Pos.	99	84	15	
Bile duct invasion				
Neg.	67	62	5	0.095
Pos.	90	74	16	
Duodenal invasion				
Neg.	93	83	10	0.340
Pos.	64	53	11	
Portal vein invasion				
Neg.	75	69	6	0.065
Pos.	82	67	15	
Arterial invasion				
Neg.	138	117	21	0.068
Pos.	19	19	0	
Perineural invasion				
Neg.	117	100	17	0.596
Pos.	40	36	4	
Lymph node metastasis				
Neg.	44	40	4	0.437
Pos.	113	96	17	
Lymph vessel invasion				
Neg.	24	23	1	0.269
Pos.	127	108	19	
Vascular invasion				
Neg.	86	76	10	0.629
Pos.	65	55	10	
Local tumor spread				
pT1	3	3	0	0.267
pT2	7	5	2	
pT3	53	49	4	
pT4	94	79	15	
Location				
Head	119	102	17	0.7471
Body	32	29	3	
Whole	6	5	1	
Residual disease status				
R0	114	98	16	0.798
R1	43	38	5	
R2	0	0	0	

be significant by the univariate analyses. The analysis identified lymph node metastasis as the only variable for independently predicting overall survival ($P = 0.0004$; Table 3), whereas CY was found not to be significant.

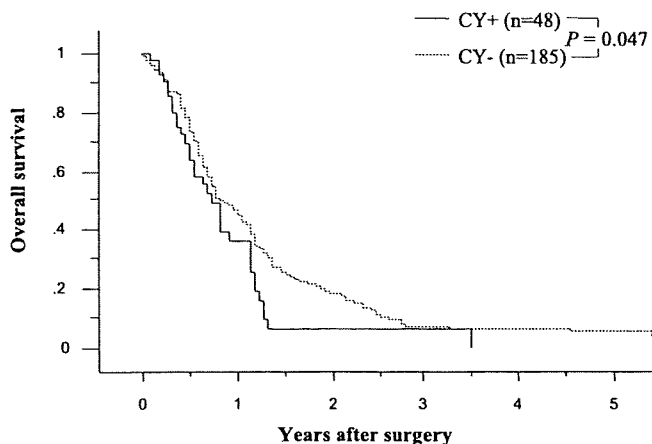


FIGURE 1. Comparison of survival curves of patients with pancreatic cancer with (CY+) and without (CY-) tumor cells in peritoneal washings. The overall survival for CY+ patients was significantly worse than for CY- patients ($P = 0.047$).

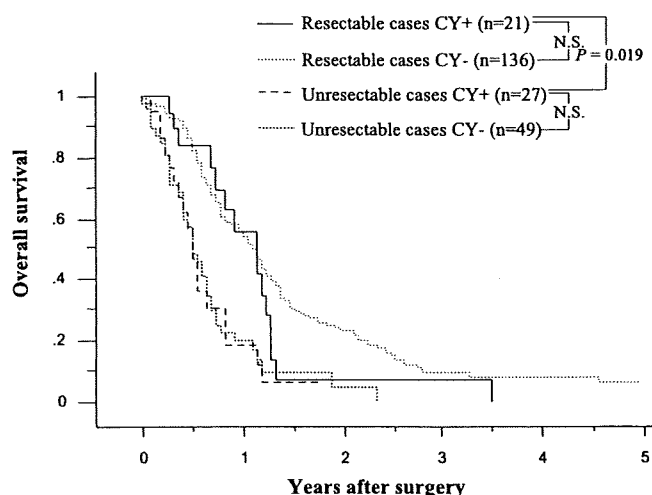


FIGURE 2. Comparison of survival curves of patients with pancreatic cancer who underwent curative resection with (CY+) and without (CY-) tumor cells in cytologic washings. The median survival time of CY+ patients was 13.6 months and that of CY- patients was 13.5 months ($P = 0.269$). Comparison of survival curves of patients with pancreatic cancer who did not undergo curative resection with (CY+) and without (CY-) tumor cells in peritoneal washings. The median survival time of CY+ patients was 5.9 months and that of CY- patients was 6.1 months ($P = 0.977$). Among pancreatic cancer patients with positive peritoneal cytology, patients with resectable lesions lived longer than patients with nonresectable lesions ($P = 0.019$).

DISCUSSION

Exfoliation of free malignant cells is a well-described feature of human carcinomas. Malignant transformation of cells alters the expression of surface adhesion molecules and thus facilitates their release into the peritoneal cavity.¹² Microscopic occult peritoneal metastases are thought to precede the emergence of macroscopic peritoneal metastases.^{13,14} In gynecologic malignancies, presence of malignant cells in

TABLE 3. Multivariate Analysis of Patients With Resectable Pancreatic Cancer

Variable	Odds Ratio	95% CI	P
Tumor size (≥ 2.0 cm)	1.714	0.915–3.208	0.092
Invasion of anterior pancreatic capsule	1.172	0.757–1.813	0.478
Invasion of retroperitoneal tissue	1.288	0.827–2.005	0.263
Portal vein invasion	1.371	0.860–2.184	0.184
Perineural invasion	1.481	0.930–2.358	0.098
Lymph node metastasis	2.322	1.456–3.703	0.0004*
Vascular invasion	1.075	0.712–1.623	0.732
CY+	1.061	0.589–1.912	0.843

*Statistically significant.
CY+ indicates positive peritoneal washing cytology.

peritoneal washings has been proven to have a strong negative impact on prognosis and therefore has been incorporated into the staging systems of these malignancies.¹⁵ Similarly, peritoneal washing cytology has been used extensively in gastric cancer,^{16–18} and the results are reflected in the Japanese clinical staging scheme.¹⁹ However, the significance and prognostic value of peritoneal washing cytology have yet to be established in other gastrointestinal malignancies, including pancreatic cancer.²⁰

Several recent studies have reported that patients with pancreatic cancer who are CY+ are more likely to have advanced stage disease, early metastasis, and a poor prognosis.^{2–9} In some series, overall survival of CY+ patients was shorter than that of CY– patients.^{2,5,9} CY+ status has not been reported to be an independent prognostic variable of survival because it seems to be dependent on tumor stage.⁵ Some investigators have concluded that tumor cells in the peritoneal washings are precursors of macroscopic dissemination, and have recommended that CY+ patients not undergo resection even if they would otherwise be surgical candidates.²¹ However, we have previously found no correlation between CY status and the incidence of peritoneal carcinomatosis during follow-up and concluded that CY+ in the absence of gross peritoneal deposits does not represent an absolute contraindication to radical surgery.⁷ In addition, Meszoely et al⁹ reported that overall survival and disease-free survival are not affected by the presence of tumor cells in peritoneal washings of patients who underwent curative resection. These results suggest that not all cells shed by a pancreatic cancer develop into peritoneal metastases.

While maintaining that surgery cannot in theory be recommended for CY+ patients, Yachida et al⁸ acknowledged that it may be premature to state this categorically given the paucity of outcome data. To the authors' knowledge, the analysis in the current study is based on the largest data set in the literature (Table 4). Consequently, these results should be weighted more heavily than those from smaller studies.

Although the overall survival for CY+ patients was worse than for CY– patients, CY status did not predict survival within the group of patients who underwent resection

TABLE 4. Published Studies on Peritoneal Washing Cytology in Pancreatic Cancer

Series	Year	n	CY+	
			n (%)	Resected Cases
Martin and Goellner ²²	1986	20	5 (25)	0
Warsaw ²	1991	40	12 (30)	1
Lei et al	1994	36	3 (8)	0
Leach et al ⁴	1995	60	4 (7)	1
Fernandez del Castillo et al ³	1995	94	16 (17)	0
Merchant et al ⁵	1999	228	34 (15)	2
Nakao et al ¹	1999	74	21 (28)	13
Jimenez et al ⁶	2000	117	24 (21)	0
Yachida et al ⁸	2002	134	19 (14)	19
Meszoely et al ⁹	2004	168	27 (16)	13
Current study	2006	233	48 (21)	21

CY+ indicates positive peritoneal washing cytology.

or in the group who did not. Resectability was a much stronger determinant of outcome, and long-term survival in CY+ patients has been documented in this study and others.^{5,7} Thus, it should be considered an independent prognostic factor, and patients whose pancreatic cancer is resectable should not be denied based on CY status alone.

