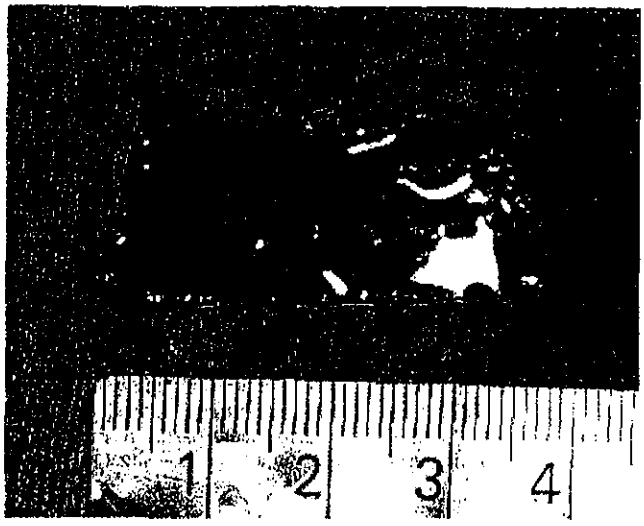

Fig. 2 When the two orifices of the right hepatic veins were different, we made a trapezoidal sheet to make a suitable cylindrical graft (the length of the upper edge was 3.0 cm, and the length of the lower edge was 4.0 cm, in case 2), which could adjust the different orifices

Fig. 3 The *arrowhead* shows the reconstructed middle hepatic vein using the thick interposing vein graft made from the right great saphenous vein

inferior right hepatic vein (IRHV) [10] was observed on preoperative computed tomography; thus, the right hepatic vein could be sacrificed, preserving the venous drainage of segment VI of the liver via the IRHV. Limited resectioning of segments III and VIII of the liver was performed, with complete removal of the right hepatic vein and segmental resection of the middle hepatic vein. We decided to reconstruct the middle hepatic vein to preserve the remnant liver function as much as possible.

Using intraoperative ultrasound prior to resectioning, we estimated the middle hepatic vein defect to be 9 mm in diameter and 21 mm long. The diameter of the GSV was

Fig. 4 Three-dimensional computed tomography revealed the patency of the reconstructed middle hepatic vein 3 weeks after surgery in case 1

2.5 mm. Thus, the required number of small pieces and length of the great saphenous vein were calculated to be 3 (=21/2.5×3) and 81 mm (=3×3×9), respectively. The constructed vein graft was 9 mm in diameter and 23 mm long.

The vein graft was first anastomosed to the proximal end of the middle hepatic vein and then to the distal end (Fig. 3). After reperfusion, adequate venous flow through the reconstructed hepatic vein was confirmed by Doppler ultrasonography. The patency of the reconstructed middle hepatic vein was confirmed by three-dimensional computed tomography 3 weeks after surgery (Fig. 4). The postoperative course was uneventful, and the patient is alive with pulmonary recurrence 1 year and 2 months after surgery.

Discussion

We successfully applied the present GSV graft to interpose the major hepatic veins or portal veins in five patients. No patient developed venous thrombosis or postoperative edema of the lower leg. Although it takes 1 h for a cylindrical graft to be made, this method can create a vein graft with a wider range of diameters and lengths and can avoid the troublesome postoperative edema of the lower legs.

The GSV is often used to bypass the coronary artery in the treatment of ischemic heart disease. This vein itself is too thin for one to use to reconstruct the thick major hepatic veins or portal veins, and size-mismatch at the anastomosis will cause the occlusion of the vein graft [2]. Urayama et al. reported remodeling a vein graft to reconstruct the jugular and portal veins, making twice the diameter and half the length of the original GSV [3]. However, the GSV is sometimes very thin (the diameter is

less than 5 mm) and the vein graft may not be thick enough to interpose a major hepatic vein or portal vein.

The significance of reconstruction of the major hepatic vein is controversial. In a highly selected situation, interpositioning of the major hepatic vein is indispensable for curative hepatectomy and rescue of the patient [11, 12]. However, due to the presence of the intrahepatic anastomosis of venous branches of the liver [13] or the appearance of arterio-portal shunting to avoid venous congestion [14], the sacrificing of one major hepatic vein is not fatal, although the relative indication for venous reconstruction has recently been established in the era of liver transplantation [15]. In fact, venous reconstruction might not have been indispensable in cases 1 to 3. However, at least 30% of patients who developed liver metastasis from colorectal cancer and underwent hepatic resections reportedly developed hepatic recurrence; repeat liver resection for recurrent liver metastasis should be considered [16]. If technically feasible, reconstruction of the major hepatic vein, if possible, would enable the possible congestion or necrosis of the remnant liver to be avoided and would extend the surgical indications for recurrent liver metastases in the remnant liver.

In conclusion, we present a simple and safe method of customizing a vein graft, using the great saphenous vein. This simple method can be used to create vein grafts with a wide range of diameters and lengths. They are useful for the reconstruction of the major hepatic or portal veins, without the postoperative edema of the lower legs.

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Extended Radical Resection Versus Standard Resection for Pancreatic Cancer

The Rationale for Extended Radical Resection

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Objectives: This clinical study was carried out to clarify the indications for extended radical resection for pancreatic carcinoma.

