DISCUSSION

Resectional surgery provides the only chance of cure for patients with pancreatic cancer. However, in most cases the operation is non-curative, and an extremely high recurrence rate is observed. Consequently, a number of adjuvant treatments have been tried in the hope of prolonging survival. GITSG performed the first randomized controlled trial to evaluate the effect of adjuvant treatment in a group of 43 patients with pancreatic cancer. They concluded that adjuvant chemoradiotherapy after curative resection prolonged patient survival (6). However, subsequent larger studies carried out in Europe failed to show any evident benefit of adjuvant chemoradiotherapy (8–10). Similarly, the value of systemic chemotherapy in an adjuvant setting also remains controversial owing to the scarcity of convincing evidence. Only three randomized controlled trials have been reported to assess adjuvant chemotherapy for pancreatic cancer in the literature (Table 5). Bakkevold et al. (7) claimed that adjuvant combination chemotherapy using 5-FU, doxorubicin and mitomycin C (AMF) prolonged the median survival time in a cohort of postoperative patients with pancreatic or ampullary cancer. However, their results were not definitive, because there was no detailed documentation of the data. Takada et al. found no advantage of adjuvant treatment using mitomycin C and 5-FU in a larger number of patients (18). Neoptolemos et al. (9,10) conducted a prospective randomized trial (ESPAC-1) to assess the effects of two types of adjuvant treatments, namely, chemotherapy and chemoradiotherapy. They concluded that chemotherapy alone improved the survival rate and that chemoradiotherapy may even have had an adverse effect on survival. However, their conclusion remains a subject of debate because of the unorthodox and complex design of the study.

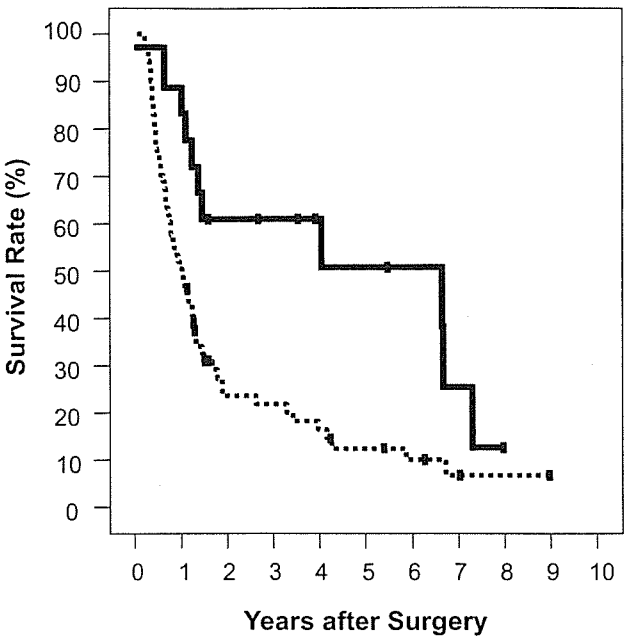

Figure 3. Cumulative survival rate categorized by the disease stage according to the fifth edition of the UICC TNM classification. Solid line: stages I and II; dotted line: stages III, IVa and IVb.

In contrast to the ESPAC-1 trial, our study was simple in design, allowing the comparison of survival between two patient groups: one group with adjuvant chemotherapy and the other group without adjuvant chemotherapy. Patients were stratified according to the institution and stage of the disease in order to minimize the influence of possible prognostic factors. Furthermore, patients with a positive histological margin were excluded from the study with the objective of excluding possible bias introduced by one of the strongest prognostic factors, the status of the resectional margin (19). However, this last criterion did interfere with the rapid recruitment of patients. It took almost 8 years to carry out the registration and randomization of 89 patients. Fortunately, there have been no remarkable changes in the diagnosis or treatment of pancreatic cancer during this period, and the trial could be continued without any major revisions of the protocol. Only two previous trials have evaluated adjuvant treatment for patients with R0 resection (6,7). Both encountered similar difficulties and a smaller number of patients were enrolled

Table 5. Randomized controlled trials of adjuvant chemotherapy for pancreatic cancer

Author	Year of publication	Disorder	Chemotherapy	Number of cases	MST (months)	5-year SR (%)	Significance
Bakkevold et al.	1993	PC and AMP (R0)	AMF	31	23	4	NS with generalized Wilcoxon's test
			Observation	30	11	8	
Takada et al.	2002	PC (R1)	MF	81	NA	11.5	NS with the log-rank test
			Observation	77	NA	18.0	
ESPAC	2004	PC (R1)	5-FU + LV	147	20.1	21	$P = 0.009$ the with log-rank test
			No chemotherapy	142	15.5	8	
Present study		PC (R0)	FP	45	12.5	26.4	NS with the log-rank test
			Observation	44	15.8	14.9	

AMF, doxorubicin + mitomycin C + 5-FU; AMP, ampullary carcinoma; LV, folinic acid; MF, mitomycin C + 5-FU; MST, median survival time; NA, not available; NS, not significant; PC, pancreatic cancer; SR, survival rate.

than in the present study. The patient characteristics, especially the stage distribution and proportion of patients with nodal involvement, were comparable among these trials.

The present study showed that adjuvant combination chemotherapy using 5-FU and cisplatin could be carried out with acceptable safety, as long as the patients met the eligibility criteria, although one patient died of sepsis after a single course of chemotherapy. The monitoring committee, after analysis of the case data, judged that this particular patient was unsuitable for enrollment into the trial. According to the recommendation of the committee, part of the study protocol was modified to clarify some requirements regarding the postoperative condition of the patients. No serious complications were encountered after the modification was carried out.

On the other hand, this trial failed to show any significant benefit of adjuvant chemotherapy in terms of either survival or recurrence, even though the absolute values of the survival rate and recurrence rate at 5 years were slightly better in the patients to whom adjuvant chemotherapy was administered. It is possible that a larger number of patients must be examined to appreciate the statistical significance of the treatment effect. However, a significant influence of the typical prognostic factors on survival was confirmed in the present trial. It is possible that the influence of adjuvant chemotherapy on survival is much weaker than that of these prognostic factors. Another possibility is that further courses of chemotherapy might reinforce the effectiveness of the treatment and allow it to become evident. However, it must also be considered that the life expectancy of patients with pancreatic cancer is extremely short. Adjuvant treatment for pancreatic cancer would be practical only when its beneficial effect can compensate for the compromised quality of life of the patient resulting from the treatment. Therefore, a distinct effect with a short treatment period, besides minimum toxicity, would seem to be the essential prerequisite of effective adjuvant chemotherapy. Otherwise, the lifetime spent with low quality of life can cancel out or even reverse the potentially beneficial effects of adjuvant treatment.

To conclude, the present trial did not prove that the regimen can be recommended as adjuvant treatment for pancreatic cancer.

Contributors

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(The affiliation of each member is the affiliation at the time of the patient recruitment.)

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Clinical Implications of Combined Portal Vein Resection as a Palliative Procedure in Patients Undergoing Pancreaticoduodenectomy for Pancreatic Head Carcinoma

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Background: The clinical implications of combined portal vein resections are controversial.

Methods: One-hundred and forty-nine consecutive patients underwent macroscopically curative pancreatectomies for pancreatic head carcinoma between January 1, 1996 and December 31, 2004. Portal vein resection was performed in 86 patients (58%). Data on surgical mortality, morbidity, perioperative outcome, pathological factors, initial recurrence site, and survival were retrospectively compared between the patients with and without portal vein resection.

Results: The incidence of postoperative pancreatic fistula was lower among patients who underwent portal vein resection. The median survival period was 14 months for the portal vein resection group and 35 months for the non-portal vein resection group, respectively. Combined portal vein resection was a significant predictor of poor survival using a multivariate analysis. Portal vein resection was strongly associated with larger tumor size, the degree of retropancreatic tissue invasion, the presence of extrapancreatic nerve plexus invasion, lymph node metastases, and positive cancer infiltration at the surgical margins.

Conclusions: Portal vein resection at the time of pancreaticoduodenectomy can be safely performed. However, most of patients requiring portal vein resection do not achieve a potentially curative resection or a favorable survival term. As a result, the aggressive application and the strict selection of portal vein resection might reduce the incidence of positive surgical margins, enabling long-term survival in patients who do not require portal vein resection.

Key Words: Pancreatic cancer—Portal vein resection—Predictive factors—Recurrence pattern—Postoperative complications.