It is unclear why free cancer cells in the abdominal cavity do not have an impact on survival. It may be due in part to differences in the biology of different histologic types. In gastric cancer, patients with undifferentiated adenocarcinoma have a higher rate of CY+ than those with differentiated adenocarcinoma,²² whereas most patients with CY+ in the current study had a moderately differentiated phenotype. However, no correlation existed between CY status and the histopathologic type of pancreatic cancer. Even in gastric cancer, a certain amount of time is needed for isolated tumor cells to develop into peritoneal carcinomatosis. Thus, some CY+ patients may die due to other patterns of metastatic spread before signs of peritoneal metastasis can develop. This may be the case with at least some CY+ patients since a high proportion of patients with this cancer die of liver metastasis.

Of the 21 patients with macroscopic peritoneal deposits, only 15 patients (71.4%) were CY+, indicating that sensitivity of the examination is a matter of concern. Various techniques such as immunocytochemistry^{7,23} or reverse-transcriptase polymerase chain reaction²⁴ have been used to improve sensitivity. The authors have previously shown that immunocytochemical staining is more sensitive than conventional staining,⁷ and reverse-transcriptase polymerase chain reaction appears to be even more sensitive in gastric cancer.²⁴ Further study is needed to determine the best method for detecting pancreatic cancer cells in peritoneal washings. However, whether an improvement in sensitivity will increase value of this examination as a prognostic determinant remains unknown.

CONCLUSION

Presence of free cancer cells in the peritoneal cavity is not clinically equivalent to the presence of macroscopic metastases. Since surgical resection remains the only modality that offers a chance for long-term survival, curative resection may be indicated regardless of the CY status whenever pancreatic cancer is localized, macroscopically resectable, and without gross distant metastasis.

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Pancreatic Head Resection With Segmental Duodenectomy

Safety and Long-Term Results

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Objective: To evaluate the usefulness and long-term results with pancreatic head resection with segmental duodenectomy (PHRSD; Nakao's technique) in patients with branch-duct type intraductal papillary mucinous neoplasms (IPMNs). A prospective study from Nagoya (Japan) and Barcelona (Spain).

Summary Background Data: Surgery should be the first choice of treatment of IPMNs. An aggressive surgery (eg, pancreatoduodenectomy) should be questioned in patients with an indolent disease or with noninvasive tumors. Recently, organ-preserving pancreatic resections for benign and noninvasive IPMN located in the head of the pancreas have been described. We have PHRSD in which the pancreatic head can be completely resected and the major portion of the duodenum can be preserved by this procedure. There have been only 4 reports concerning PHRSD with <8 patients (each one) in the English literature.

Methods: Thirty-five patients underwent PHRSD (20 men, 15 women), mean age 65.1 ± 9.0 (range, 55–75). Mean maximal diameter of the cystic lesion was 26.4 ± 5.3 mm (range, 20–33 mm) and mean diameter of the main pancreatic duct was 3.3 ± 0.5 mm (range, 3.0–4.0 mm). Alimentary tract reconstruction was performed in 20 patients by pancreatogastrostomy, duodenoduodenostomy, and choledochoduodenostomy (type A) and 15 patients by pancreaticojejunostomy, duodenoduodenostomy and choledochojejunostomy (Roux-en-Y; type B). Surgical parameters, postoperative complications, endocrine function, exocrine function, and long-term outcomes were evaluated. To compare the perioperative factors, a matched-pairs analysis between PHRSD patients and patients with pylorus preserving pancreaticoduodenectomy (PPPD) was performed. In the latter group were included 32 patients with branch-duct type of IPMN operated during the same time period that patients with PHRSD. The mean follow-up period was 48.8 months.

Results: Mean operative time after PHRSD was 365 ± 50 and mean surgical blood loss was 615 ± 251 mL. There was no mortality. Pancreatic fistula occurred in 10% and 13% with types (alimentary tract reconstruction) A and B, respectively. Noninvasive IPMN was found in 31 patients and invasive IPMN in 4 patients (11.4%). In the matched-pairs analysis between PHRSD and PPPD, the 2 proce-

dures were comparable in regard to operation time and intraoperative blood loss. The overall incidence of pancreatic fistula was higher after PPPD than after PHRSD; the difference was not statistically significant. When fistulas occurred after PHRSD they were grade A (biochemical). In contrast, pancreatic fistulas after PPPD were grade A in 78% of cases and grade B in 22% (clinically relevant fistula). The incidence of delayed gastric emptying was significantly higher in the PPPD group compared with the PHRSD group ($P < 0.01$). Endocrine pancreatic function, measured by fasting blood glucose levels and HbA1c, levels was unchanged in 94.28% of patients, in the PHRSD group, and in 87.87% in the PPPD group. Body weight was unchanged in 80% after PHRSD and in 59% after PPPD. Postoperative enzyme substitution was needed in 20% of patients after PHRSD and in 40% patients after PPPD. The 5-year survival rate was 100% in patients with benign IPMN and 42% in patients with invasive IPMN.

Conclusion: PHRSD is a safe and reasonable technique appropriate for selected patients with branch-duct IPMN. The major advantages of PHRSD are promising long-term results in terms of pancreatic function (exocrine and endocrine) with important consequences in elderly patients. Long-term outcome was satisfactory without tumor recurrence in noninvasive carcinoma. PHRSD should therefore be considered as an adequate operation as an organ-preserving pancreatic resection for branch-duct type of IPMN located at the head of the pancreas.

(*Ann Surg* 2007;246: 923–931)

The intraductal papillary mucinous neoplasm (IPMN) is well established as a special entity among the pancreatic neoplasms.¹ Recently, it was defined as a grossly variable, noninvasive, mucin producing, predominantly papillary, or rarely flat, epithelial neoplasm arising from the main pancreatic duct or major branches ducts, with varying degrees of ductal dilatation. IPMN usually produces a lesion >1 cm in diameter, and includes a variety of cell types with a spectrum of cytologic and architectural atypia. IPMN may be a progressive neoplastic lesion in which a small cystic lesion with low-grade atypia may progress to large multicystic-ductal lesions with severe atypia and complex histologic architecture and, eventually, to invasive cancer.¹

Twenty-five percent to 48% of IPMN contains invasive carcinoma.^{2–4} Preoperative assessment of the likelihood of malignancy in IPMN is often difficult.^{5–9} In some series, IPMN is classified into those predominantly involving the main pancreatic duct (main-duct type) and those predomi-

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ISSN: 0003-4932/07/24606-0923

DOI: 10.1097/SLA.0b013e31815c2a14

nantly involving the side branch of the ductal system (branch-duct type), because they have different tumor biologic behavior.^{10–13} Branch-duct type IPMN is less often associated with invasive carcinoma than main type IPMN. However, the difference in the prognosis of the main-duct type and the branch-duct type is still a controversial issue.^{2,3,7}

Among the surgical techniques performed, pancreaticoduodenectomy, distal or total pancreatectomy, are reserved for patients with invasive adenocarcinoma. However, this aggressive surgery should be questioned in patients with an indolent disease or with noninvasive tumors. Organ-preserving pancreatic resections are reasonable surgical options.^{14–20} The major problems with these techniques, such as duodenum-preserving pancreatic head resection (DPPHR) and partial resection of the pancreatic head, are the uncertainty to complete extirpation of IPMN, because IPMN tends to spread into the main or branch pancreatic ducts, and the potential postoperative complications associated to ischemia of the common bile duct and the duodenum.^{20,21} To avoid these problems, pancreatic head resection with segmental duodenectomy (PHRSD) has been described as an organ-preserving pancreatic resection.^{22,23} In this operation, the pancreatic head can be completely resected without causing ischemia of the common bile duct and the duodenum, and the major portion of the duodenum can be preserved by this procedure.

There have been only 4 reports performing PHRSD for IPMN located at the head of the pancreas, in the English literature, including no more than 8 patients in each publication.^{23–26} The aim of this study is to report the safety and long-term outcome of PHRSD from 2 tertiary referral centers and to discuss implications for operative technique and patient selection.

