netic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasonography (EUS). The tumors were classified into three subtypes based on the principal site of tumor involvement as follows: main duct type, branch duct type, and combined type (both main duct and branch duct involved). The diameter of the main pancreatic duct (MPD) was measured by ERCP. The size of the tumor was measured by ultrasonography or EUS.

All pathologic specimens were reviewed by a pathologist (T.N.) in order to confirm the diagnosis of IPMN. They were classified as IPM adenoma, borderline IPMN, carcinoma *in situ* (CIS), and invasive IPMC, according to the criteria established by the WHO. Tumors that featured minimal stromal invasion were classified as invasive carcinoma. We divided our cases into three groups: benign IPMN, CIS, and invasive IPMC. The benign IPMN group included adenomas and borderline tumors. The malignant group included CIS and invasive IPMC. Patient data including age, gender, smoking history, alcohol history, family history of malignant neoplasm, presenting symptoms, postoperative course, and previous diagnoses of pancreatitis and diabetes mellitus were evaluated for patients with IPMNs. Serum tumor markers including carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) were recorded when available. Clinical data of 36 patients have been published previously (16).

Comparisons of the clinicopathological parameters were performed using the chi-square test or Fisher's exact test (for small numbers) for qualitative variables. Student's *t* test was used for quantitative variables and a non-parametric test (Mann-Whitney U test) if the distribution was abnormal. Significant predictive factors in the univariate analysis were then subjected to multivariate analysis. Multivariate analysis was performed by the logistic regression model, and results were expressed as the relative risk using a 95% confidence interval. Overall survival rates were calculated using the Kaplan-Meyer method, and univariate analysis was performed using the log-rank test. Survival was censored if the patient was still alive or had died from other causes. Statistical analysis was performed using Stat View (Version 5.0) software (Abacus Concepts, Berkeley, CA). All continuous data are presented as mean ± standard deviation of the mean. The presence of a statistically significant difference was denoted by $p<0.05$.

Duodenum-preserving Pancreatic Head Resection (DpPHR); Distal Pancreatectomy (DP)

RESULTS

Fifty-seven patients with IPMNs were managed surgically with curative intent from March 1991

TABLE 1 Analysis of Predictors for Malignancy and Invasive Carcinoma in 57 Patients with IPMNs

			Malignancy		Invasive IPMC	
Variables		**All**	**n**	***P***	**n**	***P***
Age	≤60	24	6	0.660	4	>0.999
	>60	33	10	5		
Sex	Male	41	8	0.054	4	0.109
	Female	16	8	5		
Smoking history	Yes	32	7	0.239	4	0.485
	No	25	9	5		
Alcohol history	Yes	30	8	0.804	5	>0.999
	No	27	8	4		
History of pancreatitis	Yes	10	6	0.022	2	0.651
	No	47	10	7		
Family history of malignancy	Yes	27	6	0.351	2	0.149
	No	30	10	7		
Diabetes	Yes	14	6	0.183	6	0.005
	No	43	10	3		
Symptomatic	Yes	25	12	0.003	6	0.161
	No	32	4	3		
Location	Head	39	12	0.504	7	0.704
	Body/Tail	18	4	2		
Tumor type	Main duct or combined type	13	8	0.004	5	0.022
	Branch duct type	44	8	4		
Mural nodule	Yes	36	16	0.0003	9	0.020
	No	21	0	0		
Serum CEA	Elevated	4	3	0.084	2	0.124
	Normal	44	12	6		
Serum CA 19-9	Elevated	9	4	0.352	4	0.040
	Normal	42	12	5		
Diameter of the tumor	≥30mm	21	6	0.724	4	0.434
	<30mm	29	7	3		
Diameter of the MPD	≥7mm	6	4	>0.999	2	>0.999
	<7mm	7	4	3		

through July 2004, and variables are summarized in **Table 1**. There were 40 male (70%) and 17 female (30%) patients, with ages ranging from 29 to 77 years (mean, 62 years) in this series. There were 32 (56%) current or former smokers, and 30 (53%) patients had a history of alcohol abuse. On the other hand, 10 (18%) patients had a history of pancreatitis, 27 (47%) had a family history of malignant neoplasm, 14 (25%) had diabetes mellitus, and 25 (44%) had symptoms on presentation. Thirty-nine (68%) of 57 patients had disease localized in the head of the pancreas. Seven IPMNs (12%) were of the main duct type, 44 (77%) were of the branch duct type, and 6 (11%) were of the combined type. The diameter of the MPD in the main duct type of IPMN ranged from 3 to 15mm, with a mean size of 8±4mm. The diameter of the cyst in the branch duct type ranged from 8 to 95mm, with a mean size of 32±18mm.

Operative procedures performed were as follows: pancreaticoduodenectomy (PD) (n=3), pylorus-preserving pancreaticoduodenectomy (PPPD) (n=16), pancreatic head resection with segmental duodenectomy (PHRSD) (n=16), segmental resection of the pancreatic body (SR) (n=12), duodenum-preserving pancreatic head resection (DPPHR) (n=1), distal pancreatectomy (DP) (n=7), and total pancreatectomy (TP) (n=2) **(Table 2)**. No operative or hospital deaths occurred.

Histological diagnosis was as follows: adenoma in 40 (70%) patients, borderline in 1 (2%), CIS in 7 (12%), and invasive carcinoma in 9 (16%). The mean follow-up period of all IPMNs was 61±35 months. The mean follow-up for the subgroups was as follows: benign IPMN (adenoma and borderline), 72 months (range 19 to 139 months); CIS, 26 months (range 7 to 47 months); and invasive IPMC, 38 months (range 1 to 90 months). We then analyzed the survival rates to assess postoperative prognosis of the 57 patients with IPMNs **(Figure 1)**. Patients with invasive IPMCs had a significantly shorter 3-year survival rate than patients with adenomas or CIS (80% *vs.* 100% *vs.* 100%; $p<0.0001$) in our series, when assessed by Kaplan-Meier curves.

The diameter of the tumor in the branch duct type of malignant IPMN was significantly larger than that observed in benign IPMN (**Table 3B**; 50.8±26.6 *vs.* 28.1±11.9; $p=0.008$, respectively). The diameter of the tumor in invasive IPMC was also significantly larger than that observed in non-invasive IPMN (54.8±28.7 *vs.* 30.0±14.9; $p=0.006$, respectively). The diameters of the MPD in the main duct type proved to be larger than those of the less malignant IPMN, however, the differences were not statistically significant.

