resection has been effective in selected cases, the number of patients involved is small and thus the efficacy of these therapies remains unclear. The present study retrospectively reviewed outcomes for ICC following resection in a single cancer hospital.

Patients and Methods

We retrospectively examined consecutive ICC cases in our institution. From January 1995 to February 2008, a total of 60 patients underwent exploratory surgery with the prospect of curative resection for ICC. Cases with concomitant hepatocellular carcinoma were excluded from this study and 8 patients displayed unresectable lesions, giving an overall resectability rate of 87% (52 of 60). Of these 52 resected cases, 44 ICC patients (15 women and 29 men) who underwent potentially curative resection were analyzed in this study. Eight cases of palliative resection (R2) were excluded for the following reasons: residual para-aortic lymph node metastases (n = 2), gross residual tumor at the resection margin (n = 4), and residual liver metastases in the residual liver (n = 2).

Tumors were staged according to the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification system (6th ed).[10] Overall and disease-free survival rates were analyzed. The following clinicopathological features were analyzed: age; sex; primary site (colon/rectum); pStage (UICC); macroscopic type; preoperative serum carbohydrate antigen (CA) 19-9 level; preoperative serum carcinoembryonic antigen (CEA) level; bile duct invasion; vascular invasion; serosal invasion; number of nodules; lymph node metastases; tumor size; histologic grade; background liver status; lymph node dissection; and transfusion status. At our institution, ICC is generally treated by hemihepatectomy or extended hemihepatectomy. Systematic lymphadenectomy is not performed in the absence of metastasis to regional lymph nodes (hepatoduodenal nodes). Systemic lymphadenectomy along the common hepatic arteries and the hepatoduodenal ligament is per-

Table 1 Patient characteristics

Sex (M/F)	29/15	
Age (y) (range)	65.0 (41–85)	
pT stage (%)		
Stage I	14	32%
Stage II	8	18%
Stage IIIa	4	9%
Stage IIIb	0	0%
Stage IIIc	8	18%
Stage IV	10	23%
Macroscopic classification (%)		
Mass-forming type	41	93%
Intraductal type	2	5%
Infiltrating type	1	2%
Tumor size (cm) (median; range)	5.7 (2.0–12.0)	
Tumor number		
Solitary (%)	29	66%
Multiple (%)	15	34%
Background liver		
Normal liver	39	89%
Chronic hepatitis or liver fibrosis	4	9%
Cirrhosis	1	2%
Viral infection		
None	39	89%
Hepatitis B	1	2%
Hepatitic C	2	5%
HBC double-positive	2	5%

Table 2 Surgical procedures and results for 44 patients with intrahepatic cholangiocarcinoma

Surgical procedure	No.	%
Mortality	0	0%
Morbidity	13	30%
Transfusion	11	25%
Operation time (min)	435 (225–850)	
Blood loss (mL)	710 (260–3,440)	
Postoperative hospital stay (d)	21 (9–85)	
Type of hepatectomy		
Left hemihepatectomy	12	27%
Extended right hemihepatectomy	12	27%
Extended left hemihepatectomy	8	18%
Right hemihepatectomy	3	7%
Left trisectionectomy	3	7%
Central bisectionectomy	2	5%
Right trisectionectomy	2	5%
Limited resection	1	2%
Extended right lateral sectionectomy	1	2%
Combined resection		
Lymph node dissection	24	55%
Extrahepatic bile duct	12	27%
Stomach	1	2%
Pancreas	1	2%
Inferior vena cava	1	2%

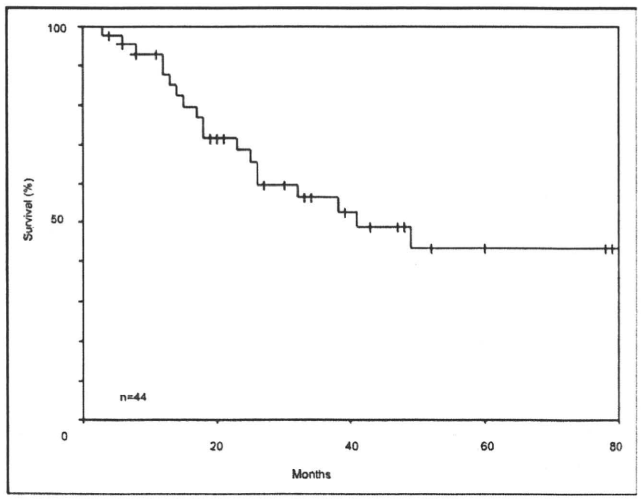

Figure 1 Kaplan-Meier overall survival for 44 patients who underwent curative resection for intrahepatic cholangiocarcinoma.

Table 3 Univariate analysis of risk factors associated with overall and recurrence-free survival for 44 patients who underwent curative resection for intrahepatic cholangiocarcinoma

Characteristic	n	5-year survival (%)	Median survival (mo)	*P**	5-year disease-free (%)	Median disease-free (months)	*P**
Overall	44	43	41		39	34	
Age (y)							
<70	31	44	32		35	15	
≥70	13	0	49	0.8140	28	41	0.309
Sex							
Male	29	44	49		35	18	
Female	15	43	41	0.8020	40	37	0.928
UICC stage							
1	14	79			83	74	
2	8	45	49	0.1560	31	34	.026*
3a	4	33	26	0.1090	0	4	.0014*
3c	8	0	41	.0141*	0	15	0.011
4	10	30	17	.0133*	20	11	.0063*
Macroscopic type							
Mass-forming type	41	42	41		37	34	
Intraductal type	2	100		0.1550	100		0.319
Infiltrating type	1	0		0.3060	0	11	0.196
Residual tumor							
R0	39	42	49		37	34	
R1	5	53		0.5470	60	0	0.908
Marginal width							
≥1 mm	27	60	82		50	67	
<1 mm	17	18	23	.0106*	21	12	.0359*
CA19-9							
<100 U/mL	34	47	49		48	41	
≥100 U/mL	10	27	17	.0215*	0	5	.002*
CEA							
<5	32	48	49		41	37	
≥5	8	32	23	0.1430	30	17	0.236
Bile duct invasion							
Absent	34	38	41		35	34	
Present	5	100		0.6090	80	67	0.792
Vascular invasion							
Absent	29	35	38		41	37	
Present	13	61	82	0.4050	23	13	0.424
Serosal invasion							
Absent	25	52	82		54	67	
Present	19	36	26	0.4700	26	14	0.193
No. of nodules							
Solitary	30	65	82		52	67	
Multiple	14	0	25	.0007*	0	6	.0022*
Lymph node metastases							
Absent	26	55			53	67	
Present	18	24	23	.0223*	15	13	.057*
Extrahepatic bile duct resection							
Absent	32	44	49		36	34	
Present	12	40	41	0.9840	41	37	0.887
Tumor size							
<5 cm	18	45	41		43	21	
≥5 cm	26	42	38	0.6480	34	18	0.359
Histological grading							
Well	14	62			53		
Mod	17	51	82	0.1490	45	17	0.161
Poor	9	12	15	.0001*	16	5	.0017*
Background liver							
Normal	39	42	38		36	18	
Injured	5	50	41	0.5540	50	37	0.217
Lymph node dissection							
Absent	20	44	49		48	41	
Present	24	41	32	0.3240	28	17	0.123
Transfusion							
Absent	33	47	41		43	17	
Present	11	38	49	0.7390	28	34	0.984

Well = well-differentiated adenocarcinoma; Mod = moderately differentiated adenocarcinoma; Poor = poorly differentiated adenocarcinoma.
*Log-rank test.

Table 4 Multivariate analysis of factors associated with overall and recurrence-free survival for 44 patients who underwent curative resection for intrahepatic cholangiocarcinoma

	Overall survival			Disease-free survival		
Risk factors	HR	95% CI	*P*	HR	95% CI	*P*
No. of tumors						
Solitary	1	—	—	1	—	—
Multiple	3.50	1.06–11.4	.039	2.98	1.15–7.71	.028
Histological grade						
Well or Mod	1	—	—	1	—	—
Poor	2.22	1.08–4.59	.030	2.01	1.07–3.73	.024

Well = well-differentiated adenocarcinoma; Mod = moderately differentiated adenocarcinoma; Poor = poorly differentiated adenocarcinoma.

formed if regional lymph nodes show metastasis, excluding para-aortic lymph nodes.