PATIENTS AND METHODS

Patient Characteristics

Data for patients undergoing PHRSD between March 1996 and March 2006 were prospectively entered into a standardized electronic database in the Department of Surgery of Nagoya University Hospital, Japan and in the Department of Surgery of Hospital Clinic, Barcelona, Spain and subsequently analyzed. All patients had branch-duct type of IPMN <30 mm in diameter located at the head of the pancreas. The indication for surgery was a symptomatic lesion in 80% of patients, mainly abdominal pain and episodes of mild pancreatitis.

Preoperative staging included computed tomography and cholangio-magnetic-resonance imaging, with most patients undergoing additional evaluation with endoscopic ultrasound and puncture fine needle aspiration for histologic studies.

The patients who underwent PHRSD consisted of 35 patients (22 men and 13 women), mean age 65.1 ± 9.0 (range, 55–75). Mean maximal diameter of the cystic lesion was 26.4 ± 5.3 mm (range, 20–33 years) and mean diameter of the main pancreatic duct was 3.3 ± 0.5 mm (range, 3.0–4.0).

Surgical Procedure

Laparotomy was done by upper midline skin incision. The gastrocolic and duodenocolic ligament is divided with

preservation of right gastroepiploic artery and vein to explore the front of the pancreas. The right gastroepiploic vein is ligated and divided at the root. The anterior-superior pancreaticoduodenal artery, the posterior-superior pancreaticoduodenal artery, and few other branches from gastroduodenal artery (GDA) toward the pancreas were ligated and divided. By conserving the right gastroepiploic artery and GDA, 5 to 7 cm of the first portion of the duodenum is preserved with good arterial circulation. The pancreas is divided on the line of the portal vein. The extrapancreatic nerve plexus between the uncinate process and the superior mesenteric artery is preserved, so the inferior pancreaticoduodenal artery is preserved. The anterior-inferior pancreaticoduodenal artery (AIPDA) is preserved and the posterior-inferior pancreaticoduodenal artery is ligated and divided. The AIPDA is ligated and divided near the major papilla (Fig. 1). The common bile duct is divided at the upper border of the pancreas. Two to 3 cm of ischemic area of the duodenum including major and minor papilla is observed. The oral side of the duodenum is divided at 5 to 7 cm from the pyloric ring. The anal side of duodenum is divided at the point of AIPDA ligation. Thus, PHRSD with preservation of GDA is completed. The length of the resected duodenum ranged from 3 to 5 cm (Fig. 2).

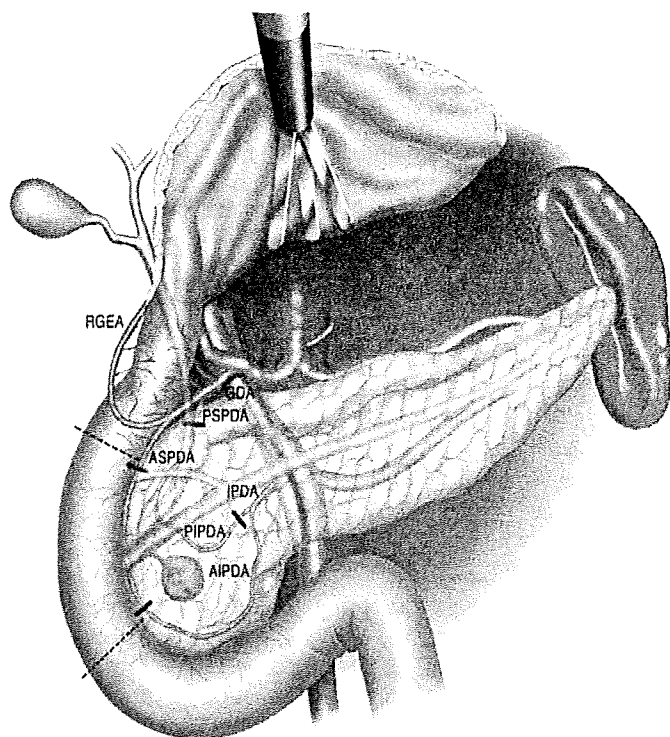


FIGURE 1. Divided lines of the pancreaticoduodenal arteries in pancreatic head resection with segmental duodenectomy. GDA indicates gastroduodenal artery; RGEA, right gastroepiploic artery; PSPDA, posterior-superior pancreaticoduodenal artery; ASPDA, anterior-superior pancreaticoduodenal artery; IPDA, inferior pancreaticoduodenal artery; PIPDA, posterior-inferior pancreaticoduodenal artery; AIPDA, anterior-inferior pancreaticoduodenal artery.

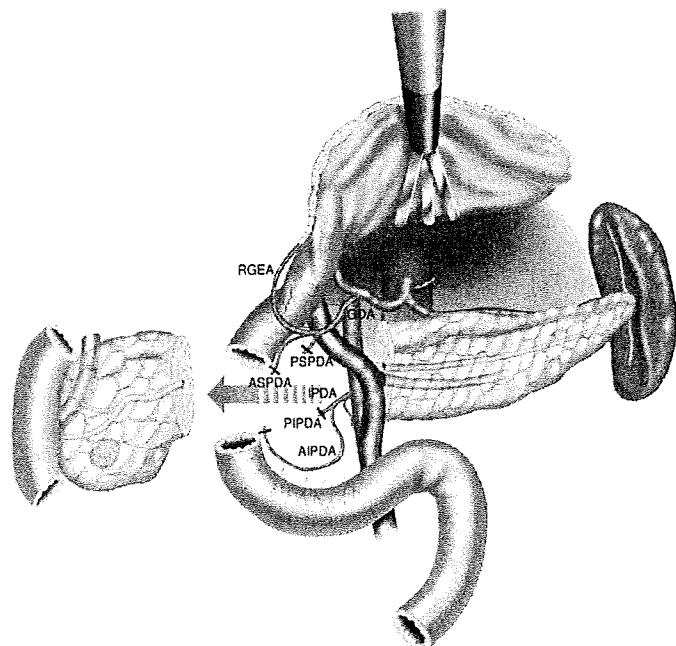


FIGURE 2. Resected portion in pancreatic head resection with segmental duodenectomy.

The reconstruction of the alimentary tract was performed according to the Nakao's original technique (type A) in 20 patients: pancreaticogastrostomy (temporary pancreatic stent into the main pancreatic duct of the remnant pancreas and drained externally), end-to-end duodenoduodenostomy, and end-to-side choledochoduodenostomy (temporary transhepatic biliary stenting) (Fig. 3). In 15 patients, reconstruction (type B) was accomplished with a 40 to 60 cm retrocolic Roux-en-Y limb of jejunum. And end-to-side pancreaticojejunostomy was constructed using duct to mucosa anastomosis; a pancreatic stent was inserted into the main pancreatic duct of the remnant pancreas and drained externally. Reconstruction was completed by end-to-side choledochojejunostomy (temporary T-tube of Kher) and finally, end-to-side Roux-en-Y enteroenterostomy 20 to 25 cm distal to the ligament of Treitz (Fig. 4). The indication for cholecystectomy was based on individual decision of the surgeon or by the presence of gallbladder stones.

CLINICAL DATA ANALYSIS

Data on operative, intraoperative, and postoperative care were prospectively collected. Preoperative parameters include patient demographics (age, gender); intraoperative parameters include total operative time, blood loss, and blood transfusion. Postoperative events were recorded according to the following definitions. Delayed gastric emptying: failure to resume oral liquid intake by postoperative day 10, and/or emesis >500 mL on or after postoperative day 5, and/or continued nasogastric drainage >500 mL on or after postoperative day 5. Biliary leak: bilious drainage from intraoperatively placed drains. Gastrointestinal bleed: guaiac-positive hematemesis, hematochezia, or melena or the sudden appearance of frank blood either on nasogastric lavage or per

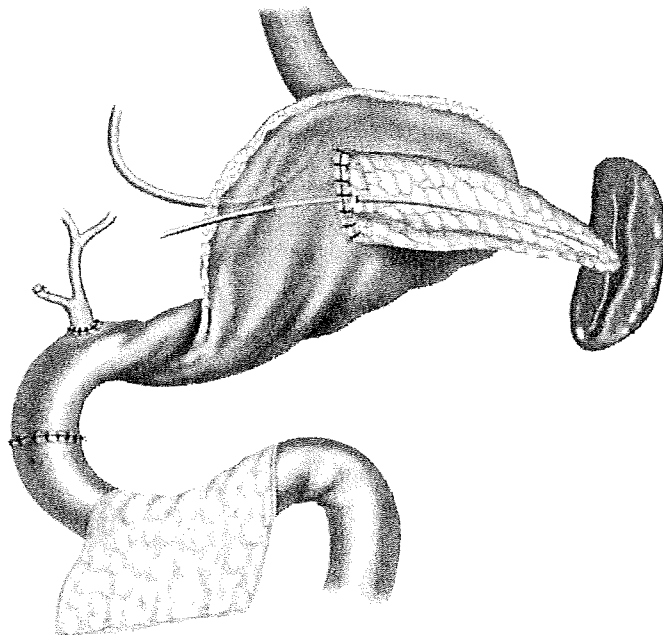


FIGURE 3. Reconstruction of the gastrointestinal tract (type A) after pancreatic head resection with segmental duodenectomy: pancreaticogastrostomy, duodenoduodenostomy, and choledochoduodenostomy.