We statistically analyzed factors predictive of malignancy and invasive carcinoma in patients with IPMNs. The 15 potential risk factors are listed in **Table 1**. Four factors were associated with malignancy by univariate analysis. The malignant group was more likely to be symptomatic, have a history of pancreatitis, present with the main duct or combined type, and contain a mural nodule. Significant predictive factors in the univariate analysis were then subjected to multivariate analysis. Among the factors analyzed, tumor type (main duct or the combined type) was an independent predictor of malignancy (**Table 4A**; risk ratio 5.47; $p=0.034$). The other four factors associated with invasive IPMC were as follows: previous diagnosis of diabetes mellitus, main duct or combined type, the presence of a mural nodule, and elevated serum CA 19-9 level. A previous diagnosis of diabetes mellitus and main duct or combined type tumor remained significantly associated with invasive IPMC on multivariate analysis (**Table 4B**; risk ratio 7.14, $p=0.042$ and risk ratio 4.07, $p=0.044$, respectively).

TABLE 2 Operative Procedures for IPMNs

	All	Benign IPMN	CIS	Invasive IPMC
PD	3	3	0	0
PPPD	16	12	0	4
PHRSD	16	10	4	2
SR	12	11	1	0
DPPHR	1	1	0	0
DP	7	4	1	2
TP	2	0	1	1
	57	41	7	9

DISCUSSION

Since the original description of IPMNs in 1982 (1), frequent reports have been published in the literature. Today, most gastroenterological surgeons

TABLE 3 Comparison of the Size in Each IPMN

(A) Comparison of the MPD Diameter in Main Duct or Combined Type of IPMN

	Benign IPMN (n=5)	IPMC (n=8)	*P* value
MPD diameter (mm)	7.1±4.3	8.8±5.2	0.549
	Non-invasive IPMN (n=8)	Invasive IPMC (n=5)	*P* value
	7.9±4.3	8.7±5.8	0.768

(B) Comparison of the Tumor Diameter in Branch Duct Type of IPMN

	Benign IPMN (n=36)	IPMC (n=8)	*P* value
Tumor diameter (mm)	28.1±11.9	50.8±26.6	0.008
	Non-invasive IPMN (n=40)	Invasive IPMC (n=4)	*P* value
	30.0±14.9	54.8±28.7	0.006

differentiate typical cases of IPMN from other mucinous or cystic tumors of the pancreas and understand the malignant potential of this neoplasm. The natural history of this disease and the factors that determine outcome in patients with this neoplasm, however, are not well understood (17). Furthermore, it is not easy to clearly distinguish between benign and malignant IPMN or non-invasive and invasive conditions with imaging tests (18-20). Preoperative or intraoperative evaluations for malignancy or invasion are needed for the appropriate management of IPMNs.

This neoplasm is often found in elderly men in the head of the pancreas (21). Age, gender, and location in our series of 57 patients showed a similar distribution. Patients with invasive IPMC had a poor prognosis and required more radical operations, for example PD or PPPD. Otherwise, non-invasive IPMN had a good prognosis, therefore, operations that preserve pancreatic or digestive function are preferable when preoperative examinations show no signs of invasion. One patient, who had undergone DPPHR, experienced ischemic necrosis of the common bile duct, and required reoperation. In order to prevent similar complications, we performed PHRSD for the low-grade malignant pancreatic head tumors after 1998 (22). We preserve the third portion and anal side of the second portion of the duodenum by conserving the gastroduodenal artery and the anterior inferior pancreaticoduodenal artery, and we resect the pancreatic head with 3 to 4cm of segmental duodenectomy including minor and major papilla. Several previous reports have demonstrated other less invasive surgical methods for IPMNs (23-26).

In this study, we analyzed factors predictive of malignancy and surgical outcomes in a large series. Our multivariate analyses demonstrated that the main duct and the combined type were independent predictive factors of malignant IPMN; in addition, both main duct or combined type and diabetes mellitus were independent predictors of invasive IPMC. However, the diameter of the MPD was not associated significantly with the extent of malignancy. Therefore, all IPMNs affecting the MPD required surgical treatment, irrespective of size. Recent reports have demonstrated that cancer was found in 60% of 140 patients with main duct type IPMNs (27). In the branch duct type of IPMNs, the tumor diameter correlated significantly with malignancy, therefore, larger tumors required more radical surgery. Tumor type and a history of diabetes are useful factors that must be preoperatively ascertained. Previous studies showed that p53 staining of resected specimen was a significant predictor of malignancy (28); however, p53 tumor expression is not available preoperatively to guide management.

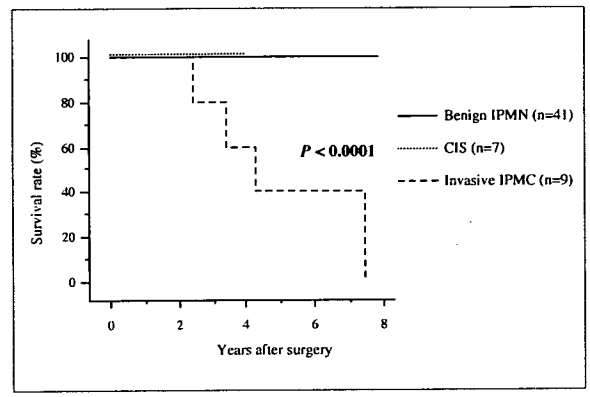

FIGURE 1 Kaplan-Meier survival curves show that patients with invasive IPMNs had a significantly shorter 3-year survival rate than patients with adenomas or carcinoma *in situ* (80% *vs.* 100% *vs.* 100%; $p<0.0001$).