Pancreaticoduodenectomy may provide the only chance of a cure for patients with carcinoma of the pancreatic head, and the prognosis of patients with locally advanced disease who undergo non-surgical treatments like systemic chemotherapy and/or radiation is limited.[1–2] Currently available high-quality imaging techniques have enabled a precise preoperative assessment of the relationship between local tumor extension and major vessels,[3–5] and portal vein or superior mesenteric vein resections have been aggressively performed in the absence of invasion to the superior mesenteric artery or common hepatic artery to increase the resectability rate and the possibility of achieving curative pancreaticoduodenectomies with a negative surgical margin in large series of patients.[6–8] Several recent studies concluded that portal vein resection at the time of pancreaticoduodenectomy could be performed with acceptable

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mortality and morbidity and with a surgical outcome and prognosis comparable to those seen in patients who undergo a pancreaticoduodenectomy without vein resection for the treatment of carcinomas of the pancreatic head.[9–13] However, portal vein resection at the time of pancreaticoduodenectomy has not yet been widely recognized as a standard surgical treatment for pancreatic head cancer because of the generally dismal prognosis of patients with this disease and a few reports suggesting that patients undergoing venous resection have a shorter survival period.[14–16]

To reevaluate the clinical implications and role of portal vein resection, the present study investigated the demographics, operative factors, morbidity, mortality, recurrence pattern, and overall survival of a series of 86 patients with carcinoma of the pancreatic head who underwent portal vein resection during the past 9 years at a single Japanese institution.

PATIENTS AND METHODS

Between January 1, 1996 and December 31, 2004, a total of 149 consecutive patients with pancreatic adenocarcinoma originating in the head, neck, or uncinate process underwent macroscopic curative pancreatectomy at the National Cancer Center Hospital, Tokyo, Japan. Curative resection was defined as the absence of apparent tumor residue in the operative field and no liver metastases or macroscopic peritoneal dissemination. During the same period, 293 patients did not undergo pancreatic resection because of far advanced locally disease. Patients with lower bile duct carcinoma, ampullary carcinoma, endocrine carcinoma, invasive adenocarcinoma derived from intraductal papillary-mucinous tumors, and other rare pancreatic malignancies were excluded from the present study.

All the patients underwent a standardized imaging assessment consisting of ultrasonography, contrast-enhanced computed tomography (CT), magnetic resonance imaging, and angiography examinations. Transarterial portographic CT and hepatic arteriographic CT were routinely performed to examine not only the local tumor invasion to major vessels but also the presence of small hepatic metastases. Preoperative evaluations for portal vein invasion were mainly based on the results of helical contrast CT scans.[5] The extent of venous involvement by the tumor was not a contraindication for operation when there was no CT evidence of tumor extension to the common hepatic or superior mesenteric artery. Multidetector-row CT (MD-CT) has been applied to estimate tumor invasion to large vessels including portal vein systems since January 2001.

During the laparotomy, local tumor invasion (including portal vein involvement) was further evaluated using intraoperative US. Peritoneal washing cytology specimens were routinely examined. Our principal criteria for performing a pancreatectomy were the absence of hepatic metastases, macroscopic peritoneal seeding, bulky lymph nodal involvements, or cancer invasion to the superior mesenteric or common hepatic artery. Limited invasion to the portal or superior mesenteric vein or a positive washing cytology specimen were not regarded as contraindications for surgery.[18] Regional nodes, including the nodes around the common hepatic celiac, the right side of the superior mesenteric arteries, and the paraaortic lymph nodes, were routinely dissected. The area of paraaortic lymph node dissection extended from the celiac trunk to the origin of the inferior mesenteric artery, and from the right margin of the inferior vena cava to the left margin of the left gonadal vein. Of the 149 patients, 143 patients (96%) received a pancreatic head resection and 6 patients (4%) received a total pancreatectomy. Resection of the portal vein was usually performed just before the specimen was delivered. Of the 149 patients, 86 patients (58%) were identified as having clinical involvement of the portal vein or superior mesenteric vein (PV/SMV) or close adherence to these vessels; these patients underwent a pancreatectomy with portal vein resection. When the cause of the adhesion to the portal vein system could not be specified as cancerous invasion or associated inflammatory changes, portal vein resection was aggressively performed. Seventy-seven patients (90%) underwent a segmental resection of the PV/SMV and 9 patients (10%) underwent a wedge excision. Auto-vein interposition using a renal vein graft was performed in one patient (1%). On the other hand, 63 patients (42%) underwent pancreatectomies without portal vein resection. Ninety-eight patients received intraoperative radiation therapy (IORT, 30 Gy of electron beam radiation with an energy of 9 MeV), which was administered to the retroperitoneal fields. This procedure was restricted to patients without contraindications who were under the age of 75 years.[19] Twelve patients who were over 75 years did not receive IORT. Thirty-nine patients did not receive IORT because of hospital renovations conducted between 1999 and 2000 and mechanical troubles with the irradiation system, respectively. Eleven of the patients received 5-fluorouracil and cisplatin and 15

received gemcitabine as an adjuvant chemotherapy regimen in a clinical trial setting conducted during the period of the present study.

The demographic and clinical variables of the two groups, including age, sex, symptoms, carbohydrate antigen 19-9 (CA19-9) level, carcinoembryonic antigen (CEA) level, operative procedure, morbidity, mortality, length of postoperative hospital stay, operative time, blood loss, and transfusion requirements, were analyzed and compared. Mortality was defined as the number of operative and in-hospital deaths. Gastric emptying was defined as the inability to resume oral intake within 10 postoperative days. A pancreatic fistula was defined as a persisting secretion of more than 10 ml/day of drainage fluid with a high amylase concentration (> 1000 U/ml) for 7 days after the placement of a drain[20] or the demonstration of pancreaticojejunal anastomosis leakage on a fistulography.

The extent of pathological features that might influence prognosis was classified as follows:[21] histologically assessed tumor size, serosal invasion (s0, absent; s1, slight invasion; s2, wide invasion; s3, invasion to other organs), retropancreatic tissue invasion (rp0, absent; rp1, slight invasion; rp2, wide invasion; rp3, invasion to other organs), bile duct invasion (ch0, absent; ch1, invasion to bile duct wall but not to mucosal layer, ch2; invasion to mucosal layer, ch3, stenosis or obstruction of bile duct wall), duodenal invasion (du0, absent, du1; invasion to proper muscle layer, du2; invasion to submucosal layer, ch3; invasion to mucosal layer), portal vein invasion (pv0, absent; pv1, invasion to adventitia; pv2, invasion to tunica media; pv3, invasion to tunica intima), extrapancreatic nerve plexus invasion (absent, present), lymph node involvement (n0, absent; n1, regional; n2, peripancreatic; n3, paraaortic involvement), differentiation of the tumor (well, papillary, mucinous/ moderately or poorly, adenosquamous), cancer infiltration at surgical margin (absent/ present), and peritoneal washing cytology specimen (negative/positive). Histopathologic variables were also compared between the two groups. The tumors were staged according to the TNM system, sixth edition.[22]

Patients were closely followed up every 1–2 months during the first year after surgery. Each follow-up visit included a physical examination, blood chemistry tests, and a measurement of the serum CA19-9 level. Ultrasound and enhanced CT examinations were performed at 3-month intervals, along with a chest radiography examination. Specific sites of first disease recurrence, and the time until disease recurrence were analyzed. Recurrence was suspected when: 1) a new local or distant metastatic lesion was found on serial images and 2) an increase in the tumor marker level was recognized. Radiologic evidence of tumor recurrence was accepted even if the patients did not undergo a biopsy. When progression of the disease was confirmed by repeated image studies, the dates of the first suspicious radiologic finding were used as the date of initial disease recurrence. One patient who died while undergoing a total pancreatectomy with portal vein resection and two patients requiring a portal vein resection who had an incomplete follow-up were excluded from the follow-up analysis.

The clinicopathological features of the two groups were compared using the chi square test with Yates' correction. Survival was calculated using the Kaplan-Meier method and was compared between groups using the log-rank test. All variables were dichotomized for analysis. A multivariate analysis using the Cox hazard model was performed to identify independent predictors of survival. All statistical analyses were performed using SPSS for Windows 11.5 software (SPSS, Chicago, IL). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 149 patients with pancreatic head carcinoma underwent resections during a 9-year period. The patients consisted of 88 men and 61 women with a median age of 62 (27–86) years. The two treatment groups were similar with respect to sex, age, and other demographic variables (Table 1.). As for the operative procedures, standard pancreaticoduonectomy and total pancreatectomy were performed more frequently in the portal vein resection group (Table 2). Pancreaticojejunostomy and duct occlusion, which was applied in patients with fragile or normal pancreases using Ethibloc® (Ethicon, GmBH) between 1996 and 2000, were performed in 107 and 36 patients, respectively. No significant difference in the management of the pancreatic remnant was seen between the two groups. The operative time, estimated intraoperative blood loss, and transfusion requirements were significantly larger in the portal vein resection group.