Methods: From July 1981 to September 2003, 250 of 391 (63.9%) patients with pancreatic carcinoma underwent tumor resection in our department. Portal vein resection was performed in 171 of these 250 (68.4%) resected cases. The postoperative survival rate was studied using the operative and histologic findings.

Results: Most of the patients who survived for 2 or 3 years were in the carcinoma-free surgical margins group.

Conclusion: The most important indication for an extended-radical resection combined with portal vein resection for pancreatic cancer is the ability to obtain surgical cancer-free margins. There is no indication for an extended resection in patients in whom the surgical margins will become cancer positive if such an operation is employed.

Key Words: pancreatic cancer, extended resection, portal vein resection, standard operation, isolated pancreatectomy

(*Pancreas* 2004;28:289–292)

Early diagnosis of pancreatic cancer remains difficult in spite of the development of imaging techniques, specific tumor markers, and molecular biology. Surgical resection provides the only chance for cure or long-term survival, but a 5-year survival of patients with pancreas head carcinoma is only 13% after resection.[1]

In 1973, Fortner[2] impressively proposed "regional pancreatectomy as a means of increasing resectability and radicality to improve the outcome for pancreatic cancer patients." Our department has been performing extended resections for pancreatic cancer since 1981, when Nakao et al[3–6] developed the catheter bypass procedure of the portal vein and isolated pancreatectomy using an antithrombogenic bypass catheter consisting of 3 components: combined resection of major vessels, including the portal vein and arteries if necessary; extrapancreatic nerve plexus excision; and retroperitoneal connective tissue clearance, including paraaortic lymph nodes.

Controversy has surrounded the efficacy of the extended radical operation. Many of the related published data consist of nonrandomized comparisons.[7–9] However, 2 prospective, randomized studies have been reported recently.[10,11] This article clarifies the indications for extended resection of pancreatic cancer based on the experiences in our department and reviews the controversy concerning the efficacy of extended radical resection for pancreatic cancer.

METHODS

From July 1981 to September 2003, 391 patients with invasive ductal carcinoma of the pancreas were operated on in our department. Two hundred fifty (63.9%) underwent surgical resection (Table 1) as follows: 62 had total pancreatectomies (TP), 112 had pancreatoduodenectomies (PD), 33 had pylorus-preserving pancreatoduodenectomies (PpPD), and 43 had distal pancreatectomies (DP). Portal vein resection was performed on 171 of these 250 (68.4%) patients.

The surgically resected specimens were examined histopathologically according to the rules of the Japan Pancreas Society,[12] and the cumulative survival rate was calculated by the Kaplan-Meier method.[13] Statistical analysis was performed using the generalized Wilcoxon test. Any P value <0.05 was considered to be statistically significant. Cox proportional hazards modeling[14] was used to explore independent predictions of survival.

RESULTS

A portal vein resection or superior mesenteric vein resection was performed in 171 of the 250 (68.4%) patients (Table 1). Reconstruction of the portal vein was performed by end-to-end anastomosis in 169 of the 171 (98.8%) patients with portal vein resection. An autograft of the external iliac

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TABLE 1. Resectability Rate of Pancreatic Carcinoma and Procedures Performed

Location	Operations	Resection	PV Resection	Resectability	Operative Deaths	TP	PD	PPPD	DP
Head	287	190	146	66.2%	9	45 (44)	112 (85)	33 (17)	0
Body tail	82	53	19	64.6%	1	10 (10)	0	0	43 (9)
Whole	22	7	6	31.8%	1	7 (6)	0	0	0
Total	391	250	171 (68.4%)	63.9%	11	62 (60)	112 (85)	33 (17)	43 (9)

PV, portal vein; TP, total pancreatectomy; PD, pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy; DP, distal pancreatectomy. Numbers in parentheses indicate portal vein resection.

vein was used in 2 patients. Combined arterial resection was undertaken in 11 patients (celiac artery, 2; common hepatic artery, 4; superior mesenteric artery, 3; and proper hepatic artery, 2). Operative death (within 30 days after surgery) occurred in 11 of the 250 (4.4%) resected patients.

Cumulative survival rates, including operative and hospital deaths according to the stage of the Japan Pancreas Society, are shown in Figure 1. No statistically significant difference was seen between the survival rates of patients in stages IVa and IVb.

Multivariate analysis demonstrated that positive extrapancreatic nerve plexus invasion (pl) ($P = 0.0021$, RR = 1.770), positive invasion of dissected peripancreatic tissue margin (dpm) ($P = 0.0110$, RR = 1.619), positive portal system vein wall invasion (pv) ($P = 0.0146$, RR = 1.454), positive lymph node metastases (n) ($P = 0.0219$, RR = 1.426), tumor size >2 cm ($P = 0.0278$, RR = 2.010), and positive serosal invasion (s) ($P = 0.0353$, RR = 1.382) were independently correlated with patient outcome.

Cumulative survival rates according to portal system vein wall invasion (pv) or invasion of dissected peripancreatic tissue margin (dpm) are shown in Figure 2. Survival for more than 2 years after surgery was seen in the dpm (−) group, even when portal system vein wall invasion was observed. No statistically significant difference was found between the survival rates of the dpm (+) group and the 141 nonresectable patients (Fig. 2).