We reviewed recent studies that investigated factors predictive of IPMN malignancy by statistical analysis (28-32). A MEDLINE search was conducted to identify articles in the English language that assessed the factors associated with IPMN malignancy from 1998 through 2004. The key words used included "intraductal papillary mucinous tumor (IPMT)," "intraductal papillary mucinous neoplasm (IPMN)," "predictive factor," and "predictor." Parameters associated significantly with IPMN malignancy are listed in **Table 5**. Our study demonstrated the presence of symptoms and a history of pancreatitis as significant factors, but other studies showed that these fac-

TABLE 4 Multivariate Analysis of Predictive Factors in Patients with IPMNs

(A) Factors predictive of malignancy	Risk ratio	95% Confidence Interval	*P* value
Tumor type (Main duct or combined type: Branch duct type)	5.47	1.14-26.27	0.034
Mural nodule (Yes: No)	7.46	0.74-75.68	0.089
Pancreatitis history (Yes: No)	3.48	0.61-19.96	0.161
Symptoms (Yes: No)	1.62	0.32-8.34	0.564
(B) Factors predictive of invasive IPMC	**Risk ratio**	**95% Confidence Interval**	***P* value**
Diabetes (Yes: No)	7.14	1.07-47.50	0.042
Tumor type (Main duct or combined type: Branch duct type)	4.07	1.65-25.51	0.044
Mural nodule (Yes: No)	5.71	0.48-67.18	0.166
Serum CA 19-9 (Elevated: Normal)	3.20	0.43-23.99	0.258

TABLE 5 Reports on the Factors Predictive of Malignant IPMN

Author	Raimond *et al.* (26) (n=45)	Sugiyama *et al.* (27) (n=62)	Wiesenauer *et al.* (28) (n=64)	Kitagawa *et al.* (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 (≥7mm)	†	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 *et al.* (29) (n=73)	Sugiyama *et al.* (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 (≥7mm)	†	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 invades 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.

REFERENCES

1 **Ohashi K, Murakami Y, Maruyama M, Takekoshi T, Ohta H, Ohashi I:** Four cases of mucin-producing cancer of the pancreas on specific findings of the papilla of Vater. Prog Diag Endoscopy 1982; 20:348-351. (In Japanese)

2 **Itai Y, Ohhashi K, Nagai H, Murakami Y, Kokubo T, Makita K, Ohtomo K:** "Ductectatic" mucinous cystadenoma and cystadenocarcinoma of the pancreas. Radiology 1986; 161:697-700.

3 **Loftus EV Jr, Olivares-Pakzad BA, Batts KP, Adkins MC, Stephens DH, Sarr MG, DiMagno EP:** Intraductal papillary-mucinous tumors of the pancreas: clinicopathologic features, outcome, and nomenclature. Members of the Pancreas Clinic, and Pancreatic Surgeons of Mayo Clinic. Gastroenterology 1996; 110:1909-1918.

4 **Sohn TA, Yeo CJ, Cameron JL, Iacobuzio-Donahue CA, Hruban RH, Lillemoe KD:** Intraductal papillary mucinous neoplasms of the pancreas: an increasingly recognized clinicopathologic entity. Ann Surg 2001; 234:313-321.

5 **Sarr MG, Kendrick ML, Nagorney DM, Thompson GB, Farley DR, Farnell MB:** Cystic neoplasms of the pancreas: benign to malignant epithelial neoplasms. Surg Clin North Am 2001; 81:497-509.

6 **Rivera JA, Fernandez-del Castillo C, Pins M, Compton CC, Lewandrowski KB, Rattner DW, Warshaw AL:** Pancreatic mucinous ductal ectasia and intraductal papillary neoplasms. A single malignant clinicopathologic entity. Ann Surg 1997; 225:637-644.

7 **Agostini S, Choux R, Payan MJ, Sastre B, Sahel J, Clement JP:** Mucinous pancreatic duct ectasia in the body of the pancreas. Radiology 1989; 170:815-816.

8 **Nickl NJ, Lawson JM, Cotton PB:** Mucinous pancreatic tumors: ERCP findings. Gastrointest Endosc 1991; 37:133-138.

9 **Warshaw AL:** Mucinous cystic tumors and mucinous ductal ectasia of the pancreas. Gastrointest Endosc 1991; 37:199-201.

10 **Klöppel G, Solcia E, Longnecker DS, Capella C, Sobin LH:** Histological typing of tumours of the exocrine pancreas. 2nd Edition. New York: Springer, 1996.

11 **Sugiyama M, Atomi Y:** Intraductal papillary mucinous tumors of the pancreas: imaging studies and treatment strategies. Ann Surg 1998; 228:685-691.

12 **Yamaguchi K, Chijiiwa K, Shimizu S, Yokohata K, Morisaki T, Yonemasu H, Tanaka M:** Intraductal papillary neoplasm of the pancreas: a clinical review of 13 benign and four malignant tumours. Eur J Surg 1999; 165:223-229.

13 **Chari ST, Yadav D, Smyrk TC, DiMagno EP, Miller LJ, Raimondo M, Clain JE, Norton IA, Pearson RK, Petersen BT, Wiersema MJ, Farnell MB, Sarr MG:** Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. Gastroenterology 2002; 123:1500-1507.

14 **Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA, Lillemoe KD:** Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Ann Surg 2004; 239:788-797.

15 **D'Angelica M, Brennan MF, Suriawinata AA, Klimstra D, Conlon KC:** Intraductal papillary mucinous neoplasms of the pancreas: an analysis of clinicopathologic features and outcome. Ann Surg 2004; 239:400-408.

16 **Kanazumi N, Nakao A, Kaneko T, Takeda S, Harada A, Inoue S, Nagasaka T, Nakashima N:** Surgical treatment of intraductal papillary-mucinous tumors of the pancreas. Hepatogastroenterology 2001; 48:967-971.

17 **Yamaguchi K, Sugitani A, Chijiiwa K, Tanaka M:** Intraductal papillary-mucinous tumor of the pancreas: assessing the grade of malignancy from natural history. Am Surg 2001; 67:400-406.

18 **Sugiyama M, Atomi Y, Kuroda A:** Two types of mucin-producing cystic tumors of the pancreas: diagnosis and treatment. Surgery 1997; 122:617-625.

19 **Procacci C, Carbognin G, Biasiutti C, Guarise A, Ghirardi C, Schenal G:** Intraductal papillary mucinous tumors of the pancreas: spectrum of CT and MR findings with pathologic correlation. Eur Radiol 2001; 11:1939-1951.

