Preoperative Indications for Extended Pancreatectomy for Locally Advanced Pancreas Cancer Involving the Portal Vein

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This retrospective study attempted to determine the indications for extended pancreatectomy for locally advanced carcinoma of the pancreas, in terms of postoperative prognosis. An extended pancreatectomy with portal vein or superior mesenteric vein (PV/SMV) resection and regional lymphadenectomy was performed in 35 of 50 consecutive cancers that extended into the retroperitoneal spaces and involved the PV or SMV. Among the many background factors in the 35 resected specimens, the degree of PV/SMV invasion by the cancer was most closely associated with prognosis, despite resection of all involved PV/SMV. This factor generally correlated with the preoperative findings on the portal phase of superior mesenteric arteriograph. In 17 selected patients in whom PV/SMV invasion had been angiographically both semicircular or less and 1.2 cm (1.4 cm on the film) or less in length, the 3-year survival rate was 59%. This survival rate was significantly higher than the 29% 3-year survival rate in all 35 patients ($p < 0.05$). Conversely, among the 18 patients in whom invasion was angiographically either beyond semicircular or more than 1.2 cm (1.4 cm on the film) in length, there were no 1.5-year survivors, and this result was even worse than that of 15 nonresectable cases. Based on postoperative survival, the degrees of PV/SMV invasion on preoperative angiography (narrowing pattern and length) are good indicators for aggressive pancreatectomy for locally advanced pancreatic cancer.

THE INCIDENCE OF ductal cell carcinoma of the pancreas has risen recently in many countries. Although surgical resection is the only curative modality for this cancer, the fact remains that most patients are diagnosed in advanced stages. At the time of surgical exploration, even though distant metastases are not detectable, we frequently observe that the pancreatic tumor extends directly into the retroperitoneal spaces and involves the superior mesenteric vein (SMV) or portal vein (PV). Such a locally advanced pancreatic cancer, stage III in the UICC (International Union Against Cancer) classification,[1] has been generally treated by radiotherapy or chemotherapy.

Aggressive *en bloc* pancreatic resection including the PV or SMV (PV/SMV) has almost been abandoned,[2,3] because of the higher mortality rate, low curability rate, and lower quality of life.

With the recent advances in postoperative care, however, both mortality and morbidity rates have been remarkably decreased after pancreatectomy.[4,5] Second, the development of a bypass catheter and an extracorporeal pump have made it easier and safer to concomitantly resect the PV/SMV.[6] Third, our previous report[7] showed that postoperative survival was significantly improved, especially when lymphatic and connective tissue resection (R2-dissection) was added to the traditional pancreatectomy. Therefore, we have attempted since 1984 to resect more advanced cancer directly extending into the retroperitoneal spaces and PV/SMV, by adding the R2-procedure plus PV/SMV-resection. This type of pancreatectomy is almost similar to Fortner's regional pancreatectomy.[8] Although he failed to improve overall survival (median survival period was 13 months with a 3-year survival rate of 3%), we must reconsider that most of his patients were in highly advanced stages. Therefore, it is suspected that he might have experienced a greater number of long-term survivors if he had applied his procedure to less advanced cancer of the pancreas. Additionally, with more strict indications, we can avoid useless laparotomy or pancreatectomy in patients whose survival period would not be thereby prolonged. Thus, the present study was conducted to detect reliable indicators of surgical resection for locally advanced cancer of the pancreas. We also analyzed the predictability of preoperative examinations.