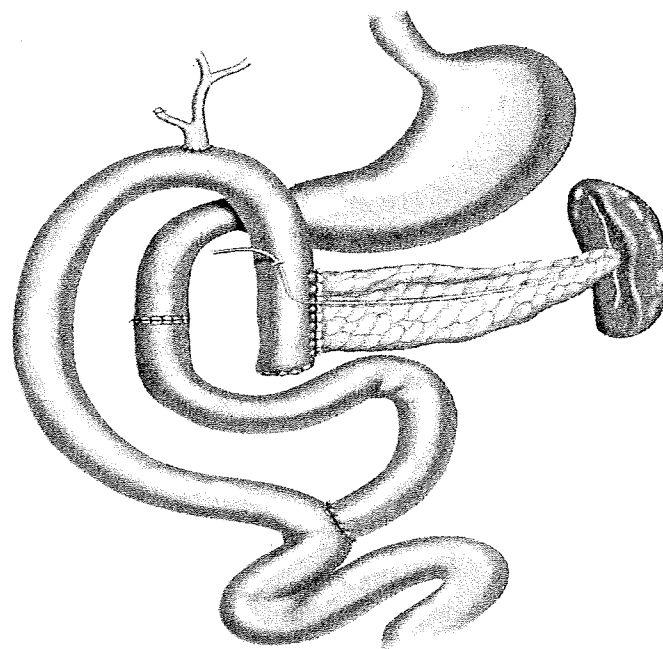


FIGURE 4. Reconstruction of the gastrointestinal tract (type B) after pancreatic head resection with segmental duodenectomy: pancreaticojejunostomy, duodenoduodenostomy, and choledochojejunostomy.

rectum. Length of stay: days from the initial operation to hospital discharge. Pancreatic fistula, according to the International Study Group on pancreatic fistula,²⁷ was designed as any measurable drainage from an operatively placed drain on

or after postoperative day 3, with an amylase content greater than 3 times the upper limit of normal serum amylase level. Those patients with fistula were then classified into 3 grades of severity according to International Study Group on pancreatic fistula clinical criteria.²⁷

To compare the perioperative factors, a matched-pairs analysis between PHRSR patients and patients with pylorus preserving pancreaticoduodenectomy (PPPD) was performed. In the latter group were included 32 patients with branch-duct type of IPMN operated during the same time period that patients with PHRSR, with some features suggesting malignancy such as jaundice, and cystic tumors greater than 35 mm in diameter.

The postoperative long-term outcomes, including pancreatic endocrine and exocrine function, and recurrence, were also evaluated. The endocrine function was measured by fasting glucose and serum hemoglobin (HbA_{1c}) levels. The exocrine function was evaluated by changes in the body weight of the patients and the need of postoperative enzyme substitution.

The median follow-up period was 37.5 months for PHRSR patients and 76.2 months for PPPD patients. Results were presented as mean \pm standard deviation. The surgical complication rates were compared with respect to the surgical procedure (PHRSR vs. PPPD) and between the 2 types of surgical reconstruction after PHRSR (type A vs. type B), using the Fisher exact test. Two-sided *P* values were always computed, and an effect was considered statistically significant at *P* < 0.05.

RESULTS

Perioperative Data in Patients After PHRSR

All tumors were resected with clear surgical margins, as shown by intraoperative frozen sections and confirmed by definitive histopathological examinations.

The mean operation time after PHRSR was 365 \pm 50 (range, 120–490 minutes). The mean intraoperative blood loss was 615 \pm 251 (range, 200–1500 mL). One patient received blood transfusions (2 units). The mean intensive care stay was 1 day.

Four patients (11.4%) developed pancreatic fistula with subsequent spontaneous resolution within 3 weeks. All fistula meet criteria for grade A fistula (transient, asymptomatic fistula, evident only by elevated drain amylase levels). Five patients (14%) developed delayed gastric emptying. Medical complications were observed in 2 patients, including pleural effusions in 1 and pneumonia in 1 patient. Twenty-four patients (62.8%) had uneventful postoperative course.

Twenty patients with PHRSR and pancreaticogastrostomy reconstruction were compared with 15 patients with PHRSR and pancreaticojejunostomy anastomosis. There was no difference in perioperative factors between the 2 groups. The postoperative mean hospital stay was 28.3 \pm 14.2 days after PHRSR with type A alimentary tract reconstruction (patients operated on at the Nagoya University). Interestingly, for only 15% of these patients the start of diet began after 21 postoperative days (delayed gastric emptying). However, the length of hospital stay was 12 \pm 4.0 days after PHRSR with type B

TABLE 1. Perioperative Data in Patients After PHRSR According to the Alimentary Tract Reconstruction of Type A (Pancreaticogastrostomy, Duodenoduodenostomy, and Choledochoduodenostomy) and Type B (Pancreaticojejunostomy, Duodenoduodenostomy, and Cholechojejunostomy)

	PHRSR		<i>P</i>
	Type A (20 Patients)	Type B (15 Patients)	
Patient characteristics			
Age (yr)	66.1 \pm 8.0	63.4 \pm 6.0	NS
Female	8	5	NS
Male	12	10	NS
Perioperative results			
Operating time (Min)	365 \pm 50	370 \pm 20	NS
Surgical blood loss (mL)	615 \pm 251	720 \pm 120	NS
Pancreatic fistula	2 (10%)	2 (13%)	NS
Biliary leakage	0	0	
Delayed gastric emptying	3 (15%)	2 (13%)	NS
Bleeding	0	0	0
Hospital stay (d)	28 \pm 14.2	12 \pm 4	<0.01

alimentary tract reconstruction (patients operated on at the Barcelona, Hospital Clinic). There were no differences in the postoperative complication rates between the 2 Institutions (Table 1). Therefore, differences in medical culture may explain the disparity of in-hospital stay in this combined experience.

Matched-Pairs Analysis and Postoperative Long-Term Follow-Up

In the matched-pairs analysis 35 patients with PHRSR and 32 patients with PPPD were included. The groups were well matched with regard to age and gender. The 2 procedures were comparable in regard to operation time and intraoperative blood loss (Table 2). The overall incidence of pancreatic fistula was higher after PPPD (22%) than after PHRSR (11%); the difference was not statistically significant. In the PPPD group, 60% had pancreaticogastrostomy technique and 40% had pancreaticojejunostomy technique. When fistulas occurred after PHRSR they were grade A (biochemical). In contrast, pancreatic fistulas after PPPD were grade A in 78% of cases and grade B in 22% (clinically relevant fistula). The incidence of delayed gastric emptying was significantly higher in the PPPD (31%) compared with the PHRSR group (14%; *P* < 0.01).

Endocrine pancreatic function measured by fasting blood glucose levels and HbA_{1c} levels was unchanged in 94.28% of patients in the PHRSR group and in 87.87% of patients in the PPPD group.

Body weight was unchanged in 80% of patients after PHRSR and in 59% of patients after pylorus-preserving (pp)-Whipple. Postoperative enzyme substitution was needed in 20% of patients after PHRSR and in 41% patients after PPPD (*P* < 0.05; Table 2).