20 **Aithal GP, Chen RY, Cunningham JT, Durkalski V, Kim EY, Patel RS, Wallace MB, Hawes RH, Hoffman BJ:** Accuracy of EUS for detection of intraductal papillary mucinous tumor of the pancreas. Gastrointest Endosc 2002; 56:701-707.

21 **Tanaka M:** Intraductal papillary mucinous neoplasm of the pancreas: diagnosis and treatment. Pancreas 2004; 28:282-288.

22 **Nakao A:** Pancreatic head resection with segmental duodenectomy and preservation of the gastroduodenal artery. Hepatogastroenterology 1998; 45:533-535.

23 **Thayer SP, Fernandez-del Castillo C, Balcom JH, Warshaw AL:** Complete dorsal pancreatectomy with preservation of the ventral pancreas: a new surgical technique. Surgery 2002; 131:577-580.

24 **Warshaw AL, Rattner DW, Fernandez-del Castillo C, Z'graggen K:** Middle segment pancreatectomy: a novel technique for conserving pancreatic tissue. Arch Surg 1998; 133:327-331.

25 **Warshaw AL:** Conservation of the spleen with distal pancreatectomy. Arch Surg 1988; 123:550-553.

26 **Kimura W, Inoue T, Futakawa N, Shinkai H, Han I, Muto T:** Spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein. Surgery 1996; 120:885-890.

27 **Salvia R, Fernandez-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, Pederzoli P, Warshaw AL:** Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Ann Surg 2004; 239:678-685.

28 **Kitagawa Y, Unger TA, Taylor S, Kozarek RA, Traverso LW:** Mucus is a predictor of better prognosis and survival in patients with intraductal papillary mucinous tumor of the pancreas. J Gastrointest Surg 2003; 7:12-19.

29 **Raimondo M, Tachibana I, Urrutia R, Burgart LJ, DiMagno EP:** Invasive cancer and survival of intraductal papillary mucinous tumors of the pancreas. Am J Gastroenterol 2002; 97:2553-2558.

30 **Sugiyama M, Izumisato Y, Abe N, Masaki T, Mori T, Atomi Y:** Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. Br J Surg 2003; 90:1244-1249.

31 **Wiesenauer CA, Schmidt CM, Cummings OW, Yiannoutsos CT, Howard TJ, Wiebke EA, Goulet RJ Jr, McHenry L, Sherman S, Lehman GA, Cramer H, Madura JA:** Preoperative predictors of malignancy in pancreatic intraductal papillary mucinous neoplasms. Arch Surg 2003; 138:610-618.

32 **Maire F, Hammel P, Terris B, Paye F, Scoazec JY, Cellier C, Barthet M, O'Toole D, Rufat P, Partensky C, Cuillerier E, Levy P, Belghiti J, Ruszniewski P:** Prognosis of malignant intraductal papillary mucinous tumours of the pancreas after surgical resection. Comparison with pancreatic ductal adenocarcinoma. Gut 2002; 51:717-722.

Clinical Implications of Peritoneal Cytology in Potentially Resectable Pancreatic Cancer

Positive Peritoneal Cytology May Not Confer an Adverse Prognosis

Suguru Yamada, MD, Shin Takeda, MD, PhD,* Tsutomu Fujii, MD, PhD,* Shuji Nomoto, MD, PhD,* Naohito Kanazumi, MD, PhD,* Hiroyuki Sugimoto, MD, PhD,* Hideki Kasuya, MD, PhD,* Yasuhiro Kodera, MD, PhD,* Tetsuro Nagasaka, MD, PhD,† Satoshi Morita, PhD,‡ and Akimasa Nakao, MD, PhD**

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. [illegible] rameters 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)

From the Departments of *Surgery II, †Laboratory Medicine, and ‡Health and Community Medicine Program, Graduate School and Faculty of Medicine, University of Nagoya, Nagoya, Japan.

Reprints: Suguru Yamada, MD, Department of Surgery II, Graduate School and Faculty of Medicine, University of Nagoya. 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. E-mail: suguru@med.nagoya-u.ac.jp.

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 ± 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 classification[11] 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 invasion, 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.

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)

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.

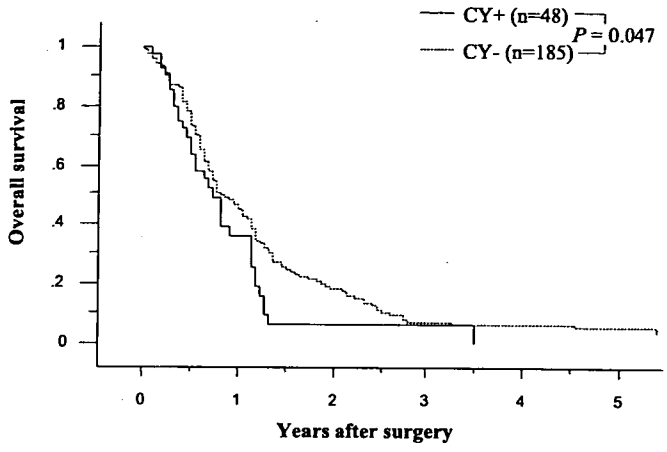

FIGURE 1. Comparison of survival curves of patients with pancreatic cancer with (CY+) and without (CY−) tumor cells in peritoneal washings. The overall survival for CY+ patients was significantly worse than for CY− patients ($P = 0.047$).

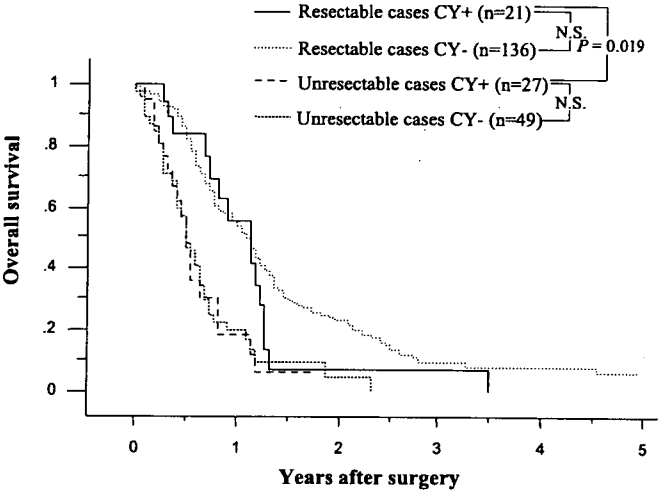

FIGURE 2. Comparison of survival curves of patients with pancreatic cancer who underwent curative resection with (CY+) and without (CY−) tumor cells in cytologic washings. The median survival time of CY+ patients was 13.6 months and that of CY− patients was 13.5 months ($P = 0.269$). Comparison of survival 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.