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Patients and Methods

During the period from 1984 to 1989, surgical laparotomy was performed in 50 consecutive patients with locally advanced adenocarcinoma of the pancreatic head and body at The Center for Adult Diseases, Osaka, Japan. Although none had hepatic metastasis or peritoneal seeding, the tumors extended directly into the retroperitoneal spaces and involved the PV/SMV in all patients. With a curative intent, 35 patients (70%) received an extended pancreatectomy with *en bloc* resection of a 3.1 ± 0.9 cm length of PV/SMV (Table 1). Additionally, peripancreatic connective tissue, including both regional and juxtaregional lymph nodes, were clearly dissected (R2) in all 35 patients. Thirty-five pancreatectomies consisted of 18 Whipple procedures (Child's method with a slight modification), 15 total pancreatectomies, and 2 (subtotal) caudal pancreatectomies. The appropriate range of the PV/SMV resection was determined with the aid of intraoperative histocytology. Bypass catheter[6] (Anthron Catheter, Tore Co. Ltd. Tokyo, Japan) combined with extracorporeal pump was used for four cases whose PV/SMV invasions were 3.5 cm or more in length. The PV/SMV reconstruction was performed by end-to-end anastomosis: PV/SMV in 16 patients, PV-graft (femoral vein)-SMV in 3 patients, and SMV-SMV in 16 patients. In four patients, superior mesenteric artery (SMA; three patients) or common hepatic artery (one patient) was resected because of identification of a small amount of cancer invasion. These arteries were reconstructed by interposing a graft obtained from the saphenous vein. The tumor invasion was still more extensive in another 15 patients, invading the root of the transverse mesocolon or the root of mesojejunum. Curative resection of the tumor was therefore abandoned, and gastrojejunostomy or choledochojejunostomy were performed.

TABLE 1. *Outcome of 35 Surgical Resections for Locally Advanced Adenocarcinoma of the Pancreas*

Procedure	No. of Patients	No. of Deaths After Surgery
Pancreatectomy		
Total	15	2
Whipple procedure (Child's method)	18	
Caudal	2	
Major vessels resected		
SMV	15	
SMV + SMA	1	
SMV + PV	15	1
SMV + PV + SMA	3	1
SMV + PV + CHA	1	

Regional and juxtaregional lymph nodes were cleared in all 35 patients. SMV, superior mesenteric vein; SMA, superior mesenteric artery; PV, portal vein; CHA, common hepatic artery.

The surgically resected specimens were studied histologically to determine the tumor size (maximum diameter), nodal involvement, and histologic type. In the present study, the PV/SMV were judged as positive for cancer invasion even when cancer cells were limited to the tunica adventitia. The length of PV/SMV invasion was measured, and the width was also classified into two grades on the basis of whether cancer invasion was beyond the semicircle of the PV/SMV or not. Before surgery, all 50 patients had undergone both celiac arteriography and superior mesenteric angiography, using a modified Seldinger technique.[9] To better delineate the SMV and PV, 20 μg prostaglandin E1 (Ono Pharmacologic Co. Ltd., Tokyo, Japan) was injected through the catheter into the SMA just before filming. All angiographs were examined to detect evidence of encasement or narrowing in the major vessels adjacent to the pancreas. The patterns of PV and SMV narrowing were categorized into five types. The length of PV/SMV invasion was determined on the angiographs, and was divided by 1.2 (magnification rate).

The cumulative survival rate was shown by life-table method. Statistical analyses performed using nonpaired t test or chi square test. P values less than 0.05 were considered to be statistically significant.

Results

Thirty-five patients received pancreatectomy, PV/SMV resection, and peripancreatic connective tissue resection, including the regional lymph nodes, for locally advanced carcinoma of the pancreas. Two died of postoperative complications within 30 days, and three are alive without disease recurrence between 1 and to 3 years after surgery. Among the remaining 30 patients, 23 patients (77%) died of cancer recurrence within 3 years after surgery (Group A) (mean survival period, 9 ± 5 months; range, 2 to 21 months). Seven patients (23%) survived 3 years or more (Group B), and five of these were disease free at 3 years.