Postoperative monitoring comprised monthly blood biochemistry testing and diagnostic imaging such as computed tomography (CT) every 6 months. The therapeutic plan for recurrent cancer at the hospital is described. Surgical resection of the recurrent disease was performed for hepatic and pulmonary metastases if certain conditions were met, as follows: (1) hepatic and extrapulmonary lesions were solitary; and (2) surgery could be safely performed. However, in the case of ICC, the following conditions were added: (1) solitary lesion at any site, and (2) metachronous use of degradable starch microsphere transhepatic arterial chemoembolization (DSM-TACE) or hepatic arterial infusion (HAI) if the patient had only hepatic metastasis or if the hepatic metastasis was critical.

Systemic chemotherapy using gemcitabine or S-1 (TS-1; tegafur, gimeracil, oteracil, and potassium), an oral fluoropyrimidine, was performed on performance status 0/1 patients with recurrence in multiple organs after 2003.

Statistical analysis

Cumulative overall and disease-free survival rates were estimated according to Kaplan-Meier methods. The log-rank test was used to compare significant differences. Values of $P < .05$ were considered statistically significant. Parameters identified by univariate analysis of overall survival with $P < .05$ were entered into a Cox proportional hazard regression model to identify independent predictors of survival. All statistical analyses were conducted using SPSS version 9.0 software (SPSS, Chicago, IL).

Results

Patient characteristics are listed in Table 1. Mean duration of follow-up was 34 months (range 3–137 months; median 25.5 months). Surgical procedures and outcomes are listed in Table 2.

Eighteen of the 44 patients died of carcinoma progression, but no patient died of other disease. The cumulative overall survival rate was 87% at 1 year, 56% at 3 years, and 43% at 5 years (Figure 1). Cumulative recurrence-free survival rate was 64% at 1 year, 47% at 3 years, and 39% at 5 years. The median survival time for all patients was 41 months (95% confidence interval [CI] 18–63 months). Using univariate analysis, we found that 6 of 19 variables for overall or recurrence-free survival provided a significant estimate of prognosis (Table 3). In this study, all 10 patients with stage IV disease had lymph node metastases along the lesser curvatures and/or common hepatic arteries. UICC stage, multiple nodules, serum CA19-9 >100 U/mL, marginal width <1 mm, presence of lymph node metastasis, and poor histologic grade indicated significantly poor overall and recurrence-free survival. Multivariate analysis of the 5 factors other than UICC stage identified the presence of multiple nodules or poor histologic grade as independent prognostic factors (Table 4).

Postoperative recurrence occurred in 25 patients, with a median postoperative period of 23 months before recurrence (range 2–74 months; Table 5). Initial cancer-directed therapies after recurrence were surgical resection (N = 4: 3 liver, 1 lung), TACE, or HAI (n = 7, all liver), systemic chemotherapy (N = 6: 4 gemcitabine, 2 S-1) and best-practice supportive care (n = 4). One patient underwent liver resection following 3 courses of DSM-TACE. Table 6 provides data on 5 patients who underwent repeated resec-

Table 5 Site of relapse

	No. of patients (n = 44)	Percent
No. of relapses	25	57%
Site of first recurrence		
Liver	9	36%
Lymph nodes	3	12%
Lung	1	4%
Local	1	4%
Peritoneum	2	8%
Multiple sites	9	36%

Table 6 Course of five patients with repeat resection of recurrent ICC

Patient	Age (y)	Sex	Macroscopic type	Maximum tumor size (cm)	Number of tumours	Histology	Vascular invasion	Lymph node metastasis	1st recurrence			2nd recurrence			3rd recurrence			Survival (mo)	Outcome
									Site	Therapy	Duration after 1st resection (mo)	Site	Therapy	Duration after 1st resection (mo)	Site	Therapy	Duration after 1st resection (mo)		
1	65	Male	MF	6	1	Well	P	A	Liver (solitary)	Resection*	4							33	NED
2	63	Male	MF	12	2	Well	A	A	Liver (solitary)	Resection	12	Local	Radiation	27				38	DFD
3	67	Male	MF	5	1	Mod	P	P	Liver (solitary)	Resection	13	Lung (solitary)	Resection	44				130	NED
4	59	Male	MF	9	1	Well	P	A	Liver (solitary)	Resection	34	Local	Chemo	42				79	AWD
5	44	Male	MF	8	1	Mod	P	A	Lung (solitary)	Resection	74	Adrenal	Resection	88	Lung (solitary)	Resection	107	137	NED

MF = mass-forming type; Well = well-differentiated adenocarcinoma; Mod = moderately differentiated adenocarcinoma; P = present; A = absent; Chemo = chemotherapy; NED = no evidence of disease; AWD = alive with disease; DFD = died from disease; DSM-TACE = degradable starch microsphere transhepatic arterial chemoembolization.

*Hepatectomy was performed after 4 courses of DSM-TACE.

tion for recurrent ICC. A second resection was performed for 5 patients with solitary recurrent cancer (liver, n = 4; lung, n = 1), and 2 of these 5 patients underwent a third resection for second recurrence (lung, n = 1; adrenal gland, n = 1). One patient (no. 5) underwent a fourth resection for recurrent lung metastasis and survived 137 months after the first resection (30 months after the fourth resection).

Median durations of survival for patients with recurrent ICC who received DSM-TACE and systemic chemotherapy were 14 months and 8 months, respectively.

Comments

This study analyzed 44 consecutive patients who received curative resection of ICC in a single institution, including 5 patients who underwent repeat resections for a solitary recurrence over 13 years.

The overall 5-year survival rate was 43% and 7 patients survived more than 5 years. Given the aggressive nature of ICC, extended resection is necessary for a curative outcome. Others have found that surgical results are more favorable with extended liver resection in patients with ICC.[4,8] In our series, 40 of the 44 patients underwent hemihepatectomy or extended hemihepatectomy, with favorable short-term outcomes and no hospital deaths. Extended hemihepatectomy therefore seems to represent a valid therapeutic option for ICC. Conversely, most previous reports state that survival data may be adversely affected by mortality rates of 1% to 7%.[4,7,8] Significant advances over recent decades in imaging modalities, surgical technique, anesthesia, and critical care medicine have greatly improved the safety of major hepatic surgery. The current study may thus more accurately reflect clinical outcomes to be expected from treatment in the era of advanced surgical techniques.

Many reports have described favorable prognostic factors after resection of ICC.[6,8,9,11] These include absence of tumor at resection margins, elevated serum CA19-9 levels, solitary lesion, absence of lymph node involvement, presence of well-differentiated adenocarcinoma, and absence of vascular invasion. In our study, multiple tumors were identified as an independent poor prognostic factor, showing a 0% survival rate after 5 years for such cases compared to 64% for patients with solitary ICC. Previous studies gave a dismal prognosis even after curative resection for patients with node-positive ICC. The 5-year survival rate for patients with node-positive ICC in this study was 24%. In the present study, some patients with lymph node metastasis lived for a long time, and lymph node metastasis was not identified by our analysis as a factor associated with poor prognosis. This is probably due to the limited number of patients. Nevertheless, no consensus has yet been reached regarding lymph node dissection, and there are several reports of dire outcomes in patients with node-positive ICC even after lymph node dissection.[12] Chou et al[13] reported that the survival rate with node-positive ICC was almost the

same as with noncurative resection even after lymph node dissection, while Inoue et al[14] reported similar results of lymph node dissection not prolonging survival. Conversely, others have reported 5-year survival rates of 23% to 34% after curative resection for node-positive ICC. The outcome of hepatectomy in patients with lymph node metastasis is poor; however, our study found no desperate need for hepatectomy in a case with regional lymph node involvement. Theoretically, adjuvant chemotherapy should be considered following resection and may prolong survival, particularly in patients with poor prognostic factors. However, no standard protocol exists to extend survival in patients with ICC and further studies are clearly needed.