Cumulative survival rates according to extrapancreatic nerve plexus invasion (pl) or invasion of the dissected peripancreatic tissue margins (dpm) are shown in Figure 3. It was difficult to obtain a cancer-free margin in the pl (+) group compared with the pv (+) group, even with extensive surgery. The prognosis for the pl (+) group is very poor.

Lymph node metastases are classified as n_0, n_1, n_2, and n_3 by the Japan Pancreas Society. Cumulative survival rates according to lymph node metastases (n) are shown in Figure 4. The negative lymph node metastases group (n_0) had a higher survival rate than the n_1 ($P = 0.0527$), n_2 ($P = 0.0014$), and n_3 ($P = 0.0001$) lymph node–positive groups. No statistically significant difference was found between the survival rates of the n_1 and n_2 groups.

DISCUSSION

Since 1981, we have been performing isolated pancreatectomy accompanied by portal vein resection using the catheter bypass procedure and extensive dissection of lymph nodes. This includes the paraaortic lymph nodes, as well as retroperitoneal connective tissues, and the extrapancreatic nerve plexus. The operability rate has increased to over 60% during this 20-year period. During the first 12 years (1981–1993), we experienced 11 operative deaths within 30 days after surgery. However, during the next 10 years (1993–September

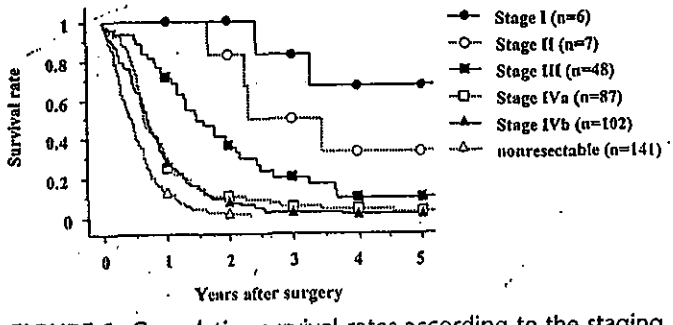

FIGURE 1. Cumulative survival rates according to the staging of the Japan Pancreas Society in pancreatic cancer.

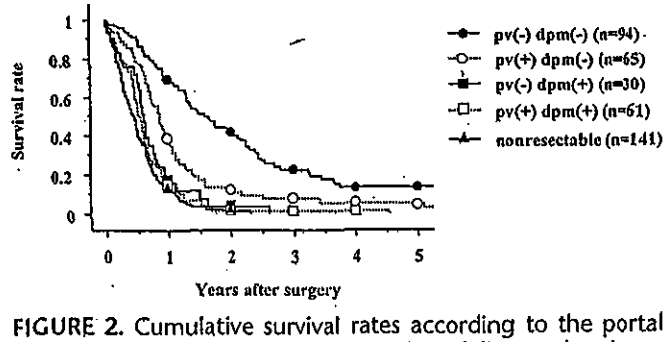

FIGURE 2. Cumulative survival rates according to the portal system vein wall invasion (pv) or invasion of dissected peripancreatic tissue margin (dpm).

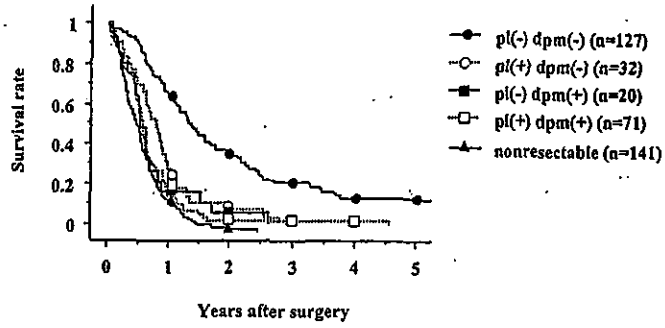

FIGURE 3. Cumulative survival rates according to extrapancreatic nerve plexus invasion (pl) or invasion of the dissected peripancreatic tissue margins (dpm).

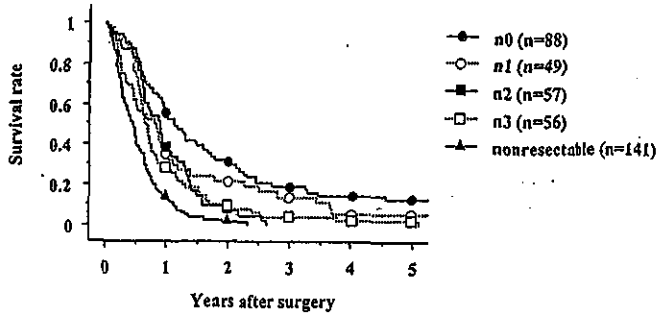

FIGURE 4. Cumulative survival rates according to lymph node metastases.

2003), there were no operative deaths. Combined resection of the portal vein has become both safer and easier with the portal vein catheter bypass procedure.