Table 2 compares both the patients and their pancreatic carcinomas in groups A and B. There are no significant differences in age, sex, location of the tumor (head or body), or tumor size. The histologic types of cancer were classified into two types: papillary/well-differentiated adenocarcinoma and moderately/poorly differentiated adenocarcinoma. The latter type represented 57% in group A, which was not significantly higher than the 43% in group B. Histologically proven nodal involvement in the regional or juxtaregional areas was seen in 28 (93%) of 30 patients. The incidence of nodal involvement did not differ significantly between the two groups. There were four patients (17%) whose major arteries were involved by cancer (SMA = 3, common hepatic artery = 1) in group A, but this incidence was not significantly higher than 0% in group B. It was histologically confirmed that

TABLE 2. *Background Factors in Association With 3-Year Survival*

Factor	Patient Survival Period <3 yr (23 patients)	Patient Survival Period >3 yr (7 patients)	p
Age (yr)	61 ± 7	63 ± 4	NS*
Sex	16/7	5/2	NS†
Tumor location (head/body)	17/6	5/2	NS†
Tumor size (cm)	3.6 ± 0.8	3.3 ± 1.4	NS*
Histologic type			
Pap + Well	10 (43%)	4 (57%)	
Mod + Poor	13 (57%)	3 (43%)	NS†
Regional lymph node metastasis			
Positive/negative	21/2	7/0	NS†
Major artery invasion‡	4 (17%)	0 (0%)	NS†
PV/SMV invasion			
Semicircular or less	12 (52%)	7 (100%)	<0.05†
Beyond semicircular	11 (48%)	0 (0%)	
Maximum length (cm)	2.6 ± 1.0	1.6 ± 0.4	<0.05*
Range	1.0–5.4	0.9–2.0	

* Nonpaired t test.
† Chi square test.
‡ Common hepatic artery, 3; superior mesenteric artery, 1.
Pap: papillary adenocarcinoma; Well: well-differentiated adenocarcinoma; Mod: moderately differentiated adenocarcinoma; Poor: poorly differentiated adenocarcinoma; PV, portal vein; SMV, superior mesenteric vein.

all 30 of the PV/SMV were involved by cancer, but the degree of cancer invasion differed significantly between the two groups. Among 23 PV/SMV invasions of group A, 12 (52%) were semicircular or less, and 11 (48%) were beyond semicircular. Conversely, the PV/SMV invasion was semicircular or less in all the patients (100%) of group B ($p < 0.05$, chi square test). Likewise, the length of PV/SMV invasion was 2.6 ± 1.1 cm (1.0 to 5.4 cm) and 1.6 ± 0.4 cm (0.9 to 2.0 cm), respectively ($p < 0.05$ in nonpaired t test).

To know whether PV/SMV invasion can be predicted by preoperative angiography, a retrospective analysis was made on the portal phase of SMA-angiography. The PV/SMV was clearly delineated in all 50 patients, and the findings were classified into the following five types (Fig. 1): (I) normal, (II) smooth shift without narrowing, (III) unilateral narrowing (Fig. 2A), (IV) bilateral narrowing (Fig. 2B), and (V) bilateral narrowing and the presence of collateral veins. Table 3 compares the patterns of PV/SMV invasion between histology and angiography in the 35 resectable patients. Among the 35 cases showing invasion, angiography resulted in 14 (40%) underestimations (as shown by a: type I and II in both groups, and type III in the group with bilateral narrowing). Likewise, there were 19 correct diagnoses (54%; shown by b) and two overestimations (6%; shown by c). Among the 22 PV/SMV invasions that were semicircular or less, however, 20 (91%) exhibited types I, II, or III. This incidence was significantly higher than the 15% (two cases) in 13 cases whose invasions were beyond the semicircle of PV/SMV ($p < 0.05$). Fifteen nonresectable cases consisted of eight cases of type IV and seven cases of type V.