Recurrence rates following curative resection remain high, with 50% to 80% recurrence reported even after curative resection.[9] In the present study of 25 patients with tumor recurrence (57%), a second resection was performed on 5 patients with solitary hepatic or pulmonary metastasis, with favorable results. The liver is the most frequent site of recurrence, followed by bone, peritoneal dissemination, and then lymph nodes.[8,12] No specific therapy has been recommended for recurrent ICC, but this study presented promise that repeated resection may improve overall survival. The efficacy of surgery for hepatic and pulmonary metastases of colon cancer is well documented, but the efficacy of repeated resection for recurrent ICC remains unclear, despite several small studies.[4,15,16] The present findings indicate that some patients with ICC have no more than a few resectable lesions, as is the case for hepatic and pulmonary metastasis of colon cancer. Indications for repeated resection were not conclusive due to the small number of patients in the present study. This is a common problem because ICC is a rare disease, and most previous studies involved only a few dozen cases from a single institution. Future analyses must comprise many more ICC patients across multiple institutions.

Conclusion

Prognosis after curative resection is poor in ICC patients with multiple nodules. In selected patients with solitary hepatic or pulmonary recurrence, repeated resection may offer long-term survival.

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Improved Survival of Left-sided Pancreas Cancer after Surgery

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Objective: Resective therapeutic strategy for left-sided pancreatic adenocarcinoma is open to debate. The post-resection outcomes and factors influencing post-resection survival for adenocarcinoma of the body and tail of the pancreas were analyzed to determine the effectiveness of surgery.

Methods: A total of 73 patients with adenocarcinoma of the body or tail of the pancreas who underwent resection between 1994 and June 2007 were evaluated for overall survival.

Results: Multiple malignancies were present in 34 of 73 patients (47%). Overall 1-, 3- and 5-year survival rates after surgery were 79%, 34%, and 30%, respectively. Presence of symptoms, multiple cancers and level of preoperative tumor marker did not influence post-resection survival. As for tumor characteristics, tumor size, histological tumor differentiation, retroperitoneal invasion, status of residual tumor and UICC staging represented significant prognostic indicators by univariate analysis. Gemcitabine, when administered as an adjuvant settings, strongly worked for improving post-resection outcome (5-year survival rate = 51%). Factors shown to have independent prognostic significance on multivariate analysis were tumor size (<3 vs. ≥ 3 cm), status of residual tumor (R0 vs. R1, 2), and postoperative administration of gemcitabine.

Conclusions: Appropriate patient selection and accurate surgical technique with postoperative adjuvant therapy could benefit survival of patients with carcinoma of the pancreas body and tail.

Key words: GI-Pancreas-Surg – HBP Surgery – Prognostic factors

Pancreatic cancer (invasive ductal adenocarcinoma of the pancreas) is the fifth leading cause of cancer death in Japan (1), and is among the most lethal neoplasms, with almost equal annual death toll and incidence (2). The pancreas is anatomically segmented into head, body and tail, and invasive carcinoma may arise from any part. Left-sided carcinoma of the pancreas has been reported as more lethal than those arising from the head (3), and some authors have even doubted the effectiveness of resection in treating left-sided carcinoma of the pancreas (4,5). In the latest decade, however, several reports have shown the effectiveness of extended resection for such tumors with 5-year survival rates of 14–19% and long-term survivors and factors for such favorable outcomes have been reported and analyzed (6–8).

Meanwhile, gemcitabine has been introduced as a drug to improve overall survival of the patients with advanced pancreatic cancer (9). And such a newly coming drug was also reported effective for improving the postoperative recurrence-free survival (10,11). The present study reviews our recent experiences with resected ductal adenocarcinoma arising in the body and tail of the pancreas, evaluating the clinicopathological characteristics, post-resection survival and factors influencing outcomes after surgery.

PATIENTS AND METHODS

Demographics, Operative Factors and Tumor Characteristics

Our policy to select the patients for resection of pancreas cancer is locally resectable neither with gross para-aortic lymph node metastasis nor with distant metastasis in the preoperative diagnostics. Between January 1994 and June 2007, a total of 426 patients underwent surgery for pancreatic tumors at Cancer Institute Hospital, Tokyo, Japan. Among these, 290 patients (68%) had invasive ductal adenocarcinoma, 43 intraductal papillary mucinous neoplasms, 18 mucinous cystic tumors, 12 serous cystadenomas, 3 acinar cell carcinomas, 29 endocrine cell tumors, 9 metastatic tumors and 22 other tumors. Of 290 patients with pancreatic adenocarcinoma, 200 patients (69%) had tumors originating from the head and 90 patients (31%) had tumors of the body or tail. Of the 90 patients with body or tail adenocarcinoma, 4 had gastrointestinal bypass operations and 4 underwent probe laparotomy. After excluding 3 patients with distant metastases (liver, 1 patient; peritoneum, 2 patients) and 6 with invasive adenocarcinoma derived from intraductal papillary mucinous neoplasm, 73 patients remained for further analyses.

The 73 patients included 44 men (60%) and 29 women (40%) with a mean age of 68.0 ± 9.2 years (median, 69 years). Various initial symptoms were present in 23 of the 73 patients (32%) on diagnosis of the malignancy, including: abdominal pain ($n = 13$), back pain ($n = 5$), nausea ($n = 4$) and diarrhea ($n = 1$). Among 50 asymptomatic patients, 3 showed elevated serum amylase levels and 4 had onset or aggravation of diabetes mellitus. Multiple malignancies were present in 34 of the 73 patients (47%). Synchronous multiple malignancies were seen in 6 patients, comprising esophageal, gastric, gallbladder and colon cancer, hepatocellular carcinoma, and malignant lymphoma ($n = 1$ each). Metachronous multiple malignancies were seen in 28 patients, including: breast cancer ($n = 5$), prostate cancer ($n = 6$), gastric cancer ($n = 4$), uterine cancer ($n = 2$), esophageal cancer ($n = 1$), hepatocellular carcinoma ($n = 1$), colon cancer ($n = 4$), lung cancer ($n = 2$) and malignant lymphoma of the stomach ($n = 1$). The period between pancreatic cancer and other primary cancers ranged from 25.6 years before occurrence of pancreatic carcinoma to 2 years after. One patient had undergone previous treatment for breast cancer, gastric cancer and uterine cancer and another had received treatment for hepatocellular carcinoma and colon cancer. Malignant lymphoma was the only tumor that developed after surgery of pancreatic cancer. All multiple cancers, except for malignant lymphoma and hepatocellular carcinoma, had been surgically resected (Table 1). All pancreatic tumors were solitary and the majority of them arose from the body of the pancreas. Thirty-six tumors (49%) exceeded 3 cm in diameter, with a mean maximum diameter of 3.3 cm.

Table 1. Clinicopathological characteristics of patients with invasive carcinoma of the body and tail of the pancreas

Age (years)	68.0 ± 9.0 (median 69; range 45–89)
Sex (male:female)	44:29
Symptom (yes:no)	23:50
Multiple primary cancers	
No	39
Synchronous	6
Metachronous	28
CA19-9 (U/ml)[a]	387 ± 1376 (median 77; range 10–11379)
Location	
Body	53
Tail	20
Operative procedure	
Distal pancreatectomy	66
Appleby's operation	3
Total pancreatectomy	2
Pancreatoduodenectomoy	2
Combined resected organ	
Portal vein	4
Colon	5
Stomach	5
Left kidney	1
Blood loss (ml)	707 ± 605 (median 530; range 50–2950)
Operation time (min)	329 ± 142 (median 345; range 162–823)
Size (cm)	3.3 ± 1.7 (median 2.8; range 1.2–8.5)
Histological differentiation	
Well	36
Mod	32
Poor	4
Undifferentiated	1
Microscopic portal vein invasion[b]	
Negative	39
Positive	22
Retroperitoneal invasion (including extrapancreatic nerve plexus)[c]	
Negative	32
Positive	39
Positive lymph nodes[d]	
0	36
1	18
≥2	18

Continued

Table 1. *Continued*

Residual tumor	
R0	55
R1	12
R2	6
UICC staging	
1a	5
1b	4
2a	21
2b	21
3	12
4	10
Postoperative chemotherapy using gemcitabine	
No	37
Adjuvant	25
After recurrence	11

[a]Data missing for 1 patient.
[b]Data missing for 12 patients.
[c]Data missing for 2 patients.
[d]Data missing for 1 patient.