In our clinical series of total pancreatectomized specimens of pancreatic head carcinoma, carcinoma development was confirmed to be continuous from the head to the body or tail.[15] Quality of life after extended TP is much less favorable compared with that of extended PD or PpPD. Therefore, we have been trying to preserve the distal pancreas whenever intrapancreatic carcinoma development from the head to the body or tail is not observed by immediate intraoperative pathologic diagnosis and immunostaining.[15,16]

The rationale for extensive dissection of lymph nodes, including paraortic lymph nodes, has been based on the high incidence of lymph node metastases[17,18] in pancreatic cancer. Most studies in support of radical pancreatectomy are nonrandomized, retrospective studies.[7,8] Contrary to many of these published reports, a nonrandomized comparison by Henne-Brums et al[9] found no survival advantage to extended retroperitoneal lymphadenectomy.

However, one prospective, randomized multicenter Italian study by Pedrazzoli et al[10] suggested a survival advantage in the patient with lymph node–positive tumors by extensive lymphadenectomy. Another prospective, randomized study by Yeo et al[11] could not prove the efficacy of an extended operation. The efficacy of the extended operation is still not clarified to date.

Pancreatic carcinoma often invades the extrapancreatic nerve plexus.[19] In pancreatic head carcinoma, complete dissection of the extrapancreatic nerve plexus (especially the second portion), together with the nerve plexus around the superior mesenteric artery, is usually necessary to obtain a carcinoma-free surgical margin. However, complete resection of the nerve plexus around the superior mesenteric artery causes severe diarrhea after surgery. Intraportal endovascular ultrasonography (IPEUS) makes it possible to diagnose not only carcinoma invasion to the portal vein,[20,21] but also to the second portion of the pancreatic head nerve plexus.[22] Postoperative survival rates of patients with positive extrapancreatic nerve plexus carcinoma invasion compare very poorly with rates in those with negative invasion of the extrapancreatic nerve plexus. If patients have no carcinoma invasion to the second portion of the pancreatic head nerve plexus, the left semicircular nerve plexus around the superior mesenteric artery is preserved to prevent diarrhea. For patients with carcinoma invasion to the extrapancreatic nerve plexus, especially to the nerve plexus around the superior mesenteric artery, there is no indication for radical resection because their condition makes it difficult to obtain a carcinoma-free surgical margin compared with portal invasion.

With portal vein resection for pancreatic cancer, it is important to obtain a carcinoma-free surgical margin.[23] If such a surgical margin cannot be obtained, even by performing extensive surgery, there is no indication for surgical resection in patients with pancreatic carcinoma.

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Pancreatic Cancer Registry in Japan

20 Years of Experience

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Abstract: The prognosis of pancreatic cancer is defined by the histology and extent of disease. Preoperative histologic diagnosis and diagnostic imaging are fundamentals in managing the disease, but it is not rare to find unexpected peritoneal dissemination or liver metastasis at the time of operation. The overall resectability rate of pancreatic cancer is 40% in Japan. Resecting the portal vein and peripancreatic plexus were performed on 40% of the patients who underwent pancreatectomy for invasive cancer in the head of the pancreas. Long-term survival was only found in patients who underwent pancreatectomy. Radical lymph node dissection, or combined resection of the large vessels, did not seem to improve survival further than the standard resection. Multidisciplinary treatments combined with surgery were performed, and various effects of postoperative chemotherapy after pancreatectomy, intraoperative- and postoperative-radiation therapy, or postoperative chemotherapy for unresectable tumor, were shown. Development of unconventional therapies and refinement of the conventional therapy should be promoted on a randomized prospective trial basis. To promote this effort, which requires the international comparisons and cooperation, JPS developed a computerized JPS registration system downloadable from the JPS website (http://www.kojin.or.jp/suizou/index.html).

Key Words: pancreatic cancer, registry, radical resection, chemotherapy, TNM

(*Pancreas* 2004;28:219–230)

The mortality rate of pancreatic cancer increases after 40 years of age and exceeds 120 deaths per 100,000 by the age of 80 (Fig. 1).[1] It is the fifth leading cause of cancer death in men and the sixth in women in Japan, as well as in the United States and European countries. The prognosis of this disease has not improved markedly in the past 20 years, and the development of new treatment modalities are being pursued.[2,3] The Japan Pancreas Society (JPS) and the National Cancer Center have jointly sponsored the National Pancreatic Cancer Registry since 1981. As of 2002, 23,302 cases have been registered from the leading 350 institutions nationwide.[4] During these past 20 years, JPS published the first English edition of *Classification of Pancreatic Carcinoma* in 1996,[5] and the second English edition in 2003,[6] with the goal of making classification simple, easy to understand, and acceptable by international standards, while not sacrificing any of the merits of the Japa-

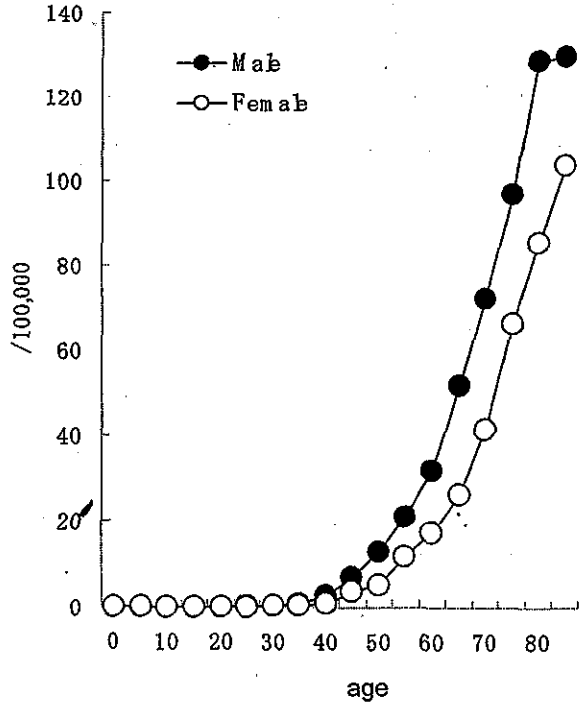

FIGURE 1. Age-corrected death due to pancreatic cancer in Japan. Modified from reference 1 and http://www.ncc.go.jp/en/statistics/.