Histopathology and Tumor Recurrence

Definitive histology of the resected lesions after PHRSR revealed 27 IPMN adenoma, 4 had carcinoma in situ,

TABLE 2. Matched Pairs Analysis Comparing Patients With PHRSD and Patients With pp-Whipple

	PHRSD (N = 35)	pp-Whipple (N = 32)	P
Patient characteristics			
Age (yr)	65.1 ± 9.0	61.7 ± 8.8	NS
Female	15	14	NS
Male	20	18	NS
Perioperative results			
Operating time (Min)	367 ± 69	375 ± 89	NS
Surgical blood loss (mL)	667 ± 185	825 ± 453	NS
Pancreatic fistula	4 (11%)	7 (22%)	NS
Biliary leakage	0	0	
Bleeding	0	0	
Delayed gastric emptying	5 (14%)	10 (31%)	0.01
Mortality	0	0	
Postoperative diabetes mellitus	2 (6%)	3 (9%)	NS
Follow-up weight:			
Unchanged	28 (80%)	19 (59%)	0.05
Increased (3 kg up)	0	0	
Loss (3 kg down)	7 (20%)	13 (41%)	0.05
Postoperative enzyme substitution	7 (20%)	13 (41%)	0.05

TABLE 3. Histopathology and Follow-Up After PHRSD and pp-Whipple

	PHRSD (N = 35)	pp-Whipple (N = 32)
Follow-up periods (mo)		
Mean	42.8 ± 27.7	76.2 ± 48.9
Median	37.5	73.4
Adenoma	27	19
Carcinoma in situ	4	6
Invasive carcinoma	4 (11%)	7 (22%)
Clinical follow-up		
Alive	33	28
Dead	2	4
Recurrence	2	4

and 4 had invasive carcinoma. Two patients with invasive cancer died 3 and 5 years after surgery with peritoneal dissemination. In the PPPD group, 6 patients had carcinoma in situ and 7 had invasive cancer. In this group, 4 patients died 3, 4, 6, and 7 years after surgery with peritoneal dissemination (2 patients) and liver metastasis (2 patients) (Table 3).

DISCUSSION

IPMN is a slow growing and low malignancy tumor. Complete removal of the tumor results in a good prognosis. However, when invasive carcinoma is found the prognosis is significantly worse. It is now known that IPMN can arise in the main duct or in the side branches ducts. The latter is less often associated with invasive carcinoma than main-duct type IPMN. However, the difference in the prognosis of the main-duct type and the branch-duct type is still a controver-

sial issue. In the series, Sohn et al²⁸ and D'Angelica et al⁷ reported that there was no significant difference in survival between the main-duct type and the branch-duct type. Therefore, the diagnosis of invasion or noninvasion is very crucial in this disease. A number of retrospective studies have been performed to identify the clinical pathologic features that can differentiate malignant IPMN from benign IPMN.^{6,7,9,10,28,29} The following features suggest malignant IPMN: jaundice, worsening or new onset of diabetes mellitus, main-duct type tumor, tumor size >30 mm, mural nodule size >5 mm, and carcinoembryonic antigen levels >110 mg/mL in pure pancreatic juice.

Several authors reported that the branch-duct type of IPMN without mural nodule was always benign; the necessity of resection in all these patients has been questioned, and conservative management with observation alone has been described.^{11,30} However, the concern for actual or potential malignancy in IPMN is real, and the recommendation to proceed with resection may be justified in most suitable candidates.^{13,30} In the present series, invasive carcinoma was found in 11% of patients with branch-duct type IPMN <30 mm in diameter. In recent series, the frequency of invasive carcinoma in branch-duct type IPMN varies from low figures 0%¹¹ and 6%³⁰ to high figures 30%²⁸ and 46%.³¹ In all reports, tumor size >30 mm is a strong predictive factor of malignant IPMN.^{7,10}

Surgical resection remains the option that gives the best chance of cure.³²⁻³⁴ For invasive IPMN, extended pancreatic resection including pancreaticoduodenectomy is required, because metastasis to the regional lymph nodes or invasion to the surrounding organs frequently occurs in these patients.^{6,28} Conversely, organ-preserving pancreatic resection is advocated for patients with benign IPMN. Various modifications of organ-preserving pancreatic resections for IPMN have been reported, DPPHR resection^{14,15} (Beger's technique),¹⁸ DPPHR with complete resection of the pancreatic head,¹⁸ inferior head resection of the pancreas,²¹ and ventral pancreatectomy.¹⁶ According to Murakami et al²⁶, there are major problems with these procedures. It is very difficult to ensure complete extirpation of IPMN with partial resection of the pancreatic head, because IPMN tends to spread into the main or branch pancreatic ducts. One patient with IPMN who died of recurrent disease 18 months after inferior head resection was reported.²¹ Postoperative ischemic necrosis or perforation of the common bile duct and the duodenum occasionally occur with DPPHR with preservation of the common bile duct.²¹ DPPHR with complete resection of the pancreatic head makes technically impossible to preserve the branches of the posterior-superior pancreaticoduodenal artery, which runs through the pancreatic parenchyma between the common bile duct and the duodenum and toward the major papilla.³⁵ In addition, if DPPHR with resection of the common bile duct is performed for complete resection of the pancreatic head, ischemia of the major papilla may also occur.³⁵

DPPHR with incomplete resection of pancreatic head and preservation of the intrapancreatic main bile duct (Beger's operation) was performed in 13 patients, with IPMN.¹⁵

A high morbidity was observed in this series, anastomosis pancreatic leakage (15%), bile duct perforation (8%), intraperitoneal bleeding (15%), delayed gastric emptying (15%), and a mortality rate of 15%. This high morbidity differs from the low morbidity of DPPHR in patients with chronic pancreatitis.^{36–38}

PPPD is the most commonly performed organ-preserving procedure for diseases of the pancreatic head region. Pancreaticoduodenectomy can be performed in experienced centers with mortality rate between 0.5%³⁹ and 3%⁴⁰; however, this procedure represents surgical overkill for benign or low-grade malignant IPMN. In the present series, there was no mortality due to either PHRS or PPPD.

After pancreaticoduodenectomy, the incidence of diabetes mellitus varies between 15% and 40%.⁴¹ In our current series, endocrine pancreatic function was unchanged in 94% and 88% after PHRS and pp-Whipple, respectively. In the present series, postoperative enzyme substitution was needed in 20% of PHRS patients and 41% of PPPD patients. Enzyme therapy was given to patients with steatorrhea or weight loss. These results suggest that endocrine and exocrine pancreatic function is better preserved after PHRS than after PPPD.

Nakao et al²² was the first to describe PHRS in 1994. In 1998,²³ he reported 14 patients with PHRS including mucin-producing cystic tumors (9 cases), annular pancreas (1 case), anomalous arrangement of the pancreato-biliary ductal system (1 case), carcinoma of the duodenum (1 case), carcinoma of the Ampulla of Vater (1 case), and cancer of the common bile duct (1 case). More recently, PHRS was performed in patients with low-grade malignant diseases of the pancreatic head region including IPMN. In the Isaji and Kawarada²⁴ series, 6 benign IPMN and 2 invasive IPMN were reported, with a follow-up of 36 and 22 months, respectively, without tumor recurrence. Alimentary tract reconstruction was performed in 4 patients with anastomosis of the pancreatic duct to the duodenum and in 4 patients with pancreaticojejunostomy. Postoperative complications occurred in 2 patients, 1 developed acute pancreatitis and 1 developed methicillin-resistant *Staphylococcus aureus* enteritis. Murakami et al²⁶ reported 8 patients with branch-duct type IPMN. In all cases a pancreaticogastrostomy, duodenoduodenostomy, and choledochoduodenostomy were performed. Complications after PHRS occurred in 4 patients, 1 with pancreatic leak, 1 with choledochoduodenal anastomosis stenosis, and 2 with delayed gastric emptying. The final pathologic diagnosis was adenoma in 7 patients and carcinoma in situ in 1 patient. Postoperative pancreatic endocrine and exocrine functions were satisfactory. All patients were alive without recurrent disease at a median follow-up of 30 months.

In this current study, PHRS was performed with 2 different alimentary tract reconstructions, pancreaticogastrostomy in 1 group and pancreaticojejunostomy in another group. Despite the anastomosis was performed with a soft pancreas, the data of our present study indicate that both techniques are safe with morbidity rates comparable.