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

			CY+	
Series	Year	n	n (%)	Resected Cases
Martin and Goellner[22]	1986	20	5 (25)	0
Warshaw[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.

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 al[9] 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 al[8] 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 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 reaction[24] 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.

REFERENCES

1. Nakao A, Fujii T, Sugimoto H, et al. Oncological problems in pancreatic cancer surgery. *World J Gastroenterol.* 2006;12:4466–4472.
2. Warshaw AL. Implication of peritoneal cytology for staging in early pancreatic cancer. *Am J Surg.* 1991;161:26–30.
3. Fernandez-del Castillo C, Rattner DW, Warshaw AL. Further experience with laparoscopy and peritoneal cytology in the staging of pancreatic cancer. *Br J Surg.* 1995;82:11127–11129.
4. Leach SD, Rose JA, Lowy AM, et al. Significance of peritoneal cytology in patients with potentially resectable adenocarcinoma of the pancreatic head. *Surgery.* 1995;82:472–478.
5. Merchant NB, Conlon KC, Saigo P, et al. Positive peritoneal cytology predicts unresectability of pancreatic adenocarcinoma. *J Am Coll Surg.* 1999;188:421–426.
6. Jimenez RE, Warshaw AL, Fernandez-del Castillo C. Laparoscopy and peritoneal cytology in the staging of pancreatic cancer. *J Hepatobiliary Pancreat Surg.* 2000;7:15–20.
7. Nakao A, Oshima K, Takeda S, et al. Peritoneal washings cytology combined with immunocytochemical staging in pancreatic cancer. *Hepatogastroenterology.* 1999;46:2974–2977.
8. Yachida S, Fukushima N, Sakamoto M, et al. Implications of peritoneal washing cytology in patients with potentially resectable pancreatic cancer. *Br J Surg.* 2002;89:573–578.
9. Meszoely IM, Lee JS, Watson JC, et al. Peritoneal cytology in patients with potentially resectable adenocarcinoma of the pancreas. *Am Surg.* 2004;70:208–214.
10. Japan Pancreatic Society. *Classification of Pancreatic Carcinoma,* 2nd English ed. Tokyo: Kanehara, 2003.
11. Sobin LH, Wittekind CH. *TNM Classification of Malignant Tumours,* 6th ed. New York: Wiley-Liss, 2002.
12. Yang AD, Camp ER, Fan F, et al. Vascular endothelial growth factor receptor-I activation mediates epithelial to mesenchymal transition in human pancreatic carcinoma cells. *Cancer Res.* 2006;66:46–51.
13. Bernstein LR, Liotta LA. Molecular mediators of interactions with extracellular matrix components in metastasis and angiogenesis. *Curr Opin Oncol.* 1994;6:106–113.
14. Wu CC, Chen JT, Chang MC, et al. Optimal surgical strategy for potentially curable serosa-involved gastric carcinoma with intraperitoneal free cancer cells. *J Am Coll Surg.* 1997;184:611–617.
15. Grimshaw RN, Tupper WC, Fraser RC, et al. Prognostic value of peritoneal cytology in endometrial carcinoma. *Gynecol Oncol.* 1990;36:97–100.
16. Boku T, Nakane Y, Minoura T, et al. Prognostic significance of serosal invasion and free intraperitoneal cancer cells in gastric cancer. *Br J Surg.* 1990;77:436–439.
17. Bonenkamp JJ, Songun I, Hermans J, et al. Prognostic value of positive cytology findings from abdominal washings in patients with gastric cancer. *Br J Surg.* 1996;83:672–674.
18. Kodera Y, Yamamura Y, Shimizu Y, et al. Peritoneal washing cytology: prognostic value of positive findings in patients with gastric carcinoma undergoing a potentially curative resection. *J Surg Oncol.* 2001;78:175–181.
19. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma-2nd English edition. *Gastric Cancer* 1998;1:10–24.
20. Kienle P, Koch M. Are micrometastases of the peritoneum equivalent to distant metastases? *Dig Surg.* 2002;19:453–458.
21. Makary MA, Warshaw AL, Centeno BA, et al. Implications of peritoneal cytology for pancreatic cancer management. *Arch Surg.* 1998;133:361–365.
22. Bando E, Yonemura Y, Takeshita Y, et al. Intraoperative lavage for cytological examination in 1,297 patients with gastric carcinoma. *Am J Surg.* 1999;178:256–262.
23. Benevolo M, Mottolese M, Cosimelli M, et al. Diagnostic and prognostic value of peritoneal immunocytology in gastric cancer. *J Clin Oncol.* 1998;16:3406–3411.
24. Kodera Y, Nakanishi H, Ito S, et al. Quantitative detection of disseminated free cancer cells in peritoneal washes with real-time reverse transcriptase-polymerase chain reaction. *Ann Surg.* 2002;235:499–506.

Pancreatic Head Resection With Segmental Duodenectomy

Safety and Long-Term Results

Akimasa Nakao, MD, PhD, and Laureano Fernández-Cruz, MD, PhD, FRCS†*

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 procedures 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 HbA1, 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-

From the *Gastroenterological Surgery (Department of Surgery II), Nagoya University Graduate School of Medicine, Nagoya, Japan; and †Surgical Department, ICMD Hospital Clínic de Barcelona, Barcelona, Spain.

Reprints: Laureano Fernández-Cruz, MD, PhD, FRCS, Department of Surgery, University of Barcelona, Hospital Clínic, Villarroel 170, Escalera 6, 4th Floor, E-08036 Barcelona, Spain. E-mail: lfcruz@clinic.ub.es.

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 punction 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).