Figure 3 compares the length of PV/SMV invasion determined by the histopathology of the resected specimen with those diagnosed by preoperative angiography. In this figure, the angiographic lengths of PV/SMV invasion were expressed as 0 cm for 13 cases with type I or II patterns, shown by open circles. Even excluding these 13 cases, the true length of PV/SMV invasion was longer than the angiographic length in all but one case. There was a parallel relationship, however, between the two types of measurement ($y = 0.68 \times -0.17$, $r = 0.766$, $p < 0.01$). Among the 17 cases whose PV/SMV invasions were 2 cm or less (area delineated by dotted line), 1.2 cm of invasion was the longest based on angiographic diagnosis. Although the true lengths of cancer invasion were not known for the 15 nonresectable cases, angiography showed invasion of 1.5 cm or more in length. There were 17 patients in whom PV/SMV invasion was angiographically 1.2 cm or less in length and who were type I, II, or III.

Figure 4A shows the cumulative survival rates in the 35 overall resectable cases and 15 nonresectable cases.

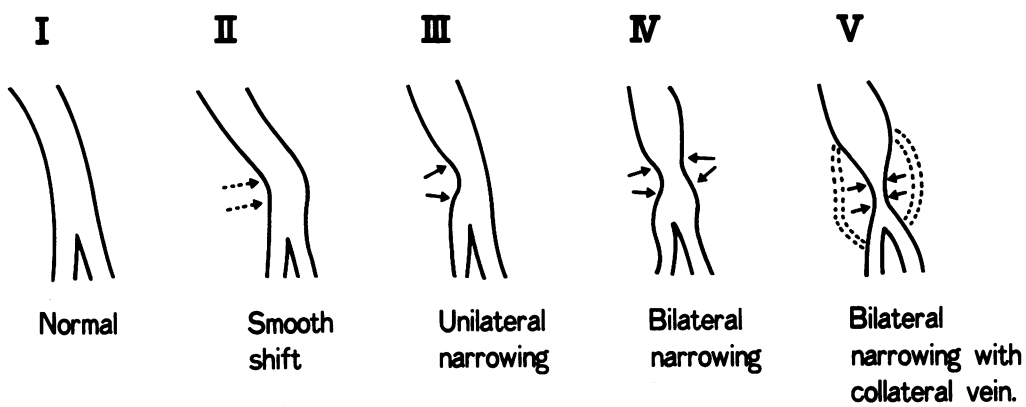

FIG. 1. Angiographic typing of PV/SMV invasion.