The major advantages of PHRS are as follows: (1) To complete resection of the pancreatic head, safely, without

ischemia of the common bile duct and duodenum. (2) Preservation of endocrine pancreatic function probably by maintaining the duodenal passage of foods resulting in a physiologic entero-insular axis. (3) Exocrine pancreatic function was altered little in some patients, requiring postoperative enzyme substitution. Body weight was unchanged in the majority of patients.

Because of limited oncologic radicality, PHRS is only an adequate option in patients with benign and noninvasive IPMN. The lesion and resection margins should therefore be examined by frozen section during the operation. The resection should be extended if the ductal margin shows malignant invasive disease. In these circumstances, the lymph node dissection should be completed including the areas of hepatic hilum, celiac trunk, and along the superior mesenteric artery.

CONCLUSIONS

PHRS is a safe and reasonable technique appropriate for selected patients with branch-duct IPMN. The major advantages of PHRS are promising long-term results in terms of pancreatic function (exocrine and endocrine) with important consequences in elderly patients. Long-term outcome was satisfactory without tumor recurrence in noninvasive carcinoma. PHRS should therefore be considered as an adequate operation as an organ-preserving pancreatic resection for branch-duct type of IPMN located at the head of the pancreas.

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Discussions

PROFESSOR H. BEGER: Thank you for an elegant presentation with convincing data regarding a new indication for DPPHR including a segmental resection of the duodenum. Your data are in accordance with recently published data regarding application of this limited surgical procedure for primary benign lesions of the pancreatic head as a standard procedure.

To achieve complete removal of the lesion, it is necessary to perform total extirpation of the head. You have done this in a large series of patients with side branch IPMN lesions. However, for this specific type of IPMN lesion, 30% multifocality has been reported. To choose the appropriate surgical procedure, the surgeon needs to be able to discriminate benign from malignant lesion. During the surgical procedure, frozen section is mandatory to be complete in terms of having all the IPMN tissue removed or to switch to a pp-Whipple procedure in cases of an invasive carcinoma. How did you manage the multifocality in side-branch IPMN lesions and completeness of the resection? You have applied this limited surgical procedure in 4 patients, who ultimately had an invasive ductal pancreatic cancer. However, DPPHR in advanced pancreatic cancer is an inadequate procedure. As a consequence of this failure, using duodenum-preserving resection, 2 patients developed local recurrence of the cancer in a short postoperative period. Recurrence may even have developed in patients after incomplete resection of benign IPMN lesions as we experienced in 2 of 4 patients, in which we applied a subtotal duodenum-preserving resection of the pancreatic head. For recurrent benign lesions after subtotal head resection, a pp-Whipple was applied. From this institutional experience, we concluded that, in all patients with cystic neoplastic head lesions, we needed to perform a total

DPPHR including a segment of the duodenum, to ensure completeness of removal of the neoplastic lesion.

I am wondering about your techniques of reconstruction. In the Barcelona patients for biliary reconstruction you used a second large single jejunal loop. Did you observe using 2 excluded jejunal loops, signs of malabsorption? Please comment on this. We are using 1 excluded jejunal loop similar to the Nakao-technique, performing a pancreaticojejunostomy and implantation of the common bile duct in the preserved duodenum.

PROFESSOR L. FERNANDEZ-CRUZ: Concerning your first question, I think these operations should be performed in patients with benign lesions and, in the group of patients with premalignancy lesions, we know that they probably would not be malignant. I say probably, because certainty in discriminating between benign and malignancy is very difficult in this group of patients. What we do in Barcelona is to undertake endoscopic ultrasonography and aspiration cytology on all of our patients, and by doing so we can discriminate benign from malignant lesions in a high number of patients. In Japan, they use endoscopic retrograde cholangiopancreatography, aspirate the pancreatic juice and they measure carcinoembryonic antigen levels. When they see that it is above 110, the patients probably do have malignant tumors and, for them, the endoscopic retrograde cholangiopancreatography helps in discriminating between benignancy and malignancy. In most of our patients, we were successful in dealing with benign lesions. However, 11% were malignant. But, let me just remind you that, in Edinburgh in the last International HPB meeting, I presented our experience in Barcelona and we showed that with this operation we can perform a retroportal lymphadenectomy similar to the Whipple procedure.

Concerning the long Roux-en-Y, we use this for reconstruction after performing the pancreatic head resection to prevent the reflux of alimentary tract content into the bile duct.

PROFESSOR N. SENNINGER: To me, the obvious benefit, of what you do differently, is to preserve a better blood perfusion to parts of the players in the game—to the bile duct and maybe to the residual pancreas. All the other things are a sort of modification of the duodenum or partly DPPHRs. I am not so sure that you, in the long run, are able to show a benefit of your modification, because the mortality and morbidity come predominantly from the pancreatic anastomosis. All the other parts also contribute but this is a minority. Still, you are doing the same pancreatic anastomosis. You have to anastomose the residual pancreas and although you have zero mortality at the moment, for which you should be congratulated, you know that just by performing 100 you will see some mortality.

As regards the benefit for nutrition, what did you do, except for enzyme replacement, to really find a benefit be-

cause the entero-insulinic access is a sort of myth that has accompanied pancreatic surgery for a long time but nobody, so far, has proven a benefit for that. And may I just add 1 example? We did one of these local preserving procedures in a 26-year-old woman where all the pathologists and all the radiologists said it was a lesion and it turned out to be an aggressive tumor. We could have easily done an extended Whipple procedure and, at the moment, we are reluctant to do it in these cases.

PROFESSOR L. FERNANDEZ-CRUZ: I think the results are there and I will not comment further on them. Concerning your last comment on the myth in the patients with preserving pancreatic head resection, I think Professor Beger and Marcus Büchler did a beautiful study in patients with total gastrectomy for gastric cancer and they investigated whether the different types of reconstruction could influence the possible outcome in terms of endocrine pancreatic function. I think that by preserving the duodenum, there is a real benefit. It was published and demonstrated by these 2 authors and I do not think it is a myth. I think it is supported by our results. As for exocrine pancreatic function, unfortunately, we did not measure fecal elastase. We did so in some patients but this was not presented today. I think that the only way to know whether the exocrine pancreatic function is preserved is by measuring fecal elastase. Nevertheless, patients in the group of pancreatic resections with duodenectomy needed less enzyme substitution compared with pylorus preserving Whipple. This is, therefore, a beneficial effect of the operation.

MR C. RUSSELL: I enjoyed this article greatly and it was a reminder of work that my group undertook on the vascular supply of the duodenum. The reason why duodenal preservation is feasible is that the submucosal anastomotic networks are the same as in the stomach in contrast to the segmented blood supply of the small intestine. Perfusion studies show that there is a submucosal anastomosis between one end of the duodenum and the other, thus perfusate injected distally will reflux up to the pylorus. We found that preservation of the duodenum was safe, provided that a reasonable length of the inferior pancreaticoduodenal artery was preserved. So, my first question is, why did you resect the small segment because, if you are dealing with benign disease, you can divide it at the ampulla without damaging the duodenum.

The second point is that my disappointment with duodenal preservation was the failure to show a clinical advantage. Our 9 patients with duodenal-preserving pancreatectomy were no different from matched controls that had a pylorus preserving pancreatectomy regarding weight and quality of life. Indeed, your long lengths of stay show that some of these patients do take quite a long time to recover possibly because the anastomosis that you do functions al-

most as another pylorus. I wondered if you did emptying studies during the postoperative period to show why they took a mean of 48 days to recover.

PROFESSOR L. FERNANDEZ-CRUZ: Concerning the technical aspects of the operation and your comments referring to your work in this area, I recall that the great majority of your patients were chronic pancreatitis patients, and generally, they are a different type of patient. The great majority have impairment of both exocrine and endocrine pancreatic function. That is why you cannot expect to see good results in the endocrine and exocrine pancreatic function because you start with impairment in these 2 important functions of the pancreas. I do not think your group of patients with chronic pancreatitis is comparable. Our group of patients had normal pancreatic function with no signs of chronic pancreatitis.