The rate of postoperative complications was similar between the two groups, but the incidence of pancreatic fistula was lower in the vein resection group ($P = 0.023$). One postoperative death occurred in a patient who had undergone a total pancreatec-

TABLE 1. *Demographic characteristics of 149 patients with or without portal vein resection*

Characteristics	Total Patients (n = 149)		No portal vein resection (n = 63)	Portal vein resection (n = 86)	*P* value
Sex					
M	88 (59%)		39 (62%)	49 (57%)	0.614
F	61 (41%)		24 (38%)	37 (43%)	
Age, median (range), yrs	62 (27–86)	62<	36 (57%)	38 (44%)	0.137
Diabetes mellitus	54 (36%)		20 (32%)	34 (40%)	0.421
Cardiac comorbidity	8 (5%)		5 (8%)	3 (3%)	0.411
Chronic obstructive lung disease	4 (3%)		1 (2%)	3 (3%)	0.844
Chronic hepatitis	4 (3%)		4 (6%)	0 (0%)	0.064
Jaundice	88 (59%)		36 (57%)	52 (60%)	0.811
Pancreatitis	15 (10%)		5 (8%)	10 (12%)	0.643
Duodenal stenosis	4 (3%)		2 (3%)	2 (2%)	1.000
No symptoms	38 (26%)		18 (29%)	20 (23%)	0.586
CEA, median (range), ng/ml	3.1 (1–122)	3.1<	23 (37%)	56 (65%)	0.611
CA19-9, median (range), U/ml	240 (1–37070)	240<	27 (43%)	46 (53%)	0.246

TABLE 2. *Operative procedures and findings in 149 patients undergoing pancreaticoduodenectomy with and without portal vein resection*

Procedures and findings	Total Patients No. (n = 149)	No portal vein resection (n = 63)	Portal vein resection (n = 86)	*P* value
Operation				0.005
PD	69 (46%)	21 (33%)	48 (56%)	
pyrolus preserving PD	74 (50%)	41 (65%)	33 (38%)	
Total pancreatectomy	6 (4%)	1 (2%)	5 (6%)	
Management of the pancreatic remnant				0.227
Pancreaticojejunostomy	107 (72%)	50 (79%)	57 (66%)	
Duct occlusion	36 (28%)	12 (21%)	24 (34%)	
Intraoperative data				
Surgery time, mean ± SD min	625 ± 148 (314–1105)	568 ± 135	667 ± 144	0.000
Blood loss, mean ± SD ml	1447 ± 867 (280–7950)	1120 ± 533	1686 ± 982	0.000
Transfusion, Yes	42 (28%)	7 (11%)	35 (41%)	0.000

tomy with portal vein resection, yielding an in-hospital mortality rate of 1%. The patient had postoperative bleeding, probably originating from a skeltonized hepatic artery on postoperative day 4. Mortality, the reoperation rate, and the postoperative hospital stay were not significantly different between the two groups (Table 3).

The median follow-up period was 18 months (range, 3–84 months). The overall median survival period for the 149 patients was 18 months, and the 5-year survival rate was 27%. The median survival period and the 5-year survival rate were 14 months and 12%, respectively, for the portal vein resection group and 35 months and 46%, respectively, for the non-portal vein resection group (Fig. 1). Combined portal vein resection was a significant predictor of poor survival ($P = 0.006$). Sixteen other clinicopathological variables were investigated to determine whether they were of prognostic significance. The results of the log-lank test are shown in Table 4. In the univariate analysis, the indicators of an unfavorable prognosis included a CA19-9 value higher than 240 U/ml ($P = 0.0048$); a tumor size larger than 35 mm ($P = 0.0021$); the presence of serosal invasion (s1, s2 and s3) ($P = 0.0011$), duodenal invasion (du2 and du3) ($P = 0.0096$), portal vein invasion (pv1, pv2, and pv3) ($P = 0.0303$), extrapancreatic nerve plexus invasion ($P = 0.0077$), or lymph node metastases (n2 and n3) ($P = 0.0019$); cancer infiltration at the surgical margins ($P = 0.0329$); and the application of IORT ($P = 0.0357$). When the significant prognostic factors identified by the univariate analysis were assessed using a multivariate analysis, the following factors were found to be independently associated with a poor prognosis: combined portal vein resection, presence of duodenal invasion, and a CA19-9 value higher than 240 U/ml, with hazard ratios (95% confidence intervals) of 2.246 (1.092–3.624), 1.705 (1.092–2.661), and 1.690 (1.074–2.659), respectively. Patients were staged according to the TNM system, sixth edition, as follows: stage IA (patients without portal vein resection, n = 1 [2%] /

TABLE 3. *Surgical morbidity in 149 patients undergoing pancreaticoduodenectomy with or without portal vein resection*

Variables	Total Patients (n = 149)	No portal vein resection (n = 63)	Portal vein resection (n = 86)	*P* value
Surgical morbidity				
Rupture of pseudoanuerysm *	6 (4%)	2 (3%)	4 (5%)	0.975
Hemorrhage from surgical site	3 (2%)	2 (3%)	1 (1%)	0.785
Gastric emptying delay	42 (28%)	21 (33%)	22 (26%)	0.396
Pancreatic fistula # *	36 (24%)	21 (33%)	14 (16%)	0.023
Biliary fistula	3 (2%)	2 (3%)	1 (1%)	0.785
Enteric fistula	1 (1%)	0 (0%)	1 (1%)	1.000
Wound or drain site infection	11 (7%)	6 (10%)	5 (6%)	0.590
Intraabdominal abscess	3 (2%)	3 (5%)	0 (0%)	0.146
Liver abscess	3 (2%)	1 (2%)	2 (2%)	1.000
Ileus	3 (2%)	1 (2%)	2 (2%)	1.000
Gastric ulcer	1 (1%)	0 (0%)	1 (1%)	1.000
Cholangitis	3 (2%)	1 (2%)	2 (2%)	1.000
Ascites	1 (1%)	1 (2%)	0 (0%)	0.875
Systemic morbidity				
Mental disturbance	6 (4%)	2 (3%)	4 (5%)	0.975
Respiratory failure	2 (1%)	0 (0%)	2 (2%)	0.618
Liver dysfunction	4 (5%)	1 (2%)	3 (3%)	0.844
Mortality	1 (1%)	(0%)	1 (1%)	1.000
Reoperation	5 (3%)	3 (5%)	2 (2%)	0.722
Postoperative hospital stay (day)	43 ± 26 (12–254)	40 ± 14	44 ± 32	0.314

* Total pancreatectomies were excluded.
\# Pancreatic fistula was defined as the presence of amylase-rich fluid for 7 days after the operation.

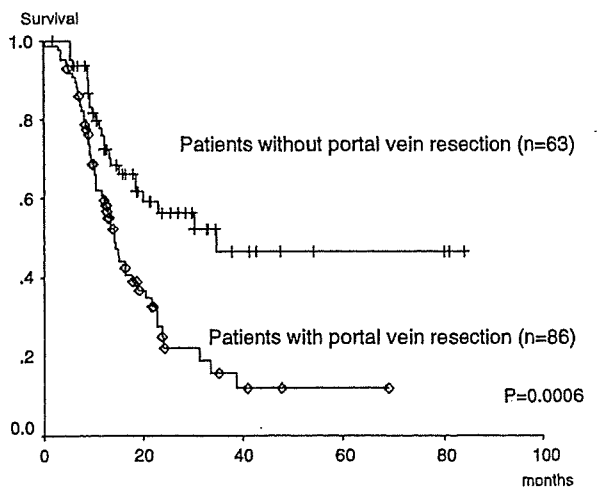

FIG. 1. Actuarial 5-year survival curve (Kaplan-Meier) for 149 patients who underwent pancreatectomies for pancreatic head carcinomas with portal vein resection (n = 86) or without portal vein resection (n = 63). The differences were statistically significant (*P* = 0.0006).

patients with portal vein resection, n = 0), stage IB (n = 1 [2%] / n = 0), stage IIA (n = 15 [24%] / n = 9 [11%]), stage IIB (n = 31 [49%] / n = 38 [44%]), stage III (n = 0 / n = 0), and stage IV (n = 15 [24%] / n = 39 [45%]).