Operative procedures included 66 distal pancreatectomies with splenectomy. Appleby's operation was applied for three patients who had tumors invading to the celiac trunk. For two tumors originating from the body and extending to the level of the gastroduodenal artery, Whipple procedure was performed. As for procedures in detail, distal pancreatectomy was performed in a retrograde manner until 2000, while antegrade distal pancreatectomy was performed for 54 patients from 2001 onwards, involving division of the splenic artery and vein before dissecting the pancreatic body and tail from the retroperitoneum (12). The peripancreatic lymph nodes were routinely removed according to the operative procedure. At the start of resection, the precaval and intercavoaortic nodes between the level of the left renal vein and the inferior mesenteric artery were dissected after Kocherization. These nodes were just picked and examined by frozen section, when the patients were 76 years old or above.

Intraoperative blood loss was <1000 ml in 57 patients, and 11 patients (15%) received blood transfusion during surgery. Combined resection and reconstruction of the portal vein was performed in four patients. Among 73 patients, 11 underwent combined resection of other organs due to direct invasion of the tumor, involving the colon in 5 patients, stomach in 5 and left kidney in 1.

Histologically, 36 patients (49%) had well differentiated tubular adenocarcinoma, while histology showed poor differentiation in 4 patients. Among 61 patients for whom status of portal vein invasion was recorded, 22 (36%) showed positive invasion of the portal vein system by the tumor. Microscopic invasion to retroperitoneal tissues, including the extrapancreatic nerve plexus, was seen in 50 patients (66%). Among 72 patients in whom status of lymph node metastasis was described, 36 (50%) had positive lymph nodes and 18 (25%) had solitary node metastases. Metastasis to para-aortic lymph nodes was seen in nine patients. Microscopic residual tumors were identified on the posterior dissecting surface in 12 patients. Meanwhile 6 patients had R2 resection: 3 at the posterior dissected surface and 5 at the pancreatic cut-stump (2 patients had both at the posterior dissected surface and at the pancreatic stump). According to UICC classification, stages III and IV accounted for 22 patients (30%). In this study, when tumor was found invading to the nerve plexus around the superior mesenteric artery, such tumor was assigned to T4. The 10 stage-4 diseases comprised 9 with para-aortic lymph node metastasis and 1 with the other distant lymph node metastasis. In our department, chemotherapy for invasive pancreatic cancer has been performed using gemcitabine since May 2002. The reasons for using or refraining from gemcitabine varied. Among 18 patients undergoing surgery before May 2002, 16 had no chemotherapy and the remaining 1 had chemotherapy by gemcitabine after recurrence. From April 2002 and March 2005, we participated in the multicenter randomized controlled trial of postoperative adjuvant therapy using gemcitabine. During this period, the patients were treated with this drug during 3 months after surgery, according to the allocation. Among 55 patients after May 2002, the agent was used in an adjuvant setting for 25 patients, while 10 received gemcitabine for recurrent disease. The remaining 20 patients (11 without recurrence and 9 with recurrence) were not treated using gemcitabine. Follow-up information was obtained through direct contact with patients, by investigating the family register and by reviewing hospital charts.

Statistics

Both uni- and multivariate methods were used to determine the prognostic significance of various factors in pancreas cancer patients. The primary outcome variable analysed was survival. All continuous data are presented as mean $\pm$ standard error of the mean. Differences in proportions of categorical variables were evaluated using Pearson's χ^2. Survival curves were generated using Kaplan–Meier methods and were compared using the log-rank test. Patients alive as of June 2008 were censored at the time of follow-up. Multivariate Cox regression analysis was used to identify factors independently associated with survival. Values of $P < 0.05$ were considered statistically significant.

RESULTS

There was neither 90-day nor in-hospital mortality after surgery. Overall 1-, 3-, and 5-year survival rates

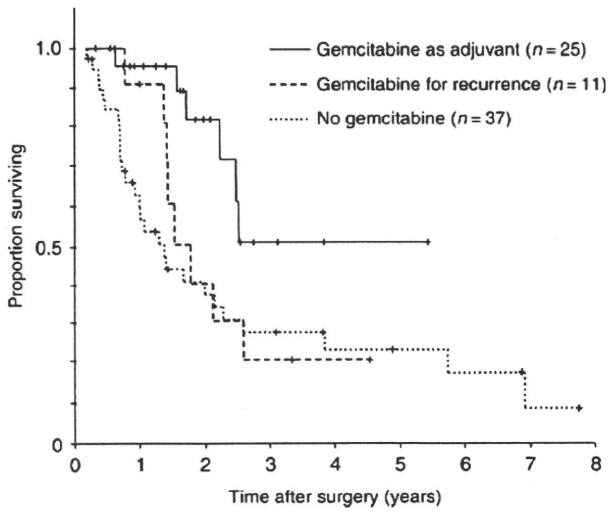

Figure 1. The cumulative 5-year survival rate of patients with postoperative adjuvant use of gemcitabine was 51%, being significantly better than that of those who underwent gemcitabine chemotherapy for recurrent tumors ($P = 0.04$) or who received no gemcitabine ($P = 0.006$). The survival of the patients treated with gemcitabine for recurrent tumor was comparable to those without chemotherapy ($P = 0.54$).

after surgery were 79, 34 and 30%, respectively. All deaths after discharge were due to tumor recurrence, except for 1 patient who died from acute exacerbation of hepatitis B immediately after chemotherapy for gastric malignant lymphoma with swelling of mediastinal lymph nodes, which was found 2 years after surgery for pancreatic cancer.

Univariate Analysis

Presence of symptoms, multiple cancers and level of preoperative tumor marker did not influence post-resection survival. Combined resection of other organs due to direct invasion of the tumor or to secure adequate surgical margins were not significant predictors after surgery. Neither increased intraoperative blood loss <1000 ml nor red blood cell transfusions showed significant prognostic impact on post-resection survival.

As for tumor characteristics, tumor size, histological tumor differentiation, retroperitoneal invasion (including extrapancreatic nerve plexus), status of residual tumor and UICC staging represented prognostic significance. Status of lymph node metastases had no significant effect on patient survival after surgery. Positive para-aortic lymph nodes in nine patients did not influence postoperative outcome. As for postoperative chemotherapy, the patients with postoperative adjuvant use of gemcitabine fared very good to achieve 5-year survival rate of 51%. Contrarily, the outcome of patients who underwent gemcitabine chemotherapy for recurrent tumors was significantly worse than those with adjuvant gemcitabine ($P = 0.04$) and was comparable to those without chemotherapy ($P = 0.54$). As a whole, use of gemcitabine significantly improved the post-resection outcome of the patients with body and tail pancreas cancer (Fig. 1).

Multivariate Analysis

Possible prognostic factors were selected from univariate analyses and from a review of the literature for further multivariate analyses. When integrated, all data were dichotomized from the results of univariate analyses as follows: multiple primary tumors (absent vs. present), histological differentiation (well vs. others), residual tumor (R0 vs. R1 or R2), number of positive lymph nodes (0 vs. ≥ 1) and postoperative use of gemcitabine (not performed vs. performed). The factors of age, sex, operative procedure and UICC staging were not included for multivariate analysis. Factors displaying independent prognostic significance were: (i) tumor size (<3 vs. ≥ 3 cm); (ii) residual tumor; and (iii) postoperative use of gemcitabine.

Recurrences were found in 45 (62%) patients: in the liver in 9, liver and other site in 6, lung (only or with other sites) in 4, peritoneum in 6, lymph node in 5, pancreas bed in 4 and remnant pancreas in 4. In seven patients, tumor marker suggested recurrence without evidence of imaging diagnostics.