As to your second question, I think it is necessary to preserve the arteries that were described. Once we removed the head of the pancreas with the second part of the duodenum, when we do the vascular preservation and the ligation of the arteries that were discarded, all patients experienced a change in the color of the duodenum. The second part of the duodenum became black in most of them. That is why I think the preservation of these arteries is crucial and we should be

very meticulous in their preservation. I think, in this area, the Santorini and the Wirsung duct go to this area and I think should be resected with the head of the pancreas.

PROFESSOR A. KINGSNORTH: You are trying to sell the operation on the basis that you get poor endocrine and exocrine function after the standard Whipple but this is improved with your operation. You did not tell us, though, in the matched pairs group, which had pancreaticojejunostomy and which had pancreaticogastrostomy because we now know that the exocrine function after pancreaticojejunostomy is much better. Now, the Japanese have been performing pancreaticogastrostomy. Did you match pair for that in your Whipples operations or did they all receive the Spanish pancreaticogastrostomy?

PROFESSOR L. FERNANDEZ-CRUZ: No. In the pylorus-preserving group, the patients operated on in Nagoya had a pancreaticogastrostomy and, in Barcelona, a pancreaticojejunostomy.

PROFESSOR A. KINGSNORTH: So you controlled for the type of pancreatic reconstruction?

PROFESSOR L. FERNANDEZ-CRUZ: Yes.

A Proposal of an Appropriate Surgical Approach for Cancer of the Ampulla of Vater: Retrospective Analysis of 73 Resected Cases

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KEY WORDS:

Cancer of the ampulla of Vater; Less invasive surgery; Clinicopathologic factor; Prognosis; Retrospective analysis

ABBREVIATIONS:

Pancreatoduodenectomy (PD); Pylorus-preserving Pancreatoduodenectomy (PpPD); Pancreatic Head Resection with Segmental Duodenectomy (PHRSD); Endoscopic Ultrasound (EUS); Intraductal Ultrasound (IDUS)

ABSTRACT

Background/Aims: Because early ampullary cancer has a good prognosis, less invasive surgery should be considered. But recent reports point out limitations of ampullectomy.

Methodology: Between April 1975 and March 2005, seventy-three patients with ampullary cancer were treated. The survival rates of different clinicopathologic features were analyzed retrospectively.

Results: Macroscopically, N(-) (negative lymph node metastasis), Panc(-) (no invasion of the pancreatic parenchyma) patients had a significantly longer 5-year survival rate than N(+) (positive lymph node metastasis), Panc(+) (invasion of the pancreatic parenchyma) patients (61.1% vs. 23.1%, 62.2% vs.

21.9%). Histologically, n(-), panc(-), and du(-) (no invasion of the duodenum) patients also had a significantly longer 5-year survival rate than n(+), panc(+), and du(+) (invasion of the duodenum) patients (63.3% vs. 21.1%, 64.3% vs. 29.8%, 83.3% vs. 36.8%, respectively). Patients with Panc(+), Du(+), mixed type and tumors other than the exposed type had significantly more lymph node metastases.

Conclusions: We propose PpPD and regional lymph node dissection as the reasonable operative method. If the tumor is preoperatively diagnosed as Panc(-), Du(-) and N(-), less invasive surgery may be indicated.

INTRODUCTION

The periampullary area is anatomically complex and represents the junction of three different epithelia, the pancreatic, bile ducts and the duodenal mucosa. Tumors of the ampulla of Vater, therefore, arise from any one of these epithelia (1). Tumors arising from the ampulla of Vater are uncommon, and account for less than 1% of all gastrointestinal malignancies (2). They have relatively good prognoses after resection. The overall 5-year survival rate ranges from 34% to 68% (1-10), which is better than that of distal biliary (27-33%) or pancreatic head adenocarcinoma (15-16%) (2,9,11,12).

Pancreatoduodenectomy (PD) is the current treatment for advanced ampullary cancer, and pylorus-preserving pancreatoduodenectomy (PpPD) has been increasingly performed for early ampullary cancer in recent years. However, local resection (ampullectomy) has been attempted not only for benign lesions but also for early cancer as an alternative to PD or PpPD.

Because the prognosis of this disease varies according to its stage, selection of the appropriate surgical procedure must be dictated by its stage. Most surgeons have generally felt local resection or less in-

vasive surgery for early cancer to be most appropriate, but their indications remain controversial.

In this study, we retrospectively reviewed a series of 73 consecutive patients undergoing resection for ampullary cancer and analyzed the correlation between clinicopathologic features and survival of patients in order to propose the most appropriate surgical approach for ampullary cancer.

METHODOLOGY

Patients

Between April 1975 and March 2005, 73 patients with cancer of the ampulla of Vater were treated at Nagoya University Hospital. They were comprised of 44 males and 29 females and their ages ranged from 42 to 76 years (mean: 62.4 years). The follow-up period ranged from 0.5 to 145.5 months (mean: 35.4 months). Clinical information was obtained through medical record review and direct patient contact. Tumor size ranged from 0.7 to 9.0cm (mean: 2.4cm). All tissue specimens were evaluated in accordance with the General Rules for Surgical and Pathological Studies on Cancer of the Biliary Tract issued by the Japanese Society of Biliary Surgery (13). This study was approved by the Ethics Committee of the hospi-

tal. Informed consent was obtained from all patients for the subsequent use of resected specimens.

Statistical Analysis

Patient survival rate was calculated by the Kaplan-Meier method, and the difference between the groups was tested by the log-rank test. The correlation between macroscopic factors and lymph node metastasis was analyzed by chi-square test. Statistical significance was noted if the *P* value was < 0.05. Statistical analyses were performed using Stat View (Version 5.0) software (Abacus Concepts, Berkeley, CA).

RESULTS

Survival Rate by Operative Procedures

All patients underwent surgery, and a radical procedure was performed in 66 patients (90.4%). The 5-year survival rate of all patients was 38.8%. The operation was a PD in 40 patients, a PpPD in 22, a total pancreatectomy in one, a pancreatic head resection with segmental duodenectomy (PHRSD) (14) in 3 and a bypass in 7. The operative procedure before 1990 was PD, and PpPD was typically performed after that time. There was no significance in the survival rates between PD and PpPD (Figure 1).

Survival Rate by Macroscopic Factor

The 5-year survival rates by surgical stage were 85.7% in stage I, 34.6% in stage II, 44.1% in stage III and 0% in stage IVa and IVb (data not shown) (13). There were 33 N(-) patients (negative lymph node metastasis diagnosed preoperatively) and 32 N(+) patients (positive lymph node metastasis diagnosed preoperatively). The N(-) patients had a significantly longer 5-year survival rate than the N(+) patients (61.1% vs. 23.1%; *P*=0.0005, data not shown). Pancreatic invasion by the tumor was graded on a two-point scale: Panc(-) (no invasion of the pancreatic parenchyma diagnosed preoperatively) and Panc(+) (invasion of the pancreatic parenchyma diagnosed preoperatively). Thirty-four patients were Panc(-) and 31 were Panc(+). The Panc(-) patients also had a significantly longer 5-year survival rate than the Panc(+) patients (62.2% vs. 21.9%; *P*=0.015, data not shown). Duodenal invasion of the tumor was graded on a two-point scale: Du(-) (no invasion of the duodenum diagnosed preoperatively) and Du(+) (invasion of the duodenum diagnosed preoperatively). Eleven patients were Du(-) and 56 were Du(+). The Du(-) patients had a tendency for better prognosis, but this was not significant (*P*=0.13, data not shown). The tumor was morphologically graded as a "tumor with ulcer (tumor predominant)" type in 21 patients, "ulcer with tumor (ulcer predominant)" type in 9, "exposed tumor" type in 29 and "non-exposed tumor" type in 8. The prognosis for the "exposed tumor" type was significantly better (*P*<0.0001, data not shown).

Survival Rate by Pathological Factor

The 5-year survival rates of comprehensive stage were 88.9% in stage I, 44.2% in stage II, 27.4% in

stage III and 0% in stage IVa and IVb (data not shown) (13). There were 28 n(-) patients and 34 n(+) patients. The n(-) patients had a significantly longer 5-year survival rate than the n(+) patients (63.3% vs. 21.1%; *P*=0.0003) (Figure 2A). Twenty-eight patients were panc(-) and 31 were panc(+). The panc(-) patients also had a significantly longer 5-year survival rate than the panc(+) patients (64.3% vs. 29.8%; *P*=0.016) (Figure 2B). Eleven patients were du(-) and 45 were du(+). The du(-) patients also had a significantly longer 5-year survival rate than the du(+) patients (83.3% vs. 36.8%; *P*=0.029) (Figure 2C). The patients who lacked lymph vessel invasion, vascular invasion, surgical margins and perineural invasion had a better prognosis than patients who had these factors (*P*=0.0083, *P*=0.012, *P*=0.0068, *P*=0.047, respectively, data not shown).