A comparison of the clinicopathologic features of the two groups is shown in Table 5. Portal vein resection was strongly associated with tumor size (*P* = 0.013), retropancreatic tissue invasion (*P* = 0.001), extrapancreatic nerve plexus invasion (*P* < 0.001), lymph node metastases (*P* = 0.009), cancer infiltration at the surgical margins (*P* = 0.002), and IORT (*P* = 0.014).

The degree of histological portal vein invasion was assessed among 86 patients with portal vein resection. The degree of histological portal vein invasion (pvp0 = 28, 33%; pvp1 = 11, 13%; pvp2 = 28, 33%; and pvp3 = 19, 21%) was not significantly different, but none of the 58 patients with histological portal vein invasion (pv1–3) survived for 5 years (Fig. 2). A tumor size (>35mm) (*P* = 0.0087) and a Ca19-9 value (>240 U/ml) (*P* = 0.0175) were unfavorable prognostic factors assessed in 16 clinicopathologic factors among 86 patients undergoing portal vein resection.

Table 6 shows the anatomic locations of all the initial recurrences. Initial recurrence at a single site occurred in 28 patients (72%) without portal vein resection and in 53 patients (75%) with portal vein resection. Initial recurrence at two or more sites occurred in 11 patients (28%) without portal vein resection and in 18 patients (25%) with portal vein resection. The leading recurrence site was the liver, in

TABLE 4. *Univariate analysis of predictors of survival*

Variables		No. of patients	Median survival	*P* value
		149	months	
Age (years)	< = 62	75 (50%)	18	0.9610
	> 62	74 (50%)	28	
Sex	Male	88 (59%)	18	0.6747
	Female	61 (41%)	18	
CA19-9 (U/ml)	< 240	76 (51%)	30	0.0048
	> = 240	73 (49%)	13	
Size (mm)	< 35	79 (53%)	23	0.0021
	> = 35	70 (47%)	12	
Serosal invasion	s0	120 (81%)	20	0.0011
	s1 = 8,S2 = 6,S3 = 11	25 (19%)	12	
Retropancreatic tissue invasion	rp0 = 8, rp1 = 47	55 (37%)	19	0.7765
	rp2 = 92, rp3 = 2	94 (63%)	18	
Bile duct invasion	ch0 = 53,ch1 = 5	58 (39%)	20	0.4064
	ch2 = 5, ch = 86	91 (61%)	17	
Duodenal invasion	du0 = 55,du1 = 21	76 (51%)	24	0.0096
	du2 = 34,du3 = 39	73 (49%)	14	
Portal vein invasion	pvp0 = 87	91 (61%)	20	0.0303
	pvp1 = 11,pvp2 = 28,pvp3 = 19	58 (39%)	15	
Extrapancreatic nerve plexus invasion	absent	107 (72%)	23	0.0077
	present	42 (38%)	12	
Lymph node metastases	n0 = 26, n1 = 67	95 (64%)	23	0.0019
	n2 = 26, n3 = 28	54 (36%)	13	
Differentiation	Well,pap, muc	31 (21%)	20	0.7817
	mod,por,adscc	118 (79%)	16	
Portal vein resection	No	63 (42%)	35	0.0006
	Yes	86 (58%)	14	
Cancer infiltration at surgical margins	negative	107 (72%)	20	0.0329
	positive	42 (28%)	12	
Peritoneal cytology	negative	136 (93%)	18	0.2718
	positive	11 (7%)	13	
IORT	Yes	98 (66%)	14	0.0357
	No	51 (34%)	30	
Adjuvant chemotherapy	Yes	26 (17%)	19	0.4303
	No	123 (83%)	14	

TABLE 5. *Clinicopathologic comparison of 149 patients with or without portal vein resection*

Variables		No portal vein resection (n = 63)	Portal vein resection (n = 86)	*P* value
Size (mm)	< 35	41 (65%)	38 (44%)	0.013
	> = 35	22 (35%)	48 (56%)	
Serosal invasion	s0	56 (89%)	68 (79%)	0.126
	s1 = 8,S2 = 6,S3 = 11	7 (11%)	18 (21%)	
Bile duct invasion	ch0 = 53,ch1 = 5	27 (43%)	31 (36%)	0.497
	ch2 = 5, ch = 86	36 (57%)	55 (64%)	
Duodenal invasion	du0 = 55,du1 = 21	32 (51%)	44 (51%)	1.000
	du2 = 34,du3 = 39	31 (49%)	42 (49%)	
Retropancreatic tissue invasion	rp0 = 8, rp1 = 47	33 (52%)	22 (26%)	0.001
	rp2 = 92, rp3 = 2	30 (48%)	64 (74%)	
Extrapancreatic nerve plexus invasion	absent	59 (94%)	48 (56%)	0.000
	present	4 (6%)	38 (44%)	
Lymph node metastases	n0 = 26, n1 = 67	48 (76%)	47 (55%)	0.009
	n2 = 26, n3 = 28	15 (24%)	39 (45%)	
Cancer infiltration at surgical margins	negative	54 (86%)	53 (62%)	0.002
	Positive	9 (14%)	33 (38%)	

34 patients (34%). Local recurrence at the primary site without apparent distant metastases occurred in 3 patients (11%) without portal vein resection and in 10 (19%) patients with portal vein resection. The recurrence patterns and sites were similar between the two groups.

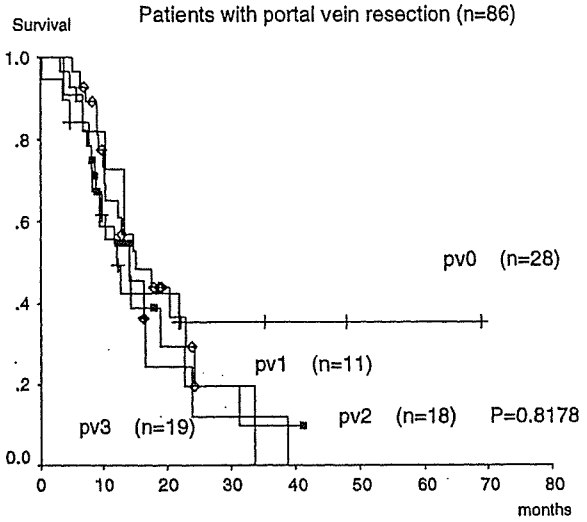

FIG. 2. Actuarial 5-year survival curve (Kaplan-Meier) for 86 patients who underwent pancreatectomies with portal vein resection, according to pathological portal vein involvement: pv0 (absent), n = 28; pv1 (invasion to adventitia), n = 11; pv2 (invasion to tunica media), n = 18; pv3 (invasion to tunica intima), n = 19. The differences were not statistically significant ($P = 0.8178$).

DISCUSSION

Portal vein resection at the time of pancreaticoduodenectomy was more common in the current study than in previous reports (with more than 30 patients undergoing portal vein resection) (Table 7). Previously, angiographic findings were used to determine whether a combined vein resection was indicated,[3] but helical CT images can now be used to precisely evaluate the relationship between the tumors and the portal and/or superior mesenteric vein without major arterial invasions, not only allowing the preoperative identification of unresectable advanced disease, but also increasing the incidence of vein resection to achieve a wider retroperitoneal surgical margins.[4,5] In addition, portal vein resection during pancreatico-duodenectomy has now been established as a standard operative procedure,[10,13,14] encouraging the use of vein resection even if tumor involvement of the portal vein is only suspected or if the tumor is only located adjacent to the portal vein, with concomitant obstructive pancreatitis.

Portal vein resections during pancreaticoduodenectomy have been safely performed with acceptable mortality and morbidity in the present study as well as in previous large series.[8–17] The postoperative complications rate was similar between patients who underwent portal vein resection and those who did not, but pancreatic fistulas were less common in patients with portal vein resection. Patients with vein resection associated with large tumors probably had a high incidence of obstructive pancreatitis with pancreatic duct dilation, possibly reducing the formation of postoperative pancreatic fistulas.[23] Patients undergoing portal vein resection might recover promptly after resection because of lower incidence of pancreatic fistula and could receive adjuvant chemotherapy with safe. Careful attention should be paid to patients with portal vein resection who have fragile pancreases and pancreatic ducts that are not dilated. The portal vein resection group had a longer operative time, much more blood loss, more blood transfusions, and a higher use of combined gastrectomies (Whipple procedure). Such intraoperative factors could be gradually improved by a team of well-trained and experienced pancreatic surgeons, since the complexity and magnitude of the operative procedure does not enhance postoperative severe complications.[10,14] The prolonged hospital stay not only after pancreaticoduodenectomy but also other surgical resections has been a serious problem in Japan. One of the major causes of the prolonged hospital stay in the present series might be due to the higher occurrence of pancreatic fistula or gastric empty. However, Japanese patients generally tend to stay in the hospital until all drains and/or tubes are pulled out and they feel completely well, even if no complications occurred. Recently, we pull out drains or tubes at the out-patient clinic when their postoperative course is uneventful, and the hospital stay period has been remarkably reduced.