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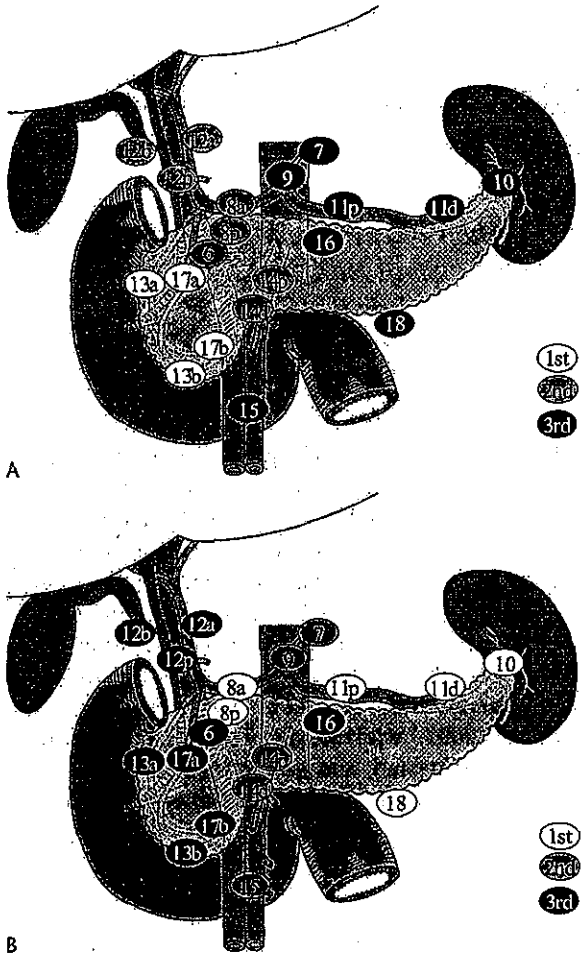

FIGURE 2. Lymph node groups for tumor of the pancreas in JPS classification system. The tumor is located in the head (A) or body and tail (B). Open circle, the 1st group; shaded circle, 2nd group; solid circle, 3rd group. Names of lymph nodes are described elsewhere.[6]

nese classification scheme. The classification of some prognostic factors has been refined and simplified, and the histologic classification is now compatible with the WHO classification system (1996). By providing standardized criteria and terminology, it facilitates comparison of clinical and pathologic data, with the ultimate goal of contributing to improving the results of treatment.[6] In this paper, current perspectives of pancreatic cancer in Japan are described based on this database according to the latest version of JPS classification.[6]

PATIENTS AND METHODS

Annually, attending physicians register patients diagnosed with pancreatic neoplasms. The questionnaire used in this study included patient history of the illness, family history, clinical symptoms and laboratory findings, extent of the disease conclusively defined by image diagnosis, surgical and pathologic findings, and pre-, intra-, and postoperative anticancer treatments. Each factor of the tumor extent was recorded as a conclusive finding from physical examination, imaging, surgical exploration, and pathologic findings. Physicians were requested to follow the patient's survival and type of recurrence annually. Registered data were entered to a database, and inappropriate cases and duplicate registrations were excluded. FilemakerPro software was used for the database and SPSS software was used for the statistical analysis. The cumulative survival rate was calculated using actuarial method and was tested by Wilcoxon-Gehan method. Any P value <0.05 was considered to be statistically significant.

JPS Classification Version 5

All data were described and analyzed according to the latest versions of JPS[6,7] and UICC[8] classifications. Both JPS and UICC independently changed their classifications in 2002. That same year, the American Joint Committee on Cancer (AJCC) revised cancer staging for exocrine pancreas, which was identical to that of the UICC classification.[9] The new JPS edition is based on data from the National Pancreatic Cancer Registry[2–4] and treatment results at individual hospitals. Additionally, to reduce human-based error in the process of registration and analysis, we developed a computerized JPS registration system based on the latest versions of classification. The application automatically calculates various factors with a simple click of buttons and checkboxes. Both Japanese and English applications can be downloaded from the JPS website (http://www.kojin.or.jp/suizou/index.html). The principal points of revision in the JPS system compared with the UICC system follow.

T Category

In the JPS classification system, the T factor is a function of 9 independent factors including tumor size (TS), distal bile duct invasion (CH), duodenal invasion (DU), serosal invasion (S), retropancreatic tissue invasion (RP), portal venous system invasion (PV), arterial system invasion (A), extrapancreatic nerve plexus invasion (PL), and invasion of other organs (OO).