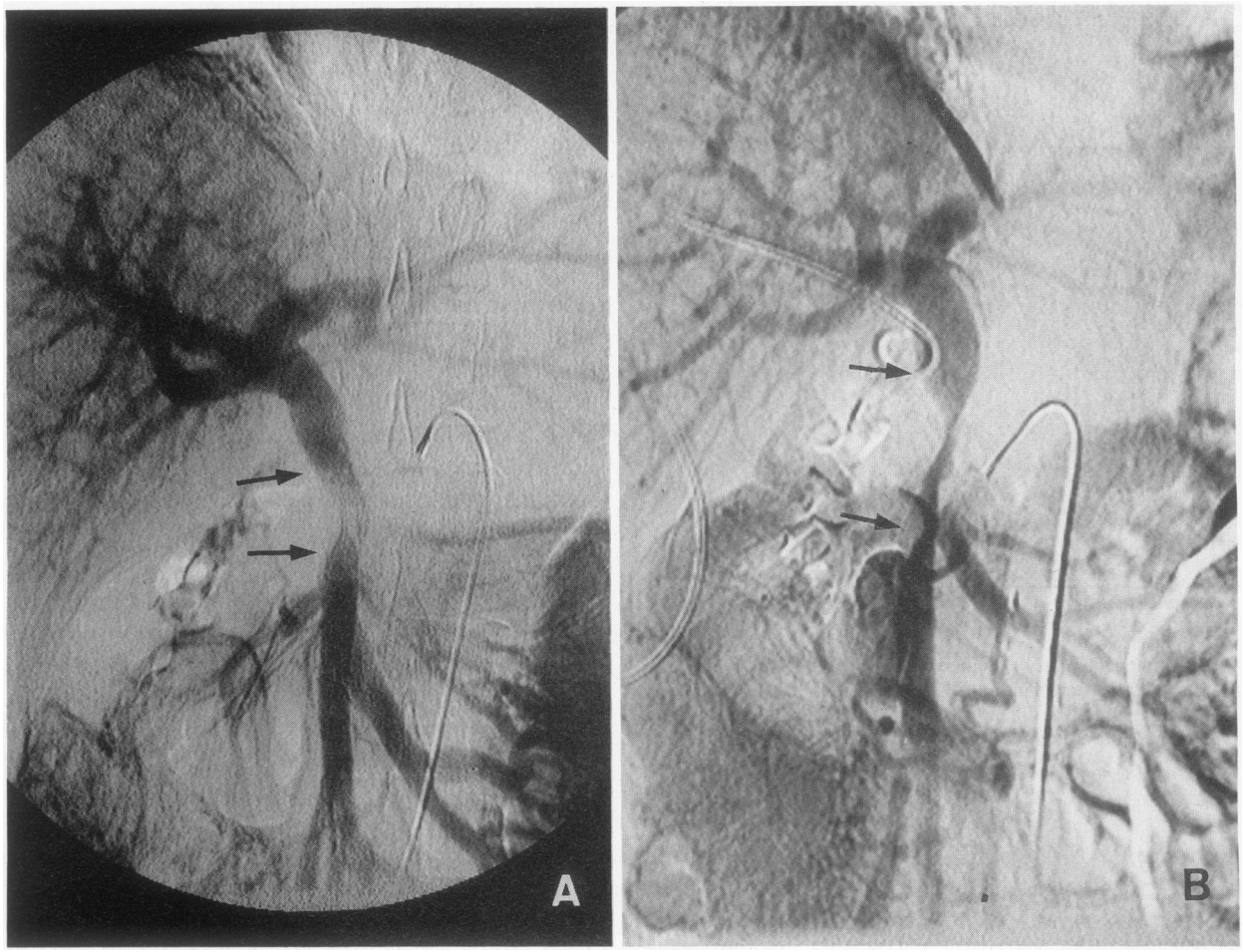

FIG. 2. Portal phase of SMA angiography, (A) types III and (B) type IV narrowing. The length of the narrowed portion (between arrows) is determined on the angiographic film and divided by 1.2 (magnification rate).

The 3-year survival rate was 29% and 0%, respectively ($p < 0.05$ at 2 and 3 years). Figure 4B shows the cumulative survival rates of two subgroups: 17 patients in whom PV/SMV invasion had been angiographically diagnosed as type I, II, or III, and 1.2 cm or less in length; and 18 patients in whom invasion had been diagnosed as type IV or V, or more than 1.2 cm in length. In the former subgroup, the 3-year survival rate was 59%. This figure was significantly higher than the 29% in all resectable cases ($p < 0.05$). Conversely, there were no 1.5-year survivors in the latter subgroup. The survival rate was generally lower than that of the 15 nonresected patients (Fig. 4A) in whom curative resection was abandoned because the retroperitoneal invasion was extensive.

TABLE 3. *Comparison of the Patterns of PV/SMV Invasion Between Histology and Angiography*

PV/SMV Invasion in Resected Specimen	Portal Phase of SMA angiography				
	I	II	III	IV	V
Semicircle or less (n = 22)	5* (23%)	7* (32%)	8† (36%)	2‡ (9%)	0
Beyond semicircle (n = 13)	1* (8%)	0	1* (8%)	6† (46%)	5‡ (38%)

The incidence of types I–III (or types IV–V) narrowing differs significantly between unilateral and bilateral invasion groups ($p < 0.01$) (chi square test).

* Underdiagnosis, 14 cases (40%).

† Correct diagnosis, 19 cases (54%).

‡ Overdiagnosis, 2 cases (6%).

PV, portal vein; SMV, superior mesenteric vein; SMA, superior mesenteric artery.