DISCUSSION

Pancreatic ductal adenocarcinoma remains the fifth leading cause of cancer deaths in Japan (1) and has traditionally displayed a 5-year survival rate $<10\%$ after curative resection. Resectability rate for body and tail lesions is reportedly less than that for head, neck or uncinate lesions, as proximal lesions often cause obstructive jaundice and present earlier, while the disease is still localized to the pancreas, whereas distal lesions tend to have vague, non-specific symptoms and often go undiagnosed until a relatively advanced stage. Recently, however, improvements in pancreatic resection and perioperative adjuvant treatment have combined to produce therapeutic success for such ominous tumors. Several groups have reported markedly improved 5-year survival rates approaching 20% (6–8,13) for patients undergoing curative resection. Furthermore, a study reported an outstanding 5-year survival rate of 42% after surgery for locally advanced pancreas body and tail cancer without additional treatment (14). As for long-term prognosis after resection, relatively large series from specialized centers have shown more than 10 long-term survivors after resection (7,8), although only three 5-year survivors had been reported for pancreatic body and tail lesions before 1996 (6).

The present study showed the 5-year survival rate of 30% and included seven patients who survived longer than 5 years. According to an analysis of prognostic factors, such good outcome might largely be due to postoperative use of gemcitabine. As shown in Table 2 and Fig. 1, the patients with adjuvant gemcitabine fared very good to have 5-year survival rate of 51%. Twenty patients with recurrence and no gemcitabine treatment did not survive longer than 3 years with median survival time of 0.73 year, while 11 patients with gemcitabine for recurrent disease showed two 3-year survivors with median survival time of 1.8 years. The

Table 2. Univariate survival analysis after surgery for invasive carcinoma of the body and tail of the pancreas

	Survival rate (years)				Median	
	n	1	3	5	survival time	*P*-value
Age						
<70	38	75	38	32	2.2 (1.3–3.1)	0.95
≥70	35	84	29	29	2.1 (1.4–2.9)	
Sex						
Male	44	72	24	24	1.8 (1.2–2.4)	0.09
Female	29	89	51	40	3.8 (1.3–6.4)	
Symptom						
No	50	78	31	23	2.2 (1.2–3.1)	0.51
Yes	23	82	39	39	2.5 (1.0–4.0)	
Multiple primary cancer						
No	39	87	31	31	2.2 (1.9–2.6)	0.11
Synchronous	6	50	–	–	0.8 (0–2.0)	
Metachronous	28	75	47	32	1.2 (0.3–4.9)	
CA19-9 (U/ml)[a]						
≤37	21	80	45	30	2.6 (1.8–3.3)	0.32
>37	51	78	29	29	1.8 (1.2–2.4)	
Location						
Body	53	75	36	29	2.2 (1.4–2.9)	0.69
Tail	20	89	30	30	2.1 (1.2–3.1)	
Concomitantly resected organ						
No	59	83	35	29	2.2 (1.9–2.6)	0.50
Yes	14	64	29	29	1.4 (0.6–2.3)	
Blood loss (ml)						
<1000	57	81	41	35	2.2 (1.7–2.8)	0.10
≥1000	16	65	10	0	1.7 (0.9–2.4)	
Blood transfusion						
No	62	80	38	33	2.2 (1.6–2.7)	0.26
Yes	11	73	0	0	1.7 (0.7–2.6)	
Size (by pathology) (cm)						
<3	37	85	61	61	6.9	**0.003**
≥3	36	73	17	13	1.7 (1.3–2.1)	
Histological differentiation						
Well	36	88	40	33	2.5 (2.0–3.1)	**0.05**
Mod	32	71	34	34	1.5 (1.1–2.0)	
Poor and undifferentiated	5	60	0		1.6	
Microscopic portal vein invasion[b]						
No	39	89	46	37	2.6 (0.5–4.7)	0.64
Yes	22	79	32	32	2.5 (1.1–3.9)	
Retroperitoneal invasion (including extrapancreatic nerve plexus)[c]						
Negative	24	83	51	38	3.8 (1.6–6.1)	**0.05**
Positive	47	77	21	21	1.7 (0.9–2.5)	
Positive lymph nodes[d]						
0	36	88	40	35	2.2 (1.8–2.5)	0.42
1	18	72	36	–	2.5 (1.3–3.8)	
≥2	18	76	14	–	1.8 (1.2–2.3)	
Residual tumor						
R0	55	84	41	36	2.3 (1.6–2.9)	**0.03**
R1	12	49	25	–	1.0 (0.3–1.6)	
R2	6	83	0		1.7 (0.9–2.5)	
Postoperative chemotherapy using gemcitabine						
No	37	65	30	25	1.4 (0.8–2.0)	**0.04**
Adjuvant	25	95	51	51	–	
After recurrence	11	90	20	–	1.8 (1.3–2.3)	
UICC staging						
Ia	5	80	80	53	6.9	**0.009**
Ib	4	100	50	–	2.6	
2a	21	94	44	44	2.2 (2.0–2.4)	
2b	21	78	45	–	1.8 (1.3–2.2)	
3	12	75	11	11	1.4 (0.8–2.0)	
4	10	50	10	–	0.7 (0.6–0.7)	

[a]Data missing for 1 patient.
[b]Data missing for 12 patients.
[c]Data missing for 2 patients.
[d]Data missing for 1 patient.
Bold typeface indicates significant values of each factor for prognosis after surgery.

survival of the patients without gemcitabine (5-year survival rate = 23%, median survival time = 1.4 years) is comparable to other reported series (7,8). As pancreatic ductal adenocarcinoma is principally a generalized disease even in resected patients, use of adjuvant therapy is the most promising way to improve outcomes after surgery. Several studies have reported fluorouracil-based chemotherapy as effective for pancreatic carcinoma in the adjuvant setting (15,16), although two Japanese studies could not confirm any benefit from fluorouracil-based adjuvant chemotherapy (17,18). Gemcitabine has been introduced as a drug to improve overall survival and provide definite clinical benefit, such as reducing cancer pain (9). A German and Japanese group recently reported the definite effectiveness of postoperative adjuvant chemotherapy using gemcitabine to improve recurrence-free survival (10,11). Evaluating the effectiveness of this agent in the present study was difficult, since the application of gemcitabine was not randomly controlled in our series. However, the 5-year survival rate of around 50% for patients who received postoperative adjuvant gemcitabine would indicate the possible anti-tumor power of this agent.

Table 3. Factors from multivariate analysis influencing survival

Factor	Hazard ratio	95% confidence interval	*P*-value
Tumor size			
<3 cm			
≥3 cm	2.57	1.21–5.48	0.014
Residual tumor (R0 vs. R1, 2)			
R0			
R1, 2	2.65	1.26–5.57	0.010
Postoperative use of gemcitabine			
Not performed			
Performed	0.42	0.20–0.93	0.031

One of the notable features of the present series was the high ratio (34%) of carcinoma of the body and tail of the pancreas among all resected invasive ductal adenocarcinoma. Almost all western series have included <10% body and tail tumors among all resected pancreas cancers (6,19). Another report from Japan (8) have shown 30% of body and tail carcinomas of all resected tumors and a nationwide survey by the Japanese Pancreas Society reported that cancer of the body and tail of the pancreas comprise 17.5% of all resected tumors (20). Such a high ratio of body and tail cancer in Japanese series might suggest racial differences in this carcinoma, or alternatively, characteristics of tertiary referral centers specializing in cancer treatment. In the present series, 51 of the 76 patients (67%) had no subjective symptoms on diagnosis of tumor, suggesting relatively early diagnosis by an effective system at outpatient clinics. Another characteristic finding of this series was a low rate [7% (5 of 76)] of poorly differentiated tumor. Such high-grade tumors account for around 40% in western reports (6,19). A Japanese nationwide survey reported that poorly differentiated tumor comprised 10.6% of resected cases (20). Histological differentiation is reportedly one of the tumor-related factors identified as predictive of post-resection survival (19,21–23). Comparable overall survival between this series and others would suggest differences in criteria for pathological diagnosis.