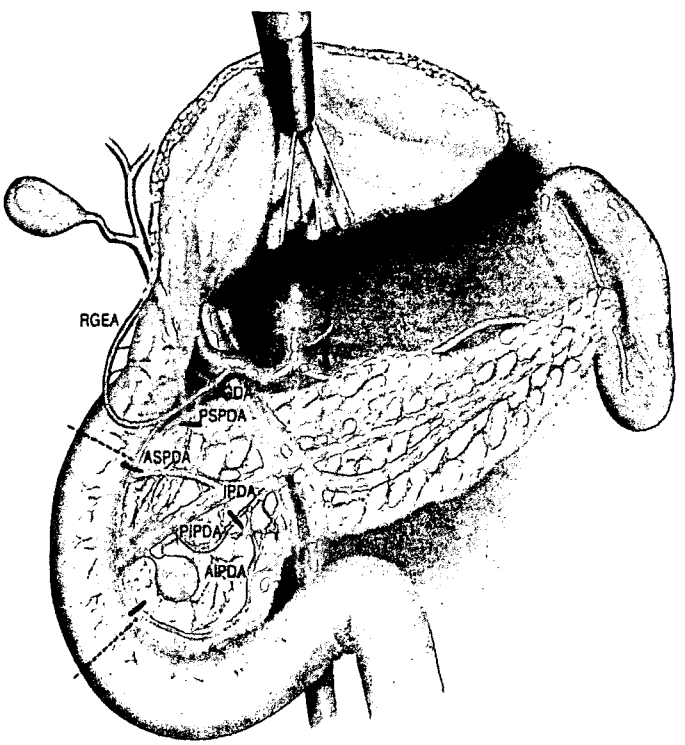

FIGURE 1. Divided lines of the pancreaticoduodenal arteries in pancreatic head resection with segmental duodenectomy. GDA indicates gastroduodenal artery; RGEA, right gastroepiploic artery; PSPDA, posterior-superior pancreaticoduodenal artery; ASPDA, anterior-superior pancreaticoduodenal artery; IPDA,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

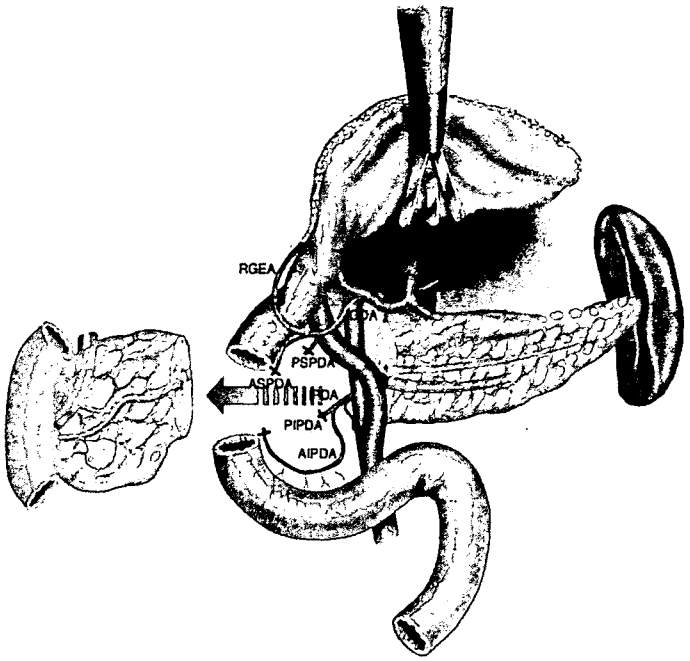

FIGURE 2. Resected portion in pancreatic head resection with segmental duodenectomy.

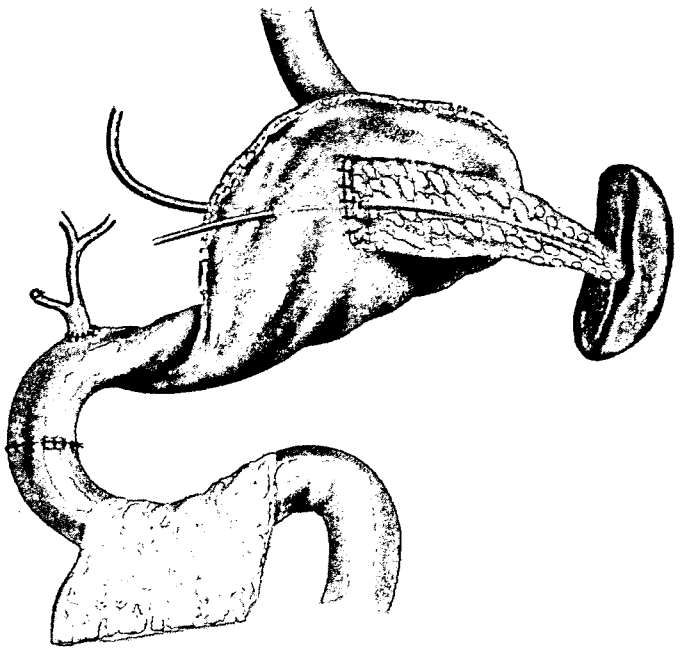

FIGURE 3. Reconstruction of the gastrointestinal tract (type A) after pancreatic head resection with segmental duodenectomy: pancreaticogastrostomy, duodenoduodenostomy, and choledochoduodenostomy.

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, hematoochexia, or melena or the sudden appearance of frank blood either on nasogastric lavage or per

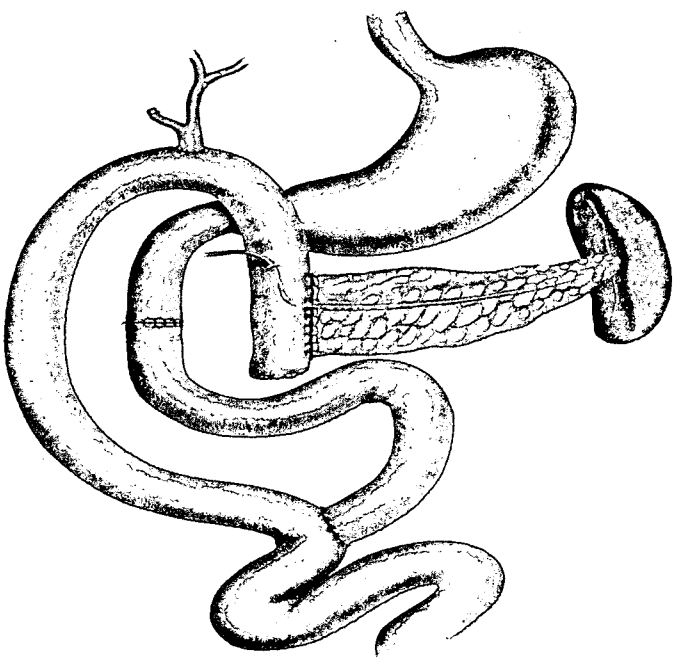

FIGURE 4. Reconstruction of the gastrointestinal tract (type B) after pancreatic head resection with segmental duodenectomy: pancreaticojejunostomy, duodenoduodenostomy, and cholecochojejunostomy.