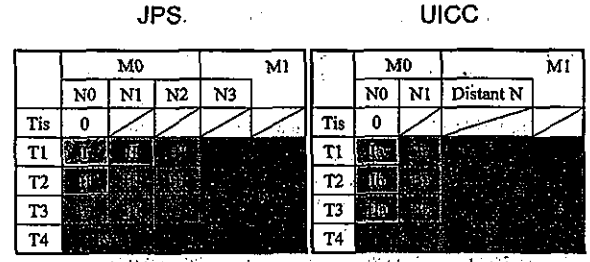

FIGURE 3. Staging system in JPS and UICC classifications Tis, noninvasive tumor. In JPS classification, metastasis to the 3rd group (N3) is equivalent to M1.

TABLE 1. Histologic Classifications of Registered Patients

I. Epithelial tumors	*11819*				
A. Exocrine tumors		11023			
1. Serous cystic tumors			*0*		
a. Serous cystadenoma				0	
b. Serous cystadenocarcinoma				0	
2. Mucinous cystic tumors			*328*		
a. Mucinous cystadenoma				0	
b. Mucinous cystadenocarcinoma				328	
3. Intraductal tumors			*229*		
a. Intraductal papillary mucinous tumors				229	
i. Intraductal papillary mucinous adenoma					*229*
With mucin hypersecretion				0	
Without mucin hypersecretion					*0*
ii. Intraductal papillary mucinous adenocarcinoma					
With mucin hypersecretion					*0*
Without mucin hypersecretion					*0*
b. Intraductal tubular tumor				0	
i. Intraductal tubular adenoma					*0*
ii. Intraductal tubular carcinoma					*0*
4. Atypical hyperplasia and carcinoma in situ			*16*		
5. Invasive ductal carcinomas			*10336*		
a. Papillary adenocarcinoma				1029	
b. Tubular adenocarcinoma				8765	
Well-differentiated type					*2148*
Moderately differentiated type					*3724*
Poorly differentiated type					*1142*
No information of differentiation					*1751*
c. Adenosquamous carcinoma				247	
d. Mucinous carcinoma				148	
e. Anaplastic carcinoma				19	
f. Invasive mucinous cystadenocarcinoma				56	
g. Invasive carcinoma originating in an intraductal tumor				72	
6. Acinar cell tumors			*87*		
a. Acinar cell adenoma				0	
b. Acinar cell adenocarcinoma				87	
B. Endocrine tumors		307			
C. Combined tumors		8			
D. Epithelial tumor with uncertain differentiation		111			
1. Solid pseudopapillary tumor				0	
2. Pancreatoblastoma				0	
3. Undifferentiated carcinoma				111	
E. Unclassifiable		44			
F. Miscellaneous		353			
II. Nonepithelial tumor	*0*				
Angioma			0		
Lymphangioma			0		
Leiomyosarcoma			0		
Malignant histiocytoma			0		
Malignant lymphoma			0		
Paraganglioma			0		
Other			0		
III. No histologic diagnosis	*11483*				

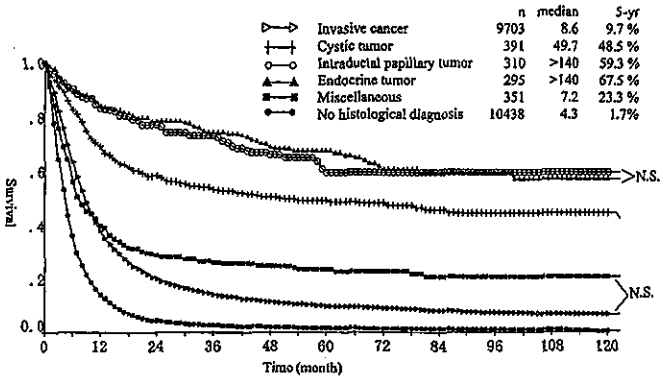

FIGURE 4. Histology and overall survival. Cumulative survival of all patients with or without pancreatectomy was calculated by actuarial method and tested by Wilcoxon-Gehan method. Any *P* value <0.05 is regarded as statistically significant. N.S., not significant.

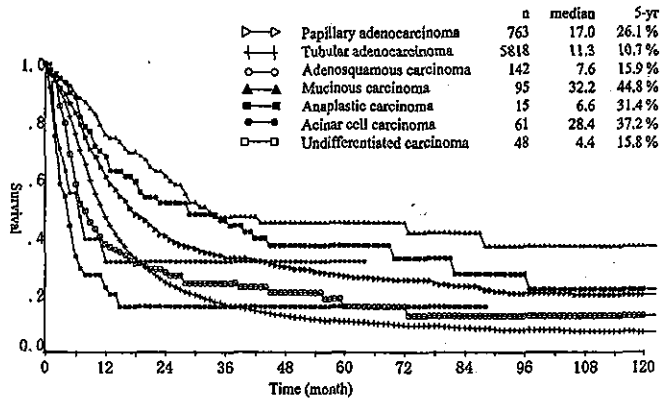

FIGURE 6. Subtype of invasive cancer and survival after pancreatectomy. Tubular adenocarcinoma includes well-, moderately, and poorly differentiated tubular adenocarcinoma together with tubular adenocarcinoma without description of differentiation, as indicated in Figure 7.