In the present study, the median survived period was 14 months in patients with portal vein resection, and 35 month with non-portal vein resection, respectively. A significant reduced survival was recognized in patients undergoing portal vein resection. Recent studies have reported a median survival period ranging from 12 to 23 months in patients with pancreatic carcinoma who underwent portal vein resection.[6–9,11,12,14,17] In most of the reports, survival did not differ between patients who did and those who did not undergo portal vein resections.[9–14] Fuhrman et al.[13] suggested that venous involvement was a function of tumor location, rather than an indication of aggressive tumor biology, since no difference in size, nodal positivity, or tumor DNA content were observed between patients with and without vein resections. Tseng et al. confirmed their early experience in a large series, but the incidence of positive surgical margins was higher and the rate of histopathologic vein invasion was 61% (n = 38) in patients who required vascular resection in their recent

TABLE 6. *Recurrence pattern and sites in 146 patients with or without portal vein resection*

Recurrence and sites		Total Patients (n = 146) No	No portal vein resection (n = 63)	Portal vein resection (n = 83)*	*P* value
Recurrence	Yes	110 (74%)	39 (62%)	71 (86%)	0.003
	No	36 (26%)	24 (38%)	12 (14%)	
Initial recurrence site					
Single site		81 (74%)	28 (72%)	53 (75%)	NS
	Liver	34 (42%)	18 (64%)	16 (30%)	
	Peritoneum	26 (31%)	5 (18%)	21 (40%)	
	Local	13 (16%)	3 (11%)	10 (19%)	
	Lymph nodes	2 (2%)	2 (7%)	0 (0%)	
	Pleural	2 (2%)	1 (4%)	1 (2%)	
	Bone	4 (5%)	0 (0%)	4 (8%)	
	Brain	1 (1%)	0 (0%)	1 (2%)	
Multiple sites		29 (26%)	11 (28%)	18 (25%)	NS
	Liver, peritoneum	6 (21%)	2 (18%)	4 (22%)	
	Liver, local	3 (10%)	3 (27%)	0 (0%)	
	Liver, lung	1 (3%)	0 (0%)	1 (6%)	
	Liver, pleural	1 (3%)	0 (0%)	1 (6%)	
	Local, peritoneum	3 (10%)	2 (18%)	1 (6%)	
	Local, lung	4 (14%)	1 (9%)	3 (17%)	
	Local, lymph nodes	4 (14%)	2 (18%)	2 (11%)	
	Bone, lymph nodes	1 (3%)	0 (0%)	1 (6%)	
	Peritoneum, lymph nodes	2 (7%)	0 (0%)	2 (11%)	
	Liver, skin, peritoneum	2 (7%)	1 (9%)	1 (6%)	
	Liver, peritoneum, lung	1 (3%)	0 (0%)	1 (6%)	
	Liver, local, pleural	1 (3%)	0 (0%)	1 (6%)	

NS, not significant.
* An operative death occurred in one patient. The recurrence pattern was not fully evaluated in two patients.

study.[14] On the contrary, the present study showed that portal vein resection was one of the most unfavorable predictors, when analyzed using a multivariate analysis. Portal vein resection was strongly associated with a larger tumor size, extensive retropancreatic tissue invasion, the presence of extrapancreatic nerve plexus invasion, lymph node metastases, and cancer infiltration at the surgical margins. The present data suggested that patients requiring vein resection had more aggressive cancers and were less likely to be cured, even if precise preoperative and intraoperative assessments suggested a curative resection. As a result, the aggressive application and the strict selection of portal vein resection might reduce the incidence of positive surgical margins, enabling long-term survival similar to that of patients who do not require portal vein resection. Ishikawa et al.[24] reported that large tumors and retroperitoneal invasion were risk factors for death from distant metastases.

Portal vein resection is important for local macroscopic cancer control to reduce the incidence of positive retroperitoneal surgical margins, but portal vein resection on its own cannot achieve a favorable survival term in most patients requiring portal vein resection because distant recurrences are common.

Histological vein involvement was reported to be an important factor determining survival.[12,25] Extensive invasion to the portal vein wall seems to be a characteristic of aggressive cancers, but extensive retroperitoneal cancer infiltration sometimes occurs in patients requiring portal vein resection even if histological evidence of tumor invasion to the vein wall is not present, resulting in a dismal outcome similar to that of patients with histological vein involvement.[24–26] The presence of histological invasion in 39% (n = 58) of the patients was an unfavorable predictor according to univariate analysis, but not according to a multivariate analysis.

Another reason for these similar survival results might be suggested by Ishikawa's report,[27] which described positive intraoperative cytology findings in several patients who underwent pancreatectomies without evidence of macroscopic vein involvement and in which additional resection of the portal vein confirmed cancer invasion in most of the cases. Their results suggest that a precise assessment of venous involvement is difficult and that venous involvement may exist in patients who are not thought to require vein resections.

In spite of limitation of various preoperative imaging studies, intra-operative ultrasonography is another useful tool not only to evaluate tumor invasion to the portal vein, but also to confirm the presence of invasion to the common hepatic or superior mesenteric artery and tiny hepatic metasta-

TABLE 7. *Large series (n > 30) examining portal vein resection for pancreatic carcinoma, conducted between 1994 and 2004*

Reference	Year	Observation period	No. of total patients	No. of patients with portal vein resection	Histologic invasion to portal vein	Positive surgical margin in patients with portal vein resection	Hospital mortality (%)	Median survival in patients with portal vein resection (months)	Median survival in patients without portal vein resection (months)
Takahashi (6)	1994	1976–1992	137	79 (58%)	48 (61%)	40 (51%)	9.5	14	NA
Nakao (7)	1995	1981–1993	101	89 (88%)	44 (49%)	NA	8.0	NA	NA
Harrison (8)	1996	1983–1995	332	58 (17%)	NA	16 (27%)	5.0	13	17
Leach (9)	1998	1990–1995	75	31 (41%)	13/18 (72%)	4 (13%)	0.0	22	21
Van Geenen (18)	2001	1992–1998	215*	34 (16%)	1 (3%)	20 (59%)	0.0	14	NA
Hartel (11)	2002	1980–2001	271	68 (25%)	56 (82%)	26 (38%)	4.4	18% #	17% #
Nakagohri (12)	2003	1992–2001	81	33 (41%)	17 (52%)	NA	6.1	15	10
Tseng (14)	2004	1990–2002	291	110 (38%)	38/62 (62%)	24 (22%)	2.1	23	27
Present study	2005	1996–2004	149	86 (58%)	58 (67%)	33 (38%)	0.7	14	35

* included peripancreatic malignancy.
NA, not available.
5-year survival rate.

ses. Recently, intravascular ultrasonography seems to be more effective to evaluate the precise extension of portal vein invasion or to estimate the degree of histologic portal vein invasion.[28]

It is extremely important to determine a subgroup that might derive most benefit from portal vein resection. A smaller tumor size and a lower Ca19-9 value were favorable prognostic factors in 86 patients undergoing portal vein resection. Nakagohri et al.[12] reported that negative microscopic invasion to the portal vein was associated with longer survival. In the present study, none of the 58 patients with histological portal vein invasion survived for more than 5 years, but there was no significant survival difference among the 86 patients when analyzed according to the degree of histologic portal vein invasion. Histological vein involvement has also been reported to be a significant risk factor for liver metastases,[29] but no clear relationship between portal vein involvement and liver metastases was observed.

In conclusion, the results of the present study show that a combined pancreaticoduodenectomy and portal vein resection can be safely performed with a low incidence of postoperative pancreatic fistula formation. However, combined portal vein resections might only be required for aggressive tumors with extensive retroperitoneal invasion. Additional systemic chemotherapy should be mandatory in patients requiring portal vein resection during pancreaticoduodenectomy with a curative intent since retroperitoneal positive surgical margins and lymph node metastases are common and distant recurrences might be inevitable.