Cancer patients are at high risk of developing a second cancer after the treatment of initial cancers. According to the literature, multiple primary carcinomas in some pancreatic cancer patients might be caused by a genetic predisposition (24). In the present series, 45% of patients displayed multiple primary tumors other than pancreas cancer. All patients with metachronous multiple cancers were diagnosed as having second pancreatic malignancies during periodic checkups for a previously diagnosed cancer. However, no differences in TNM staging were found between patients with metachronous multiple tumors and those with no or synchronous tumors and post-resection survival time was similar between groups, as already reported (25). This result suggests aggressive characteristics of the tumor and the difficulty of early diagnosis for pancreatic cancer due to a lack of sensitive screening markers or diagnostic modalities.

R0 resection was an independent factor for post-resection survival in multivariate analysis in the present series (Table 3). Complete resection is reportedly important in achieving favorable survival after surgery (19,21,22,26). In the present series, median survival time for R0 resection patients was 2.3 years, comparable to other larger series (6–8,27). The most common site of final positive resection margins is the retropancreatic surface facing the celiac axis or superior mesenteric artery or retroperitoneal tissue (13,19). This part cannot be assessed in the early course of resection and further resection to achieve negative margins is usually impossible, particularly when cancer cells have infiltrated into the neural plexus around the celiac axis or superior mesenteric artery. In the present series, 14 of 47 patients with retroperitoneal invasion (30%) displayed cancer-positive dissected margins, while 1 of 24 patient without retroperitoneal invasion (4%) had residual tumor, indicating significant relationship with these factors ($P = 0.01$). Such a relationship would influence the result of multivariate analysis. Lillemoe *et al.* (28) and Kuhlmann *et al.* (29) reported that microscopic incomplete pancreatoduodenectomy gave better survival and palliation to patients with pancreas carcinoma than bypass operation. In the present series, patients with microscopic residual tumor fared similar to those with gross remnant disease after surgery and those of R1 or R2 resection altogether showed median survival of 1.3 years. The latest report of chemotherapy including gemcitabine for locally advanced and/or metastatic pancreatic carcinoma indicated median survival time of 6–8 months (30–33). Thus, our data support the role of palliative distal pancreatectomy, which is simpler and safer compared to the Whipple procedure, in patients with left-sided pancreas cancer.

As for other operative or tumor factors, only tumor size was found to be an independent predictive factor for post-resection survival. Tumor size is the factor which has long been reported as a potential prognostic factor after surgery of pancreatic cancer (5,19,27,34). Intraoperative blood loss and/or transfusion requirements are frequently reported as predictors of post-resection survival for invasive pancreatic cancers (19,21,35). In the present series, tumor size (<3 vs. ≥3 cm) had a significant relationship with volume of operative blood loss (<1000 vs. ≥1000 ml) ($P = 0.01$ by chi-square test) and tumor stage ($P = 0.04$ by chi-square test). According to such and above-mentioned interaction, operative blood loss ≥1000 ml and positive retroperitoneal invasion should not be independent factor in the multivariate context.

The present study revisited and reconfirmed the ominous outcomes of left-sided pancreatic carcinoma. However, we also verified that appropriate patient selection, accurate surgical technique and postoperative adjuvant therapy could provide benefits for the survival of patients with carcinoma of the pancreas body and tail.

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Conflict of interest statement

None declared.

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Prognostic impact of pancreatic margin status in the intraductal papillary mucinous neoplasms of the pancreas

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Background. *Intraductal papillary mucinous neoplasm (IPMN) of the pancreas often recurs after operative resection. The absolute risk and incidence of recurrence, however, especially in the remnant pancreas, is unknown.*

Methods. *We reviewed our 18-year experience of 144 surgical cases of IPMNs and selected 103 cases of benign IPMN and carcinoma in situ (CIS) for analysis of the clinicopathologic features and long-term outcome of the recurrent disease, with particular emphasis on the status of the cut margins of the pancreas.*

Results. *No patient with benign IPMN died within 5 years. Recurrences in the remnant pancreas were observed in 9 cases: 4 (4.9%) among the 81 cases of benign IPMNs and 5 (22.7%) among the 22 cases of CIS. All recurrences were considered as multicentric because none recurred at the true resection margin of the previous operative resection. The pancreatic transection margin was normal or hyperplastic in 64 patients, whereas adenoma was detected at the margin in 28 patients. The presence of adenoma had no influence on the outcome, and recurrence in the remnant pancreas was diagnosed in 5 (7.8%) of 64 adenoma-negative patients and 3 (10.7%) of 28 adenoma-positive patients. Furthermore, both overall survival and recurrence-free survival were similar between the 2 groups.*

Conclusion. *In benign IPMN and CIS, a favorable prognosis can be expected irrespective of the status of the pancreatic cut surface, although follow-up with adequate imaging studies is recommended for detection and resection of the recurrent disease. (Surgery 2010;148:285-90.)*

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INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN) IS increasingly recognized as a disease entity and is characterized by an adenomatous proliferation of pancreatic duct epithelium that may involve the main pancreatic duct or ductal branches alone or in combination.[1-3] IPMN is composed of a spectrum of diseases from benign to malignant.[1,4] This neoplasm is rare, as it accounts for only 1% of pancreatic neoplasms and 24% of pancreatic cystic neoplasms, according to previous reports.[5,6] IPMNs exhibit different degrees of malignancy, which range from adenoma with mild atypia to invasive carcinoma. Most IPMNs, including noninvasive intraductal papillary mucinous carcinomas (IPMCs), have a more favorable prognosis than pancreatic ductal adenocarcinoma, although some cases of invasive IPMC have a poor prognosis.[7-9]

Because the entire pancreatic duct is potentially at risk of developing into a neoplasm, long-term follow-up is recommended after operative resection for IPMN.[7,10] We sometimes encounter recurrence of the IPMNs in the pancreatic remnant for which repeated pancreatectomy should be considered in the absence of distant metastasis.[11] Little is known, however, about the etiology,

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risk factors, and actual incidence of recurrence in the remnant pancreas, with the exception of some studies that involved a small number of patients.[12,13] In the current study, we reviewed our institutional experience during the past 18 years to analyze the clinicopathologic features of IPMNs with particular emphasis on recurrences in the remnant pancreas and with the status of the pancreatic cut margin at the initial operative resection. The primary aim of the study was to explore the indication for additional resection of the pancreas when a cut margin is found intraoperatively to be positive for neoplastic cells.

PATIENTS AND METHODS

Patient characteristics. In all, 144 patients with IPMN who underwent operative resection between March 1991 and July 2009 were retrieved from the prospective database of the Department of Surgery II, Nagoya University. The association between various clinicopathologic parameters and clinical outcome was assessed. Because the main focus of this study was to evaluate the influence of the pancreatic cut margin status on the recurrence in the remnant pancreas, invasive IPMCs were excluded and 104 patients with benign IPMN (IPM adenoma [IPMA] and borderline IPMN) and carcinoma in situ (CIS) were selected for analyses. This case series includes 57 patients who underwent another analysis in the authors' previous publication.[14] All patients were followed for a mean period of 47.0 months or until death.

Various state-of-the-art diagnostic modalities were introduced during the 2 decades of patient accrual. Patients underwent computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP) as the standard imaging studies until the introduction of magnetic resonance cholangiopancreatography (MRCP) in 1995 that replaced ERCP. After 2000, multidetector row CT (MDCT) and endoscopic ultrasonography (EUS) were performed in addition to MRCP. After 2003, positron emission tomography was used where necessary to differentiate between IPMN and invasive adenocarcinoma. CT/MDCT or EUS was routinely performed every 6 months as a postoperative follow-up examination.

The study was approved by the hospital's ethics committee. Informed consent was obtained from all patients for the subsequent use of resected tissues.