These factors are recorded as present (yes) or absent (no), except for tumor diameter size, recorded as TS1 (≤2 cm), TS2 (2.1–4.0 cm), TS3 (4.1–6.0 cm), and TS4 (>6.0 cm). Registration until year 2000 was collected using the old JPS classification system, when the 4-grade assessment (0, none; 1, suspected; 2, definite; 3, marked or adjacent organ invasion) was converted to 2 grades (grade 0 to no, other grades to yes). UICC defines a tumor that invades the celiac or superior mesenteric artery (SMA) as T4 regardless of portal vein, peripancreatic plexus, or organ invasion, while JPS regards them as T4, independently of celiac or SMA invasion.

N Category

The JPS grouping of lymph nodes has been extensively revised. Lymph nodes removed in a conventional resection are now categorized as group 1, and the other lymph nodes are categorized into groups 2 and 3, depending on lymph flow, lymph node metastasis rate, and outcome (Fig. 2). UICC regards metastasis to the regional lymph nodes as N1 regardless of the distance from the primary site. If the group 3 nodes are metastasized, it is considered to be equivalent to distant metastasis. Lymph node dissection is defined as D factor as follows: D0, no dissection or incomplete dissection of group 1 lymph nodes; D1, dissection of group 1 lymph nodes alone; D2, dissection of group 1 and 2 lymph nodes; and D3, dissection of group 1, 2, and 3 lymph nodes. The computerized JPS registration system automatically calculates the N and D factors according to each nodal status to avoid human error and subjective definition by surgeons.

M Category

Under the old classification system, distant metastasis (M1) was assessed as lymph node metastasis beyond group 3

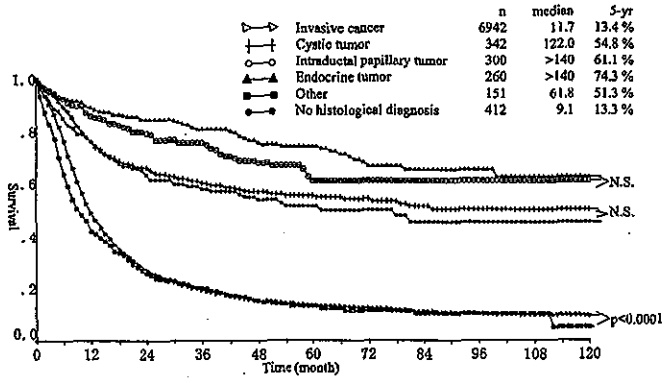

FIGURE 5. Histology and survival after pancreatectomy. Survival of the patients who underwent pancreatectomy is shown. N.S., not significant.

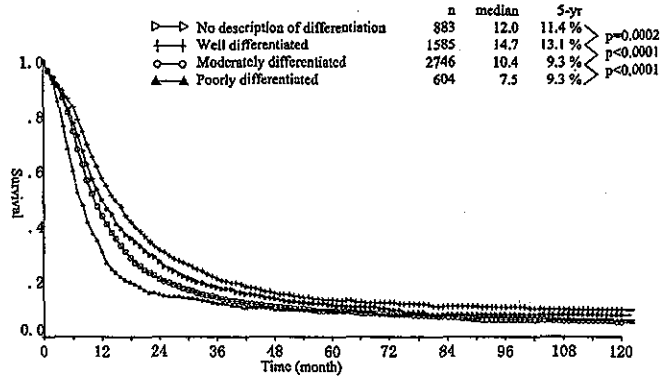

FIGURE 7. Differentiation of the tubular adenocarcinoma and survival after pancreatectomy.

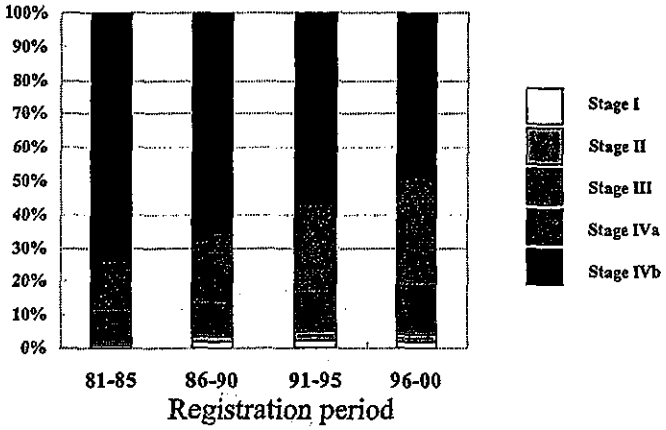

FIGURE 8. Trends of JPS stage of invasive cancer at the time of diagnosis. The stage proportion of the patients with invasive cancer is indicated according to the period of registration.

(N3), whereas in the new classification, M1 includes N3 metastasis.

Stage

Stage classifications are quite different in both systems. JPS regards the T and N factors as equivalent, while UICC regards T factors of greater prognostic value than N factors, as shown in Figure 3.