Discussion

The present study was limited to locally advanced pancreatic cancers invading both the retroperitoneal spaces and PV/SMV. As shown in Table 1, almost all patients had regional or juxtaregional lymph node metastasis. In reviewing previous reports,[10–12] such an advanced cancer commonly has been considered not suitable for the surgical resection. There have been few patients to date, however, whose survival periods have been prolonged

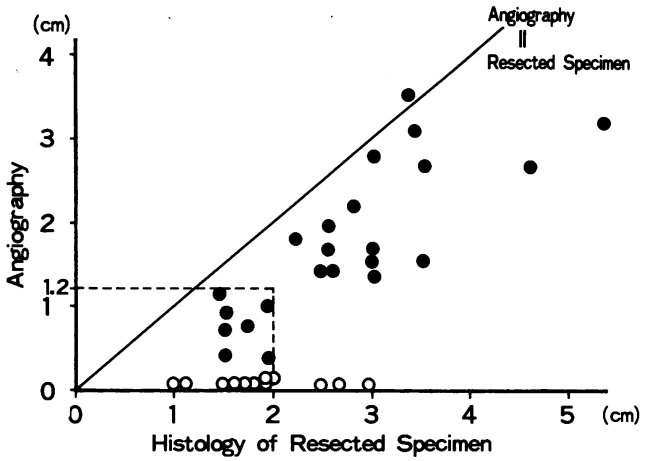

FIG. 3. A comparison of the length of PV/SMV invasion between histology and angiography. Open circles show cases in which any narrowing was angiographically observed (types I and II). Excluding the cases with type I and II narrowing, a parallel relationship is observed between the two measurements ($y = 0.68$, $x = 0.17$, $r = 0.766$, $p < 0.05$). Dotted lines show that all invasions of 2 cm or less in length were angiographically diagnosed as narrowings of 1.2 cm or less in length.

more than 3 years by chemotherapy or radiation therapy.[10-12] This agrees with our result, in which the 2-year survival rate was 0% in 15 nonresectable patients (Fig. 4A). Additionally, many previous reports have shown that pancreatic cancer was likely to recur and be fatal within 2 or 3 years after surgical resection.[7,13,14] It can be expected from this that patients who have survived the first 3 postoperative years have a high potential for cancer-free survival from that time on. This is why 3-year survival was used as a tentative parameter of operative indications in the following discussion.

During surgical resection of pancreatic cancer, nodal involvement has been considered one of the limiting factors in patient survival. In 1982, Cohen et al.[15] showed that long-term survival could not be expected for any patients with nodal involvement. Our recent report,[7] however, clarified that long-term survival was not hopeless, even in patients with nodal involvement, when lymphatic and connective tissue resection (R2-procedure) also was performed. Considering that all of our seven 3-year survivors had lymphatic metastasis in the regional or juxtaregional nodes, most might not have survived 3 years if the R2-procedure had been omitted from our operative procedure. Therefore, this kind of lymphadenectomy seems to be indispensable when surgical resection is determined for locally advanced pancreatic cancer.

In place of nodal involvement, our study has clarified that the degree (length and width) of PV/SMV invasion was more predictive of patient prognosis, despite resection of all involved PV/SMV. For this reason, the space between the SMV or PV and the posterior confines of the pancreas may be anatomically characterized as the weakest barrier against cancer spread into the mesenteric tissues, which include many lymphatic channels and nerve fibers.[16] Likewise, cancer cells within the PV/SMV wall may easily spread hematologically and result in hepatic metastasis. The more widely the cancer invades the PV/SMV, the more frequently and distant from the surgical margin cancer implantation might occur microscopically.