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Original communications

Prognostic factors after distal pancreatectomy with extended lymphadenectomy for invasive pancreatic adenocarcinoma of the body and tail

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Background. *Invasive pancreatic carcinoma originating from the body and tail usually is diagnosed at a late stage, and resection is considered a palliative procedure because of the poor prognosis. Factors predicting survival were not evaluated fully in patients with invasive pancreatic carcinoma of the body and tail who had undergone distal pancreatectomy with extended lymphadenectomy.*
Methods. *Between 1990 and 2004, 88 patients with invasive pancreatic carcinoma of the body and tail underwent distal pancreatectomy with extended lymphadenectomy. Univariate and multivariate models were used to analyze the effects of clinicopathologic factors on long-term survival.*
Results. *No operative deaths occurred. The median survival time was 22 months, and the 1-, 3-, and 5-year survival rates were 76%, 40%, and 19%, respectively. Lymph node involvement status and the degree of histologic vein invasion were independent predictors of long-term survival.*
Conclusions. *Distal pancreatectomy with extended lymphadenectomy for the treatment of invasive pancreatic carcinoma of the body and tail contributed to long-term survival in selected patients without mortality. Effective postoperative treatment should be evaluated in patients with positive lymph nodes and/or the presence of histologic vein invasion even after a curative resection because long-term survival cannot be expected. (Surgery 2006;139:288-95.)*

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THE OUTCOME AFTER conventional distal pancreatectomy for carcinoma of the body and tail of the pancreas traditionally has been associated with a dismal prognosis.[1] Recently, distal pancreatectomy consisting of an extended dissection of the retroperitoneal structures with an extended lymphadenectomy and intraoperative radiation has been advocated to improve operative results because an operation is the only chance of a cure.[2,3] However, the resectability rate of 10% to 12% is lower than that for lesions in the head of the pancreas because early tumor spreading to adjacent or distant organs, without specific symptoms, often occurs in carcinomas of the body and tail.[4,5] Recent advanced imaging modalities such as ultrasonography (US) and dynamic computed tomography (CT) have made it possible to detect small pancreatic cancers suitable for curative pancreatectomy,[6] but few populations large enough to allow a statistical evaluation of patients who have undergone cura-

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tive resections of invasive pancreatic cancer of the body and tail have been reported.

In the present study, we investigated the operative outcomes of 88 patients who underwent distal pancreatectomy with extended lymphadenectomy for invasive pancreatic adenocarcinoma of the body and tail during the past 15 years and analyzed the prognostic variables to identify suitable indications for operation in these patients.

PATIENTS AND METHODS

Between January 1, 1990, and December 31, 2004, a total of 287 patients with invasive ductal carcinoma of the pancreas underwent macroscopic curative pancreatectomy with extended lymphadenectomy at the National Cancer Center Hospital in Tokyo, Japan. Curative resection was defined as the macroscopic removal of all gross tumors without liver metastases or macroscopic peritoneal spreading. Palliative pancreatectomy was defined when macroscopic tumor remained at the operation site. Patients with islet cell carcinoma, mucinous cystic or intraductal papillary-mucinous tumors, or other rare pancreatic malignancies were excluded from the present study. The patient population consisted of 10 patients (4%) with lesions involving the entire pancreas, 189 patients (66%) with lesions involving the head of the pancreas, and 88 patients (30%) with lesions involving the body and tail of the pancreas; the last group was enrolled in the present study. On the other hand, 21 patients of the operations for invasive pancreatic adenocarcinoma of the body and tail underwent exploratory laparotomies with only biopsy examination and 11 patients underwent palliative distal pancreatectomy during the same period.

Preoperative imaging studies included not only US, dynamic thin-slice CT, and magnetic resonance imaging, but also portographic and arteriographic CT, and intraoperative US to evaluate local tumor extension to major vessels and small hepatic metastases. Peritoneal washing cytology was performed routinely just after laparotomy. A saline solution (100 mL) was instilled into the pelvis with a bulb syringe; after abdominal agitation, the cytology specimens were aspirated from the pouch of Douglas into a sterile tube containing sodium ethylenediaminetetraacetic acid. A positive peritoneal cytology was not regarded as a contraindication for operation. Preoperative assessment has not changed during this 15-year period. The operative procedures consisted of distal pancreatectomy (n = 76) and Appleby operations (n = 12). An Appleby operation, which consisted of total gastrectomy, distal pancreatectomy, and resection of the celiac, common hepatic, and splenic artery,[7] was applied to remove carcinomas of the pancreatic body with highly suspicious cancer invasion to the celiac and/or common hepatic artery. For carcinomas of the body and tail, even those without apparent invasion to the retropancreatic space, the retroperitoneal structures including Gerota fascia and left adrenal gland were removed. Regional (N1), peripancreatic (N2), and para-aortic (N3) lymph node dissections were performed routinely according to the classification of the lymph node group as defined by the Japanese Pancreas Society.[8] Lymph nodes along the common hepatic artery, splenic artery, along the inferior margin of the pancreas, or at the splenic hilum were classified as the regional lymph node group (N1). Lymph nodes along the left gastric artery, around the celiac artery, along the superior mesenteric artery, or the middle colic artery were classified as the peripancreatic lymph node group (N2). The area of the para-aortic lymph node dissections extended from the celiac trunk to the origin of the inferior mesenteric artery and from the right margin of the inferior vena cava to the left margin of the left gonadal vein. Our aggressive operative approach as described previously[2] was performed throughout the present study period. Intraoperative radiation therapy (IORT, 30 Gy of electron beam radiation with an energy of 9 MeV) was administrated to the retroperitoneal fields.[2] Fifty-four patients (61%) received IORT. The procedure was restricted to patients without contraindication who were under the age of 75 years. Nine patients who were over 75 years did not receive IORT. Twenty-five and 9 patients did not receive IORT because of the reconstruction of the hospital building between 1999 and 2000, and other mechanical troubles of irradiation, respectively. There was no patient who received external beam radiotherapy. Thirteen patients (15%) received 5-fluorouracil and cisplatinum and 10 patients (11%) received gemicitabine as an adjuvant chemotherapy regimen under a randomized clinical trial setting during the study period.

Patients were followed-up closely every 1 to 2 months for the first year after operation. Each follow-up visit included a physical examination, blood chemistry tests, and measurements of serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA). US and enhanced CT were performed at 3-month intervals, along with chest radiography.

The demographic and clinical determinant variables that were analyzed included age, sex, symptoms, CA19-9 level, CEA level, type of resection, IORT, and adjuvant chemotherapy. The pathologic

features that might have influenced prognosis were classified according to extent as follows: historically assessed tumor size, serosal invasion (s0, absent; s1, slight invasion; s2, wide invasion; s3, invasion to other organs), retropancreatic tissue invasion (rp0, absent; rp1, slight invasion; rp2, wide invasion; rp3, invasion to other organs), splenic or portal vein invasion (pv0, absent; pv1, invasion to adventitia; pv2, invasion to tunica media; pv3, invasion to tunica intima), splenic artery invasion (a0, absent; a1, invasion to adventitia; a2, invasion to tunica media; a3, invasion to tunica intima), extrapancreatic nerve plexus invasion (absent, present), lymph node involvement (n0, absent; n1, regional; n2, peripancreatic; n3, para-aortic involvement), differentiation of the tumor (well/others, moderately, or poorly), lymphatic invasion (ly0, absent; ly1, slight; ly2, moderate; ly3, marked), venous invasion (v0, absent; v1, slight; v2, moderate; v3, marked), intrapancreatic nerve invasion (pn0, absent; pn1, slight; pn2, moderate; pn3, marked), cancer infiltration at operative margin (absent/ present), and peritoneal washing cytology (absent/present). The tumors were staged according to the recently updated tumor-node-metastasis (TNM) system.[9]

Survival estimates were calculated using the Kaplan-Meier method. All variables were dichotomized for analysis. A univariate comparison of the survival curves was made using the log-rank test. Associations were considered significant if the *P* value was .05 or less. A multivariate regression analysis was performed using the Cox proportional hazards model, and variables with a *P* value of less than .10 were entered into the final model. All statistical analyses were performed using SPSS for Windows 11.5 software (SPSS, Chicago, Ill).

RESULTS

The patients consisted of 63 men and 25 women with a mean age of 66 years (range, 50-83 y). Detailed clinical data are shown in Table I. Forty patients (45%) consulted a hospital or clinic because of abdominal pain and/or body weight loss, but the pancreatic carcinomas in 39 patients (44%) without symptoms were found accidentally during medical check-ups. The number of patients undergoing resections increased remarkably during the past 5 years. Fifty-three patients (60%) underwent operation between 2000 and 2004. According to the TNM system,[9] 3 patients (3%), 1 patient (1%), 15 patients (17%), 47 patients (53%), 5 patients (6%), and 17 patients (20%) were diagnosed as stage 1A, 1B, 2A, 2B, III, and IV, respectively. Stage IV was determined according to peripancreatic (n2; n = 5) and para-aortic nodal involvement (n3; n = 12).