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 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, 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_1) 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 PHRSD patients and 76.2 months for PPPD patients. Results were presented as mean ± standard deviation The surgical complication rates were compared with respect to the surgical procedure (PHRSD vs. PPPD) and between the 2 types of surgical reconstruction after PHRSD (type A vs. type B), using the Fisher exact text. Two-sided P values were always computed, and an effect was considered statistically significant at $P < 0.05$.

RESULTS

Perioperative Data in Patients After PHRSD

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 PHRSD was 365 ± 50 (range, 120–490 minutes). The mean intraoperative blood loss was 615 ± 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 PHRSD and pancreaticogastrostomy reconstruction were compared with 15 patients with PHRSD and pancreaticojejunal anastomosis. There was no difference in perioperative factors between the 2 groups. The postoperative mean hospital stay was 28.3 ± 14.2 days after PHRDS 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 ± 4.0 days after PHRSD with type B 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.

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

	PHRSD		
	Type A (20 Patients)	Type B (15 Patients)	*P*
Patient characteristics			
Age (yr)	66.1 ± 8.0	63.4 ± 6.0	NS
Female	8	5	NS
Male	12	10	NS
Perioperative results			
Operating time (Min)	365 ± 50	370 ± 20	NS
Surgical blood loss (mL)	615 ± 251	720 ± 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 ± 14.2	12 ± 4	<0.01

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

In the matched-pairs analysis 35 patients with PHRSD 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 PHRSD (11%); the difference was not statistically significant. In the PPPD group, 60% had pancreaticogastrostomy technique and 40% had pancreaticojejunostomy technique. 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 (31%) compared with the PHRSD group (14%; $P < 0.01$).

Endocrine pancreatic function measured by fasting blood glucose levels and HbA_1 levels was unchanged in 94.28% of patients in the PHRSD group and in 87.87% of patients in the PPPD group.

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

Histopathology and Tumor Recurrence

Definitive histology of the resected lesions after PHRSD 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)	1.4–96.8	1.9–155.3
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 controversial issue. In the series, Sohn et al[28] and D'Angelica et al[7] 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), DPPHR with complete resection of the pancreatic head,[18] inferior head resection of the pancreas,[21] and ventral pancreatectomy.[16] According to Murakami et al[26], 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 PHRSD 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 PHRSD and pp-Whipple, respectively. In the present series, postoperative enzyme substitution was needed in 20% of PHRSD 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 PHRSD than after PPPD.

Nakao et al[22] was the first to describe PHRSD in 1994. In 1998,[23] he reported 14 patients with PHRSD including mucin-producing cystic tumors (9 cases), annular pancreas (1 case), anomalous arrangement of the pancreatico-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, PHRSD was performed in patients with low-grade malignant diseases of the pancreatic head region including IPMN. In the Isaji and Kawarada[24] 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 al[26] reported 8 patients with branch-duct type IPMN. In all cases a pancreaticogastrostomy, duodenoduodenostomy, and choledochoduodenostomy were performed. Complications after PHRSD 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, PHRSD 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 PHRSD 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, PHRSD 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

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.

REFERENCES

1. Longnecker DS, Adler G, Hruban RH. Intraductal papillary mucinous neoplasms of the pancreas. In: Hamilton SR, Aaltonen LA, eds. *WHO Classification of Tumors of the Digestive System*. Lyon: IARC Press; 2000:237–240.
2. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an increasingly recognized clinicopathologic entity. *Ann Surg*. 2001;234:313–321.
3. Lai ECH, Lau WY. Intraductal papillary mucinous neoplasms of the pancreas. *Surgeon*. 2005;5:317–324.
4. Falconi M, Salvia R, Bassi C, et al. Clinicopathological features and treatment of intraductal papillary mucinous tumor of the pancreas. *Br J Surg*. 2001;88:376–381.
5. Wada K, Kozarek RA, Traverso LW. Outcomes following resection of invasive and non-invasive intraductal papillary mucinous neoplasms of the pancreas. *Am J Surg*. 2005;189:632–636.
6. Salvia R, Fernández-del Castillo C, Bassi C, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. *Ann Surg*. 2004; 239:678–685.
7. D'Angelica M, Brennan MF, Suriawinata AA, et al. Intraductal papillary mucinous neoplasms of the pancreas: an analysis of clinicopathologic features and outcome. *Ann Surg*. 2004;239:400–408.
8. Sugiyama M, Izumisato Y, Abe N, et al. Predictive factors for malignancy in intraductal papillary-mucinous tumors of the pancreas. *Br J Surg*. 2003;90:1244–1249.
9. Wiesenauer CA, Schmidt CM, Cummings OW, et al. Preoperative predictors of malignancy in pancreatic intraductal papillary mucinous neoplasms. *Arch Surg*. 2003;138:610–617.
10. Kawai M, Uchiyama K, Tani M, et al. Clinicopathological features of malignant intraductal papillary mucinous tumors of the pancreas: the differential diagnosis from benign entities. *Arch Surg*. 2004;139:188–192.
11. Terris B, Ponsot P, Paye F, et al. Intraductal papillary mucinous tumors of the pancreas confined to secondary ducts show less aggressive pathologic features as compared with those involving the main pancreatic duct. *Am J Surg Pathol*. 2000;24:1372–1377.
12. Matsumoto T, Aramaki M, Yada K, et al. Optimal management of the