Suzuki et al.[17,18] reported that long-term survival was not observed in pancreatic cancer patients whose arteriographs suggested cancer invasion in the arteries adjacent to the pancreas. Despite the fact that PV/SMV involvement is more common than arterial involvement in pancreatic cancer,[19] there has been no previous report investigating patient survival in association with PV/SMV invasion on angiography. For the first time, the present report has clarified that postsurgical prognosis is very poor in patients in whom angiography showed bilateral narrowing (type IV or V) or more than a 1.2 cm (1.4 cm on the film) length of narrowing in the PV/SMV. Considering that their survival rates were worse than those of the nonresectable patients, we should have abandoned aggressive pancreatectomy in these patients. This also seems to be

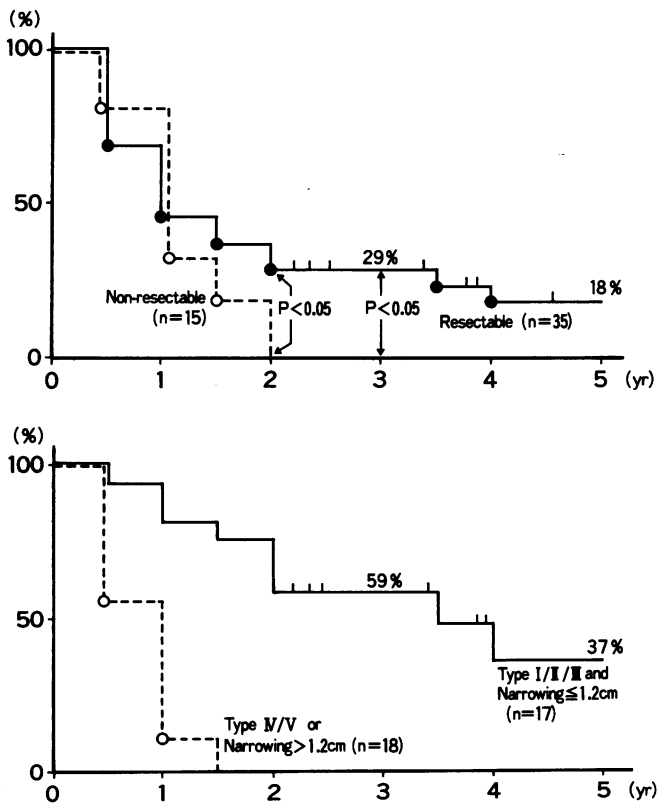

FIG. 4. (A, top) Cumulative survival rates compared between resectable and nonresectable groups. A significant difference was observed between the two groups ($p < 0.05$). (B, bottom) Cumulative survival rates in association with angiographic findings in the resectable group. In the subgroup with both type I–III narrowing and narrowing of 1.2 cm or less in length, the 3-year survival rate was 59%. This figure is significantly higher than the 29% found in all 35 patients (A). In the subgroup with either type IV–V narrowing or narrowing greater than 1.2 cm in length, the survival rate is still worse than that of the 15 nonresectable patients (A).

supported from the viewpoint of cost–performance and quality of postoperative life. Conversely, a far better prognosis can be expected for patients in whom PV/SMV narrowing is angiographically absent, unilateral, and 1.2 cm (1.4 cm on the film) or less in length. If we had selected the above-mentioned criteria as indications for aggressive operation, approximately a 60% 3-year survival rate would have been estimated by extended pancreatectomy (Fig. 4B). This result is better than many previous reports[4,7,20,21] where 3-year survival rate ranged from 20% to 45%, even in less advanced carcinoma of the pancreas.

The portal phase of SMA angiography was likely to underestimate the true invasion of the PV/SMV (Fig. 3 and Table 3). This discrepancy might be explained by the fact that the internal diameter of the PV/SMV would be unaffected during the period when cancer invasion is limited to the tunica adventitia. Therefore, we should always prepare to perform PV/SMV resection and their reconstruction when pancreatectomy is performed for carcinoma of the pancreatic head and body. This is especially emphasized when no obvious change is observed angiographically in the PV/SMV.

Finally, our angiographic classification is very simple and does not require percutaneous transhepatic portography[22] to clearly delineate any branching veins. Using this classification of the traditional SMA-angiography, we can hope that useless laparotomy or pancreatectomy can be avoided without losing any chance for cure.

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