Table 1. Charcteristics of the patients (n=88)

Parameters	*n*	*%*
Sex		
Male	63	72
Female	25	28
Age		
65> years	42	48
65<= years	46	52
Symptoms (pain or body weght loss)	40	45
Followup of Diabetes mellitus	10	11
Abnornal findings by medical check-up	39	44
HbA1C>6.0%	35/84	42
serum amylase level>140 IU/L	13/84	15
Elastase>300 ng/dl	22/79	28
CA19-9 >37 U/ml	69/88	78
CEA >5.0 ng/ml	26/88	30
1990's (date of operation)	35	40
2000's (date of operation)	53	60
UICC stage		
1A	3	3
1B	1	1
2A	15	17
2B	47	53
3	5	6
4	17	20

HbA1C, glycated hemoglobin.

No 30-day operative deaths occurred among the 88 patients during this 15-year period. The median term of the postoperative hospital stay was 33 days (range, 8-179 d). Overall, the 1-, 3-, and 5-year survival rates were 76%, 40%, and 19%, respectively (Fig 1); the median survival period was 22 months. Three patients (3%) survived for more than 10 years, and 7 patients (8%) survived for more than 5 years. Postoperatively, 30 patients (34%) had no recurrence (median follow-up term, 20 mo; range, 2-156 mo). Seven of them had diabetes mellitus before resection, and 6 of 23 patients (26%) had newly developed diabetes mellitus after resection. Recurrence in a single site occurred in 47 patients (53%) and at 2 or more sites in 11 patients (13%) at initial diagnosis. The leading recurrence site was the liver in 23 patients (39%). Other recurrence sites were local (15 patients; 25%), peritoneum (14 patients; 24%), lung (5 patients; 8%), lymph nodes (5 patients; 8%), skin (1 patient; 2%), and brain (1 patient; 2%).

Twenty clinicopathologic factors were investigated to determine whether they were of prognostic significance. The results of the log-lank test are shown in Table II. Factors such as age, sex, tumor differentiation, presence of splenic artery and ex-

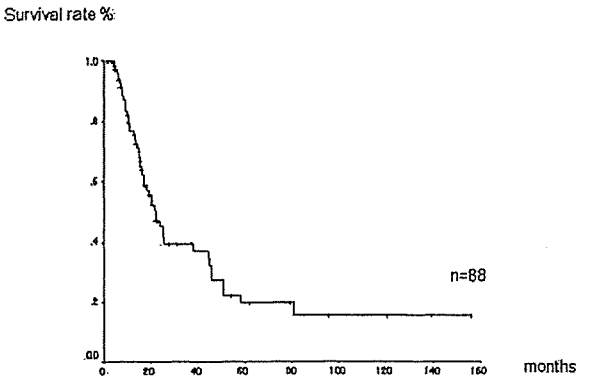

Fig 1. Actuarial 5-year survival curve (Kaplan-Meier) for 88 patients who underwent pancreatectomy for invasive pancreatic cancer of the body and tail.

trapancreatic nerve plexus invasion, IORT, or adjuvant chemotherapy did not influence survival. The 5-year survival rate was 48% in the patients who underwent adjuvant chemotherapy as a clinical trial during this period, but it was not associated significantly with survival ($P = .1209$). In the univariate analysis, the indicators of an unfavorable prognosis included a CA19-9 value higher than 1,000 IU/L (0.0181) and a CEA value higher than 5.0 ng/mL (0.008), a size of larger than 40 mm (0.0343), the presence of serosal invasion (s1, s2, and s3) (0.0051), retropancreatic invasion (rp2 and rp3) (0.0497), splenic or portal vein invasion (pv2 and pv3) (0.0036), lymph node metastases (n2 and n3) (0.0002), lymphatic invasion (ly2 and ly3) (0.0015), venous invasion (v2 and v3) (0.0489), intrapancreatic nerve invasion (ne2 and ne3) (0.0329), and positive peritoneal washing cytology (0.0084). Twelve patients who underwent Appleby operations did not survive for more than 2 years, and the median survival term was 17 months compared with 25 months in patients with distal pancreatectomy ($P = .0112$). Twenty-two patients (22%) had cancer infiltration at the operative margin and the median survival term was 17 months compared with 39 months in those who had no cancer infiltration at the operative margin. One of the 18 patients who had a positive peritoneal washing cytology survived for 59 months after operation.

Figure 2 shows the survival rate according to lymph node involvement. The actuarial 5-year survival rates of patients without lymph node involvement (n0) and patients with regional lymph node metastases (n1) were 56% and 13%, respectively. Patients with peripancreatic (n2) and para-aortic lymph node (n3) involvement did not survive for more than 2 years. Survival rates also were calculated according to the depth of invasion into the portal vein. Patients with invasion to the tunica medica or intima had a poorer prognosis than those with no invasion or invasion to the adventitia. The actuarial 5-year survival rates in patients with pv0, pv1, pv2, and pv3 were 38%, 25%, 11%, and 0%, respectively (Fig 3).

A multivariate analysis with a stepwise regression model showed that the independent prognostic factors for survival were the lymph node involvement status and the degree of splenic or portal vein invasion (Table III).

DISCUSSION

A multicenter large retrospective trial reported that the median survival period of patients with left-side pancreatic cancer was 4.5 months, with a 3-year survival rate of 3%[1]; they concluded that left-side pancreatic cancer was incurable and that resection should be considered as a palliative procedure, based on similar results in other studies.[4–11] The early detection of invasive pancreatic cancer of the body and tail suitable for curative resection[6] and improved survival after distal pancreatectomy with extended resections[2,3] have encouraged physicians to continue operative treatments for this disease, despite the dismal prognosis. Recently, the long-term survival rate has been reported to be 10% to 29%, with a median survival period of 11 to 16 months in recent series (Table IV).[2,3,5,12,13] The present study included a relatively large number of patients (n = 88) with invasive pancreatic cancer located in the body and tail who underwent macroscopic curative resections. The overall median survival period was 22 months, and the 5-year survival rate was 19%; 7 patients survived for more than 5 years. This result shows that the prognosis seemed to be determined by the biology of the tumor rather than factors related to the resection, but the aggressive operative approach provided a favorable survival rate without mortality similar to that of adenocarcinoma of the pancreatic head,[5] if a curative operation can be achieved. The higher percentage of resected patients with pancreatic carcinoma of the body and tail than other series[5] and the relatively favorable outcome might be a result of early detection of the tumor without symptoms and strict indication for operation using meticulous preoperative imaging.

Randomized controlled trials of patients with adenocarcinoma of the pancreatic head have indicated that an extended lymphadenectomy and retroperitoneal soft-tissue clearance with pancreaticoduodenectomy could be performed safely as the procedure of choice with morbidity and mortality

Table 2. Prognostic factors for survival by univariate analysis

Factors	*No. of patients (n=88)*	*Survival rate (%) 1-year*	*3-year*	*5-year*	*Median survival*	*p value*
Age (years)						
<=65	46	84	43	27	24	0.1149
>65	42	68	35	7	17	
Sex						
Male	63	77	40	14	22	0.9527
Female	25	75	35	28	17	
CA19-10						
<1000	68	82	45	24	25	0.0181
>=1000	20	61	21	0	16	
CEA						
<5.0	62	85	47	23	25	0.0080
>=5.0	26	56	22	0		
Size						
<40	41	81	48	35	25	0.0343
>=40	47	73	31	7	20	
Serosal invasion						
s0: 53	53	82	52	32	39	0.0051
s1: 13, s2: 0, s3: 22	35	68	23	0	17	
Retropancreatic tissue invasion						
rp0: 7, rp1: 28	35	82	46	32	25	0.0497
rp2: 44. rp3: 9	53	73	34	6	17	
Splenic, portal vein invasion						
pv0: 35, pv1: 5	40	81	52	36	39	0.0036
pv2: 10, pv3: 38	48	73	27	4	16	
Splenic artery invasion						
a0: 63	63	75	40	23	22	0.8083
a1: 22, a2: 3, a3: 0	25	82	38	9	22	
Extrapancreatic nerve plexus invasion						
absent	58	76	48	27	26	0.0602
present	30	76	23	9	17	
Lymph node metastases						
n0: 19, n1: 52	71	82	50	24	26	0.0002
n2: 5, n3: 12	17	50	0	0	15	
Difrentiation						
Well	26	82	47	20	25	0.5309
Ohters	62	75	37	20	20	
Lymphatic invasion						
ly0: 9, ly1: 37	46	82	50	40	25	0.0015
ly2: 37, ly3: 5	42	71	28	0	17	
Venous invasion						
v0: 14, v1: 27	41	79	50	31	24	0.0489
v2: 35, v3: 12	47	74	28	6	17	
Intrapancreatic nerve invasion						
ne0: 6, ne1: 26	32	89	61	29	44	0.0329
ne2: 42, ne3: 14	56	71	29	14	20	
Operative procedure						
distal pancreatectomy	76	78	47	23	25	0.0112
Applebye's operation	12	72	0	0	17	
Cancer infiltration at surgical margins						
negative	66	81	53	26	39	0.0128
positive	22	67	14	7	17	
Perioneal cytology						
negative	67	78	50	27	39	0.0084
positive	18	80	8	0	17	