branch duct type intraductal intraductal papillary mucinous neoplasms of the pancreas. *J Clin Gastroenterol.* 2003;36:261–265.
13. Fernandez-del Castillo C. Intraductal papillary mucinous neoplasms of the pancreas: a plea for prospective differentiation between main-duct and side-branch tumors. *Ann Surg Oncol.* 2005;12:98–99.
14. Pedrazzoli S, Sperti C, Pasquali C. Pancreatic head resection for non-inflammatory benign lesions of the head of the pancreas. *Pancreas.* 2001;23:309–315.
15. Hirano S, Kondo S, Ambo Y, et al. Outcome of duodenum-preserving resection of the head of the pancreas for intraductal papillary mucinous neoplasms. *Dig Surg.* 2004;21:242–245.
16. Takada T. Ventral pancreatectomy: resection of the ventral segment of the pancreas. *J Hepatobiliary Pancreat Surg.* 1993;1:36–40.
17. Kimura W, Morikane K, Futakawa N. A new method of duodenum-preserving subtotal resection of the head of the pancreas based on the surgical anatomy. *Hepatogastroenterology.* 1996;43:463–472.
18. Takada T, Yasuda H, Uchiyama K, et al. Duodenum-preserving pancreaticoduodenectomy. A new technique for complete excision of the head of the pancreas with preservation of biliary and alimentary integrity. *Hepatogastroenterology.* 1993;40:356–359.
19. Nagakawa T, Ohta T, Kayahara M, et al. Total resection of the head of the pancreas preserving the duodenum, bile duct and papilla with end-to-end anastomosis of the pancreatic duct. *Am J Surg.* 1997;173: 210–212.
20. Imaizumi T, Hanyu F, Suzuki M, et al. Clinical experience with duodenum-preserving total resection of the head of the pancreas with pancreaticocholedochoduodenostomy. *J Hepatobiliary Pancreat Surg.* 1995;2:38–44.
21. Nakagohri T, Kenmochi T, Kainuma O, et al. Inferior head resection of the pancreas for intraductal papillary mucinous tumors. *Am J Surg.* 2000;179:482–484.
22. Nakao A, Ohsima K, Kaneko T, et al. Pancreatic head resection with segmental duodenectomy (in Japanese). *Operation.* 1994;48:635–638.
23. Nakao A. Pancreatic head resection with segmental duodenectomy and preservation of the gastroduodenal artery. *Hepatogastroenterology.* 1998;45:533–535.
24. Isaji S, Kawarada Y. Pancreatic head resection with second-portion duodenectomy for benign lesions, low grade malignancies, and early stage carcinomas involving the pancreatic head region. *Am J Surg.* 2001;181:172–176.
25. Ahn YJ, Kim SW, Park YC, et al. Duodenum-preserving resection of the head of the pancreas and pancreatic head resection with second-portion duodenectomy for benign lesions, low-grade malignancies, and early carcinoma involving the periampullary region. *Arch Surg.* 2003;138: 162–168.
26. Murakami T, Uemura K, Yokoyama U. Pancreatic head resection with segmental duodenectomy for intraductal papillary mucinous tumors of the pancreas. *J Gastrointest Surg.* 2004;8:713–719.
27. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: An international study group (ISGPF) definition. *Surgery.* 2005;138:8–13.
28. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an update experience. *Ann Surg.* 2004;239: 788–797.
29. Bernard P, Scoazec JY, Joubert M. Intraductal papillary-mucinous tumors of the pancreas: predictive criteria of malignancy according to pathological examination of 53 cases. *Arch Surg.* 2002;137:1274–1278.
30. Matsumoto T, Aramaki M, Yada K. Optimal management of the branch duct type intraductal papillary mucinous neoplasms of the pancreas. *J Clin Gastroenterol.* 2003;36:261–265.
31. Nakagohri T, Kenmochi T, Kainuma O, et al. Intraductal papillary mucinous tumors of the pancreas. *Am J Surg.* 1999;178:344–347.
32. Kobari M, Egawa S, Shibuyya K, et al. Intraductal papillary mucinous tumors of the pancreas comprise 2 clinical subtypes: differences in clinical characteristics and surgical management. *Arch Surg.* 1999;134: 1131–1136.
33. Paye F, Sauvanet A, Terris B, et al. Intraductal papillary mucinous tumors of the pancreas: pancreatic resections guided by preoperative morphological assessment and intraoperative frozen section examination. *Surgery.* 2000;127:536–544.
34. Gigot JF, Deprez P, Sempoux C, et al. Surgical management of intraductal papillary mucinous tumors of the pancreas: the role of routine frozen section of the surgical margin, intraoperative endoscopic staged biopsies of the Wirsung duct and pancreaticogastric anastomosis. *Arch Surg.* 2001;136:1256–1262.
35. Kimura W, Nagai H. Study of surgical anatomy for duodenum-preserving resection of the head of the pancreas. *Ann Surg.* 1995;221:359–363.
36. Beger HG, Buchler M. Duodenum-preserving resection of the head of the pancreas in chronic pancreatitis with inflammatory mass in the head. *World J Surg.* 1990;14:83–87.
37. Beger HG, Buchler MW, Bittner RR, et al. Duodenum-preserving resection of the head of the pancreas in severe chronic pancreatitis; early and late results. *Ann Surg.* 1989;209:273–278.
38. Buchler MW, Friess H, Bittner R, et al. Duodenum-preserving pancreatic head resection: long-term results. *J Gastrointest Surg.* 1997;1:13–19.
39. Aranha GV, Hodul PJ, Creech S, et al. Zero mortality after 152 consecutive pancreaticoduodenectomies with pancreaticogastrostomy. *J Am Coll Surg.* 2003;197:223–231.
40. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications and outcomes. *Ann Surg.* 1997;226:248–257.
41. Martin RF, Rossi RL, Leslie KA. Long-term results of pylorus preserving pancreatoduodenectomy for chronic pancreatitis. *Arch Surg.* 1996; 131:247–252.

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 because 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 women 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.

Original Paper

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

Suguru Yamada, Tsutomu Fujii, Hiroyuki Sugimoto, Shin Takeda, Soichiro Inoue Shuji Nomoto, Naohito Kanazumi, Akimasa Nakao

Department of Surgery II, Nagoya University, Graduate School of Medicine, Nagoya, Japan
Corresponding Author: Tsutomu Fujii MD, Department of Surgery II, Nagoya University, Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Tel: +81 52 744 2249, Fax: +81 52 744 2255, E-mail: fjt@med.nagoya-u.ac.jp

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 invasive 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-

Hepato-Gastroenterology 2007; 54:10-14