Pathologic examination. All pathologic specimens were reviewed by pathologists at our institution. The tumors were classified into 2 subtypes based on the principal site of tumor involvement as follows: the main duct type, in which the lesion was located in the dilated main pancreatic duct with or without involvement of dilated branch ducts, and the branch duct type, in which the branch ducts were dilated without involvement of the main pancreatic duct. They were also graded as IPMA, borderline IPMN, CIS, and invasive carcinoma according to the criteria established by the World Health Organization (WHO).[15] An intraoperative frozen-section examination of the pancreatic transection margin was performed, and the extent of each pancreatectomy was extended if CIS or invasive carcinoma was confirmed. Overall survival (OS) and recurrence-free survival (RFS) were compared according to the histopathology of IPMN and the final pancreatic cut surface status.

Statistical analysis. The OS rates were estimated using the Kaplan-Meier method, and the differences in survival curves were analyzed using a log-rank test. A statistical analysis was performed using Stat View software (version 5.0; 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 $P < .05$.

RESULTS

Patient characteristics, surgical treatment, and survival rate. The patient characteristics of 144 cases of IPMNs are summarized in Table I. This study included 89 males (62%) and 55 females (38%), with a mean age of 64.8 years (range, 29–82). Ninety-nine (69%) of 144 patients had disease localized in the head of the pancreas. Forty-nine IPMNs (34%) were of the main duct type and 95 (66%) were of the branch duct type. Histologic diagnosis was as follows: adenoma in 78 (54%) patients, borderline in 3 (2%) patients, CIS in 22 (15%) patients, and invasive carcinoma in 41 (28%) patients. There were no operative or in-hospital deaths.

Correlations between histopathologic diagnosis and prognosis. No patient with benign IPMN died within 5 years of operative resection, and both the OS and RFS of patients with invasive carcinoma were significantly worse than benign IPMNs and CIS (data not shown).

Type of recurrence. Of 104 patients with benign IPMN and CIS, 10 patients developed recurrence (Table II). The recurrence occurred in the remnant pancreas in 9 patients, and at the peritoneal surface in 1 patient. All recurrences in the remnant pancreas were considered to be multicentric and occurred in sites other than the cut surface of the previous operative resection. The only case

Table I. Demographics and clinical characteristics of 144 patients

Characteristic	*Value*
Age (years) mean ± SD (range)	64.8 ± 9.7 (29–82)
Sex (male/female)	89/55
Follow-up period (months) mean (range)	40.9 (1–189)
Type of tumor	
Main duct IPMN	49
Branch duct IPMN	95
Tumor location	
Head	99
Body	40
Tail	5
Histopathologic rype	
Benign (adenoma—borderline)	81
Carcinoma in situ	22
Invasive carcinoma	41
Operation	
Total pancreatectomy	7
Pancreatic head resection	
PD, PPPD	45
PHRSD	43
DPPHR	1
Middle pancreatectomy	21
Distal pancreatectomy	27

DPPHR, Duodenum-preserving pancreatic head resection; *PD*, pancreaticoduodenectomy; *PPPD*, pylorus-preserving pancreaticoduodenectomy.

of peritoneal recurrence was observed in a patient with CIS, and it may be attributable to the EUS-guided fine-needle aspiration biopsy that was performed prior to the operative resection. The association between the type of histopathology and recurrence was examined. Four of 81 (4.9%) patients with benign IPMNs had recurrences in the remnant pancreas, although none had extrapancreatic recurrences (Table III). The recurrence rate among patients with CIS was higher at 22.7% (5/22 patients).

Pancreatic cut surface status. The final pancreatic transection margin was normal epithelium or hyperplasia in 64 patients (adenoma-negative group) and adenoma in 28 patients (adenoma-positive group). The pancreatic cut surface status could not be evaluated in 10 patients, and the remaining patient underwent total pancreatectomy. In the current series, 91 of 92 frozen sections were concordant with the permanent section, which is an accuracy rate of 99%. The only case of misdiagnosis had a false-positive result, by which the margin was reported intraoperatively as adenoma but turned out to be the normal epithelium on the permanent section. The incidence of recurrent IPMN in the remnant pancreas was not influenced by the presence of adenoma at the cut surface, and it was diagnosed in 5 (7.8%) of 64 adenoma-negative patients and 3 (10.7%) of 28 adenoma-positive patients, respectively (Table IV). Finally, no significant differences in OS or RFS were observed between the 2 groups (Figs 1 and 2).

DISCUSSION

The concept of IPMN was proposed by the WHO in 1996.[16] Recently, the number of asymptomatic IPMNs detected during routine screening program has increased as a result of advanced imaging modalities such as MDCT.[17-19]

Characteristically, IPMN has a broad range of histologic malignancy grades.[4,18] In addition, because IPMN often exhibits intraductal spread and skip lesions, it is difficult to define the extent of pancreatic parenchyma to be resected.[20-23] As the therapeutic strategy including indication for operative resection and extent of the pancreas to be resected depends on these factors, a precise diagnosis of malignancy grade and location is needed. Several diagnostic criteria for malignant potential of IPMN have been reported.[24-29] Operative indications include all main duct IPMNs and branch duct IPMNs of more than 30 mm in diameter or with mural nodules.[25-27]

Because of intraductal development of the IPMN, a determination of the extent of tumor spread is often difficult by imaging studies. Although we usually observe mucosa of the main pancreatic duct using an intraoperative pancreatoscope to check for residual lesions, an examination of the pancreatic cut margin through intraoperative frozen section is considered also to be an essential procedure.[30,31] Microscopic foci of tumor cells are often found at the margin even if the resection margin seemed likely to be tumor free macroscopically or by the imaging studies. This is 1 of the most important pitfalls to be bear in mind in the surgical treatment of IPMN. According to the International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas, IPMAs at the resected margin do not warrant subsequent resection because they bear only minimal risk of progression to cancer.[13] Because sufficient data have not been reported, however, we evaluated the implications of margin status.

In our series, recurrence occurred only in the remnant pancreas, and no extrapancreatic recurrence was observed with the exception of 1 patient, which is possibly of iatrogenic origin. Our

Table II. Recurrence type and prognosis of 10 cases

Patient	*age/sex*	*Surgical procedure*	*Location, type of IPMN*	*Pathology*	*Margin status*	*Duration until recurrence (years)*	*Site of recurrence*	*Second pancreatectomy*	*Second pathology*	*Prognosis (years)*
Remnant pancreas										
1	57/M	MP	Pb, BD	Adenoma	Unknown	13.0	Remnant pancreas	PR	Invasive	Alive (13.8)
2	58/F	DP	Pb, MD	CIS	Negative	7.3	Remnant pancreas	(Unresectable)		Dead (9.7)
3	68/M	MP	Pb, BD	Adenoma	Adenoma	10.4	Remnant pancreas	PD	Invasive	Alive (11.7)
4	29/M	MP	Pb, BD	CIS	Negative	5.5	Remnant pancreas	PHRSD	Invasive	Alive (8.0)
5	75/F	DP	Pb, MD	CIS	Negative	2.3	Remnant pancreas	TP	Invasive	Alive (4.1)
6	70/M	PPPD	Ph, MD	CIS	Negative	2.2	Remnant pancreas	DP	Invasive	Alive (3.9)
7	78/F	PHRSD	Ph, BD	Adenoma	Adenoma	1.7	Remnant pancreas	(Observation)		Alive (3.1)
8	72/M	PPPD	Ph, BD	Adenoma	Adenoma	0.8	Remnant pancreas	TP	Borderline	Alive (1.6)
9	61/F	PHRSD	Ph, MD	CIS	Negative	Unknown	Remnant pancreas	(Unresectable)		Dead (2.4)
Extra-pancreas										
10	57/M	DP	Pb, BD	CIS	Negative	2.9	Peritoneum	—		Dead (3.4)

BD, Branch duct type; *DP*, distal pancreatectomy; *MD*, main duct type; *PD*, pancreaticoduodenectomy; *PR*, partial resection; *PPPD*, pylorus-preserving pancreaticoduodenectomy; *TP*, total pancreatectomy.