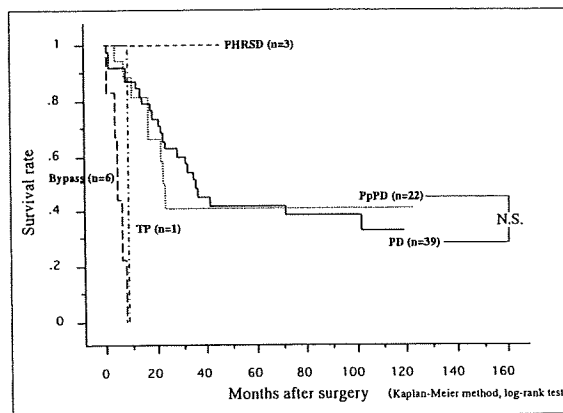


FIGURE 1 Overall survival rate by operative procedure. There was no significance in the survival rates between PD and PpPD.

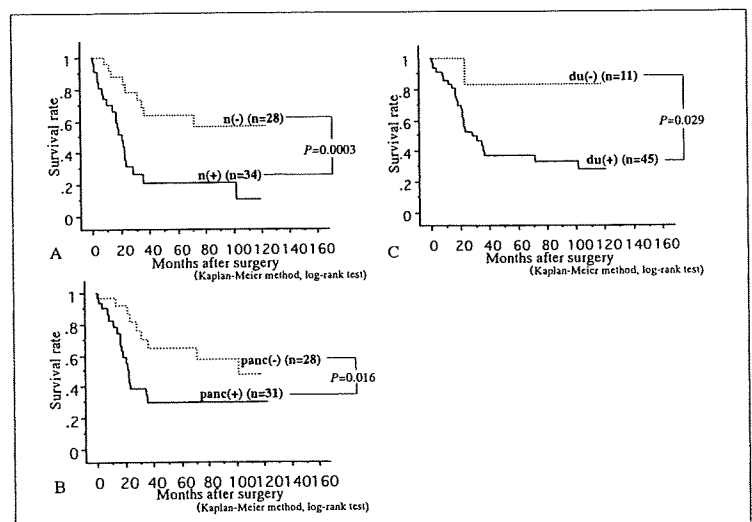


FIGURE 2 Overall survival rate by pathological factor.

(A) Overall survival rate by pathological lymph node metastasis. The n(-) patients had a significantly longer 5-year survival rate than the n(+) patients (63.3% vs. 21.1%; *P*=0.0003). (B) Overall survival rate by pathological pancreatic invasion. The panc(-) patients had a significantly longer 5-year survival rate than the panc(+) patients (64.3% vs. 29.8%; *P*=0.016). (C) Overall survival rate by pathological duodenal invasion. The du(-) patients had a significantly longer 5-year survival rate than the du(+) patients (83.3% vs. 36.8%; *P*=0.029).

Univariate Analysis for Overall Survival by Pathological Factors

Univariate analyses were performed for those clinicopathological factors that had significant correlation with survival of ampullary cancer. Lymph node metastasis, pancreatic invasion, tumor type other than the exposed type and vascular invasion were predictive of survival (Table 1). Multivariate analysis using a logistic regression model was performed, but there was no significant independent predictive factor (data not shown).

The Correlation between Macroscopic Factors and Pathological Lymph Node Metastasis

There was neither a significant correlation between tumor size and prognosis (data not shown) nor between tumor size and lymph node metastasis (Table 2). However, Panc(+) and Du(+) patients and those with mixed type tumors (tumor with ulcer type plus ulcer with tumor type) or tumors other than the exposed type ($P=0.006$, $P=0.028$, $P=0.021$, $P=0.0017$, respectively) were significantly more likely to have lymph node metastases (Table 2).

DISCUSSION

Unlike other cancers of the pancreatic head region, ampullary cancer is often detected relatively

early and has therefore been associated with better resectability and prognosis. In many patients, the initial signs, which include obstructive jaundice, hepatic dysfunction and abdominal pain, facilitate detection of this cancer (3). The increase in curative resection resulting from improved diagnostic techniques, early diagnosis, operative techniques and postoperative care is also proposed to be reasons for the improved survival rate.

The following clinicopathologic factors have been proposed to be significantly correlated with patient survival after PD for ampullary cancer: lymph node metastasis (1-4,7-9,11,15,16), resection margin (2,5,9), intraoperative blood transfusion (8,11), depth of invasion (11), perineural invasion (10), lymphovascular invasion (1), pancreatic invasion (3), and morphology (15). In our series, negative lymph nodes: the absence of pathological pancreatic invasion, duodenal invasion, vascular invasion and perineural invasion: and the morphology were found to favor prolonged survival. Lymph node metastasis, pancreatic invasion, morphology and vascular invasion were the predictive factors in univariate analyses.

The 5-year survival rate of ampullary cancer drops to zero if two or more regional lymph nodes are involved (4,17). Lymph node metastasis is extremely important in predicting the prognosis of patients with ampullary cancer. Therefore, the selection of cases without lymph node metastasis prior to resection is an essential part of achieving less invasive surgery.

However, preoperative imaging modalities have limitations in terms of diagnosing lymph node metastasis in ampullary cancer. The reported accuracy of endoscopic ultrasound (EUS) for detecting lymph node metastasis ranges from 57% to 68% (18-20). Intraductal high-frequency ultrasound (IDUS) provides complementary information in diagnosing tumor extension and demonstrates whether infiltration of Oddi's muscle layer exists, but has low sensitivity in the detection of lymph node metastasis (18). Accordingly, the identification of clinicopathologic factors capable of predicting lymph node metastasis before operation is difficult for the selection of ampullary cancers suitable for less invasive surgery.

Although the ampullary sphincter muscle may limit cancer spread to the surrounding tissues, histological evidence of tumor extension from the ampulla into the pancreatic parenchyma appears to reflect lymph node spread and regional disease. Harada *et al.* reported rates of pancreatic invasion as high as 59% and an associated increased incidence of lymph node metastasis in patients whose adenocarcinoma of the ampulla of Vater had been treated with PD (21). Bakkevold reported that histologic evidence of invasion to the duodenal muscularis propria has been shown to predict the presence of lymph node metastasis and could thus be used to make intraoperative decisions regarding the use of local excision *vs.* PD (22). In our analysis, there was a significant correlation between lymph node metastasis and macroscopic factors such as pancreatic invasion, duodenal invasion and morphology

TABLE 1 Univariate Analysis for Overall Survival of Patients

Variable	Odds ratio	95% CI	P value
Lymph node metastasis (present : absent)	3.854	1.75-8.49	0.008
Pancreatic invasion (present : absent)	2.602	1.16-5.82	0.02
Duodenal invasion (present : absent)	6.848	0.93-50.6	NS
Exposed type (absent : present)	3.777	1.71-8.35	0.001
Tumor size (≥ 2.0 cm : < 2.0 cm)	1.169	0.53-2.58	NS
Vascular invasion (present : absent)	4.607	1.58-13.5	0.0052
Perineural invasion (present : absent)	2.528	0.94-6.82	NS

TABLE 2 The Correlation between Macroscopic Factors and Lymph Node Metastasis

	Lymph node metastasis		P value
	n (+)	n (-)	
Pancreatic invasion			
Panc (+)	22	8	0.006
Panc (-)	12	20	
Duodenal invasion			
Du (+)	33	21	0.028
Du (-)	2	7	
Tumor size			
< 2.0 cm	10	11	NS
≥ 2.0 cm	15	13	
Morphology			
Protruding type	14	9	0.021
Mixed type	22	8	
Exposed type	8	17	0.0017
Others	28	10	

Protruding type, "exposed tumor" plus "non-exposed tumor" type;
Mixed type, "tumor with ulcer (tumor predominant)" plus
"ulcer with tumor (ulcer predominant)".