Table 2. Continued

Factors	*No. of patients (n=88)*	*Survival rate (%) 1-year*	*3-year*	*5-year*	*Median survival*	*p value*
IORT						
Yes	54	86	43	20	22	0.1829
No	34	61	34	21	17	
Adjuvant chemotherapy						
Yes	23	85	48	48	22	0.1209
No	65	74	37	13	22	

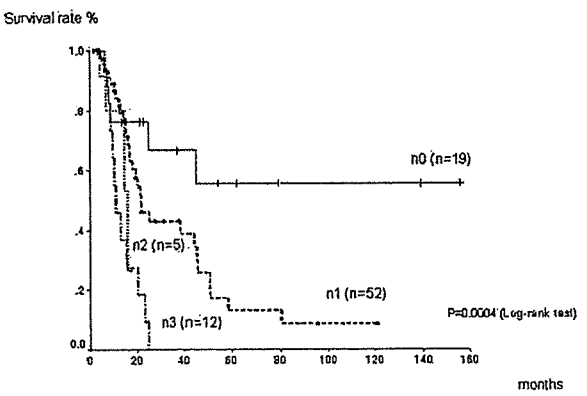

Fig 2. Actuarial 5-year survival curve (Kaplan-Meier) for 88 patients who underwent pancreatectomy for invasive pancreatic cancer of the body and tail, according to lymph node status. n0, no lymph node involvement; n1, regional lymph node involvement; n2, peripancreatic lymph node involvement; n3, para-aortic lymph node involvement. The differences were statistically significant ($P = .0004$).

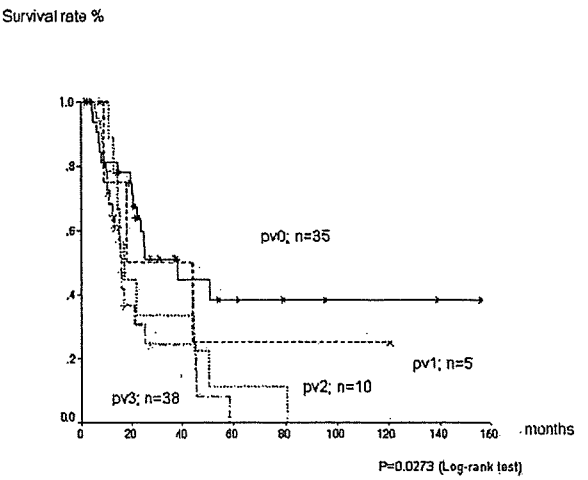

Fig 3. Actuarial 5-year survival curve (Kaplan-Meier) for 88 patients who underwent pancreatectomy for invasive pancreatic cancer of the body and tail, according to the degree of splenic or portal vein invasion. pv0, no portal vein invasion; pv1, invasion to adventitia; pv2, invasion to tunica media; pv3, invasion to tunica intima. The differences were statistically significant ($P = .0273$, log-rank test).

rates similar to those for standard resection, but provided no clear survival benefit.[14,15] Some investigators also have emphasized the effectiveness of extended resections for adenocarcinoma of the body and tail of the pancreas,[2,3,12] but the limited number of patients observed in these studies prevented a definitive result from being obtained. Extended lymphadenectomy, which has a low morbidity and mortality, might play an important role in clarifying the status of lymph node involvement and precise staging[12,16] because the preoperative assessment of lymph node metastases is extremely difficult.[17] In the present study, peripancreatic (N2) and para-aortic nodal involvement (N3) were observed in 5 patients (6%) and 12 patients (14%), respectively, similar to the rates reported by Nakao et al.[12] Lymph node metastasis was one of the most important determinants of long-term survival in this study. The 5-year survival rate in 19 patients (22%) with no lymph node involvement was 56%, but patients with N2 or N3 did not survive for more than 2 years. This result strongly suggests that the para-aortic lymph node should be examined before performing a radical pancreatic resection to avoid unnecessary operation.[18] The operative margin was another important prognostic factor in previous reports.[19,20] In our study, 22 patients (25%) had a positive operative margin despite the removal of retropancreatic tissue. Operative margin was not a significant factor in the multivariate analysis but surgeons can contribute only to local control of the disease by removing as much of the retropancreatic structures as possible while ensuring minimum mortality. Strasberg et al[21] devised the new modification of distal pancreatectomy and emphasized the clinical significance of achieving negative margin and complete N1 node dissections.

Portal vein invasion was problematic in patients with invasive cancer of the pancreatic head, but

Table 3. Multivariant analysis using Cox proportional hazard models

	Wald	*P value*	*Exp(B)*	*95%CI*
splenic vein or portal vein involvement (pv0,pv1/pv2,pv3)	3.953	0.047	2.215	1.011-4.857
lympnode metastases (n0,n1/n2,n3)	7.093	0.008	3.107	1.349-7.056

Table 4. Invasive pancreatic carcinoma of the body and tail in recent large series

Reference	*Year*	*Period of obsrevation*	*number of resections*	*Operative mortality*	*5-year actuarial survival rate (%)*	*Median survival term (months)*
Ozaki et al.[2]	1996	1980-1979	15*	0	29	15
Brennan et al.[5]	1996	1983-1994	34	0	14	12
Sperti et al.[13]	1997	1970-1993	24	2 (8%)	13	11
Nakao et al[12]	1997	1981-1995	31*	2 (7%)	10	NR
Shoup et al.[3]	2000	1983-2000	22*	0	22	16
present series	2005	1990-2004	88*	0	19	22

NR, not reported
*:extended resection

splenic vein invasion was managed easily in patients with invasive cancer of the pancreatic body and tail. Nakagohri et al[22] reported that histologic portal vein invasion was associated significantly with poor survival and that invasion to the tunica intima of the portal vein was associated with extrapancreatic plexus invasion, para-aortic nodal involvement, and a positive operative margin. Histologic portal vein invasion might be associated strongly with liver metastases, which is one of the most important recurrence sites after curative operation.[22-24] Tumor size,[25] serosal invasion,[20] and positive peritoneal cytology[26] were found to be significant determinants of long-term survival in the univariate analysis but were not independent prognostic factors in the multivariate analysis performed in the present study. It is extremely important to predict poor prognostic factors before laparotomy. Preoperative nodal staging is difficult,[17] but the degree of invasion to splenic vein might be estimated using preoperative imaging evaluation. The role of palliative operation in patients with adenocarcinoma of the body and tail of the pancreas seemed to be less important compared with those of the head because biliary and bowel obstruction is not common. If we can predict the dismal prognosis, neoadjuvant chemotherapy and external beam radiotherapy seems to be another treatment of choice preceding operation.

The Appleby procedure reportedly increases the resectability of pancreatic cancer located in the pancreatic body with suspicious invasion to the celiac artery.[27] In the present study, however, none of the 12 patients who underwent this procedure survived for more than 2 years. Thus, the indications for this procedure may need to be reconsidered because it has been applied to T4 carcinoma determined by the latest TNM classification.[9]

The effectiveness of aggressive operative approach with extended lymphadenectomy needs to be examined further in randomized controlled trials in the future. However, this procedure can be performed without operative mortality and one of the important roles seems to be precise nodal staging and to achieve clear operative margin.

In patients with invasive pancreatic cancer of the body and tail, the absence of lymph node involvement and vein invasion might contribute to long-term survival. Adjuvant chemotherapy and/or additional treatment should be evaluated when histologic examinations reveal the presence of lymph node metastases and/or vein invasion because the preoperative selection of optimal treatment strategies remains difficult.

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