Table III. Histopathology of IPMN and recurrence

		Number of patients with recurrence	
Histopathology of IPMN	n	*Remnant pancreas*	*Extra-pancreas*
Benign (adenoma and borderline)	81	4 (4.9%)	0
Carcinoma in situ	22	5 (22.7%)	1 (4.5%)

results suggested that the recurrence rate after pancreatectomy for IPMN was not increased and OS/RFS rates were not influenced when IPMA was detected on the pancreatic cut surface. This finding may indicate that neither subsequent resection nor total pancreatectomy is necessary, in accordance with the International Consensus Guidelines. Patients with positive margins may have a good prognosis because IPMN is typically slowly growing, the branch duct IPMN in particular has little possibility of becoming malignant, and only a small number of neoplastic cells are estimated to be present at the cut surface.[32,33] Additionally, this result may indicate that IPMA and CIS are good candidates for limited operations such as pancreatic head resection with segmental duodenectomy (PHRSD) and middle pancreatectomy (MP).[34,35] It may be useful to bear in mind when surveying patients postoperatively that the incidence of recurrences in patients with CIS was somewhat greater than that in patients with benign IPMN. An analysis of a greater number of patients is needed to establish the optimal method of follow-up.

In addition, invasive IPMC, which had an adverse prognosis frequently involving extrapancreatic recurrences, should be treated as a different disease entity. As in the invasive ductal adenocarcinoma of the pancreas, extended pancreatectomy with lymph node dissection and postoperative multimodality therapy could be proposed to improve the prognosis.

This study has some limitations. It covered almost 18 years, during which preoperative and postoperative diagnostic approaches improved considerably. Principles in the therapeutic approaches, however, have remained consistent, and high accuracy of the intraoperative frozen section analysis was retained throughout this time period. Furthermore, because of refinements in the diagnostic modalities, surgical cases of IPMN have increased prominently over the years, and as many as 90 of the 144 cases in the current study

Table IV. Pancreatic margin status and recurrence

Margin status	n	*Overall recurrence*	*Recurrence in the remnant pancreas*	*Recurrence in the extra-pancreas*
Adenoma	28	3 (10.7%)	3 (10.7%)	0
Negative	64	6 (9.4%)	5 (7.8%)	1 (1.6%)
Unknown	10	1 (10%)	1 (10%)	0
Total pancreatectomy	1	0	0	0

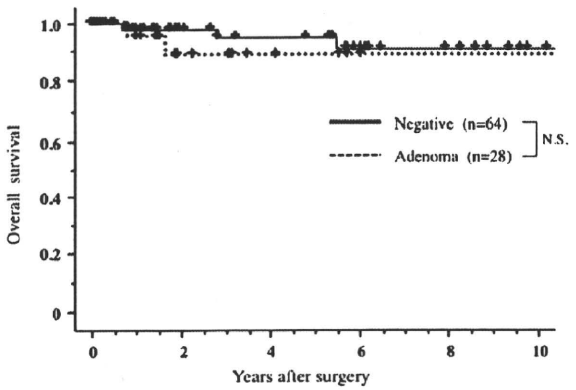

Fig 1. Pancreatic cut surface status and overall survival. No significant difference was observed between the 2 groups.

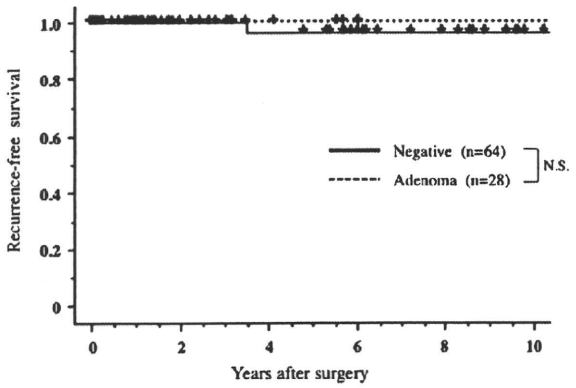

Fig 2. Pancreatic cut surface status and recurrence-free survival. No significant difference was observed between the 2 groups.

had been treated during the last 5 years. Although this study remains preliminary and may be biased by the small sample size, more reliable results are likely to be available in the future.

In conclusion, our results offered valuable insight for operative and postoperative management of IPMN. In IPMA and CIS, although periodic imaging examinations by MDCT and EUS after pancreatectomy seem to be necessary for detection of recurrent IPMN in the remnant pancreas, patients can expect to have a favorable prognosis irrespective of the pancreatic cut surface status. Therefore, organ-preserving operations such as PHRSD and MP can be indicated and no subsequent resection is needed even if IPMA is confirmed at the margin.

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Review

Selection and Outcome of Portal Vein Resection in Pancreatic Cancer

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Abstract: Pancreatic cancer has the worst prognosis of all gastrointestinal neoplasms. Five-year survival of pancreatic cancer after pancreatectomy is very low, and surgical resection is the only option to cure this dismal disease. The standard surgical procedure is pancreatoduodenectomy (PD) for pancreatic head cancer. The morbidity and especially the mortality of PD have been greatly reduced. Portal vein resection in pancreatic cancer surgery is one attempt to increase resectability and radicality, and the procedure has become safe to perform. Clinicohistopathological studies have shown that the most important indication for portal vein resection in patients with pancreatic cancer is the ability to obtain cancer-free surgical margins. Otherwise, portal vein resection is contraindicated.

Keywords: pancreatic cancer; portal vein resection; isolated pancreatectomy; catheter-bypass of the portal vein

1. History of Portal Vein Resection

The procedures for pancreatoduodenectomy (PD) and alimentary tract reconstruction after PD were established during the 1940s [1–3]. PD became the treatment of choice for cancer of the pancreatic head region. The importance of combined resection of the portal vein for pancreatic head cancer to increase resectability and radicality was emphasized by Child [4]. He performed a two-stage operation. The first stage involved ligation of the portal vein; then, after development of collateral circulation, PD combined with portal vein resection was completed as the second stage, without reconstruction of the portal vein. However, this two-stage operation had a definite disadvantage; therefore, it was never

further developed [4]. One-stage PD combined with portal vein resection using portocaval anastomosis was performed by McDermotte [5], but this procedure was not pursued either because of the possibility of Eck syndrome. Therefore, reconstruction of the portal vein is necessary. To reconstruct the portal vein after resection, homo- or autograft vessel transplantation [6–8] and the use of an artificial vessel [9,10] have been reported. The ideal reconstruction of the portal vein is end-to-end anastomosis of the portal vein [11–13]. This procedure has become quite common. The catheter-bypass procedure of the portal vein has since been developed and has contributed to portal vein resection and reconstruction with safety and ease [14]. Using this catheter bypass procedure of the portal vein, isolated PD combined with portal vein resection has been performed, which involves a non-touch isolation technique [15].

2. Catheter-Bypass Procedure and Isolated Pancreatectomy

In PD, the arteries that flow into the pancreatic head region are ligated and divided, and the drainage veins from the pancreatic head are ligated and divided before manipulation of the pancreatic head. Kocher's maneuver is not performed in isolated PD. The first step of this operation uses a mesenteric approach to dissect lymph nodes and nerve plexuses around the superior mesenteric artery, and the inferior pancreatoduodenal artery is ligated at the root (Figure 1). Catheter-bypass of the portal vein using an antithrombogenic catheter was used to prevent portal congestion or hepatic ischemia during resection and reconstruction of the portal vein or simultaneous resection of the portal vein and hepatic artery (Figures 2 and 3) [14,15]. Para-aortic lymph node dissection is performed after isolated pancreatectomy and before reconstruction of the portal vein. Portal vein reconstruction is done by end-to-end anastomosis between the portal and superior mesenteric veins. No reconstruction of the splenic vein is necessary by distal gastrectomy (Figure 4).

Figure 1. Photograph of lymph node dissection around the superior mesenteric vein and artery, by the mesenteric approach. The inferior pancreatoduodenal artery is exposed, ligated and divided. SMA, superior mesenteric artery; SMV, superior mesenteric vein; IPDA, inferior pancreatoduodenal artery.