The Radicality

JPS defines the surgical margin as pancreatic cut-end margin (PCM), bile duct cut-end margin (BCM), and dissected peripancreatic tissue margin (DPM). DPM includes every surgical margin other than PCM and BCM, ie, anterior pancreatic and retropancreatic, especially along with the vessels. On the other hand, the surgical definition of the retroperitoneal (not the retropancreatic) margin in the AJCC classification is the soft tissue margin directly adjacent to the proximal 3–4 cm of the right lateral border of SMA.[9] The radicality in JPS classification system has been changed to R0, R1, and R2 similar to the UICC classification of curability A, B, and C in the old version.

RESULTS

Histologic Classification

The histologic classification of registered patients is shown in Table 1. Tumors arising from the exocrine pancreas consist of serous and mucinous cystic tumors, intraductal tumors, carcinoma in situ, invasive ductal carcinomas, and acinar cell tumors. Of 10,336 patients with invasive carcinomas, 56 patients with invasive mucinous cystadenocarcinoma and 72 patients with invasive carcinoma originating in an intraductal tumor were excluded from the analysis for invasive cancer. Instead, 87 cases of acinar cell adenocarcinoma and 111 cases of undifferentiated carcinoma were included in the analysis. Therefore, the term "invasive cancer" herein refers to most of the invasive ductal carcinomas, acinar cell tumors, and undifferentiated carcinomas, usually recognized as common phenotypes of pancreatic cancer. The excluded 2 subtypes of invasive ductal carcinomas were included in each category from which the tumors were derived. There had been no reg-

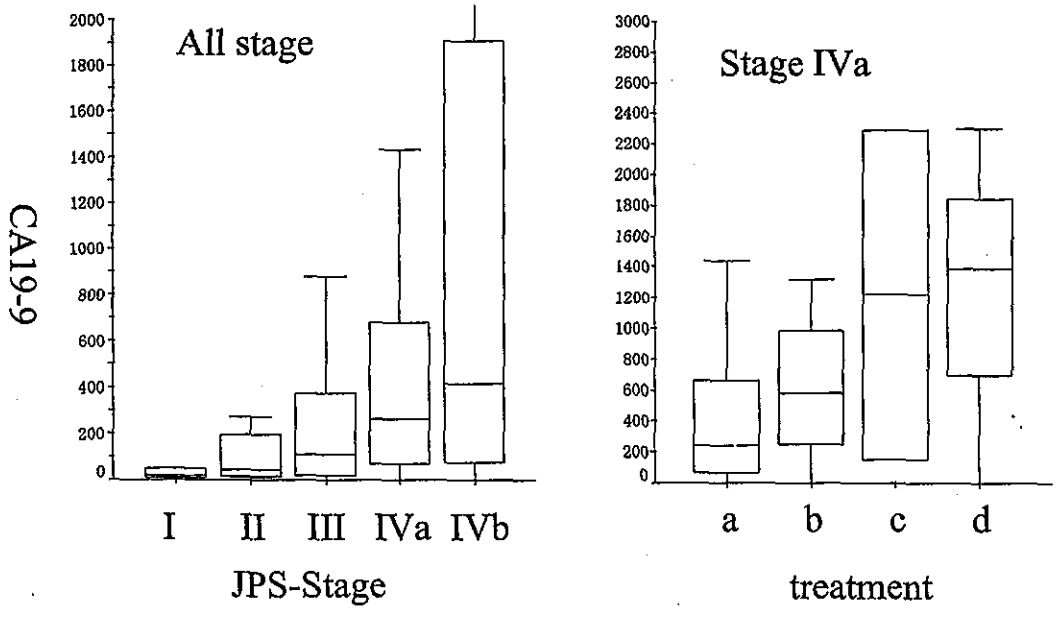

FIGURE 9. CA19-9 and the JPS stage (from cases in 2001 and 2002). The real values of CA19-9 were collected since 2001. Left: JPS stage and CA19-9. Right: Treatment of the patients with stage IVa disease and CA19-9. a, Pancreatectomy; b, palliative operation; c, exploratory laparotomy including intraoperative radiation therapy; d, no surgical procedure.

istration of nonepithelial tumors until 2002. These rare tumors may be collected by the new JPS registration system in the future. It should be noted that half of the patients were registered without histologic confirmation. These patients were excluded from the analysis even though the prognosis was very poor, as is mentioned later.

Histology and Survival

The prognosis for invasive cancer is very poor, with an overall median survival time (MST) of 8.6 months and a 5-year survival rate of 9.7% (Fig. 4). The survival rate of patients with endocrine tumors and intraductal papillary tumors is favorable, with an MST of >10 years and a 5-year survival rate of >50%. The survival rate of patients with cystic tumors is less favorable since this population includes invasive mucinous cystadenocarcinoma. The survival rate of patients without histologic diagnosis is extremely poor, with an MST of 4.3 months and a 5-year survival rate of only 1.7%. The survival rate after pancreatectomy for each histologic type is shown in Figure 5. Of 9703 patients with invasive cancer, 6942 patients (71.5%) underwent pancreatectomy, while of 10,438 patients without histologic diagnosis, 412 patients (3.9%) underwent pancreatectomy. The survival curve of the patients lacking histologic information fits that of patients with invasive cancer, though the difference in MST is statistically significant. Survival after pancreatectomy according to the subtypes of invasive cancer is shown in Figure 6. The most frequent type is tubular adenocarcinoma for which the curve is very similar to that of all invasive cancers. Survival of patients with papillary adenocarcinoma (MST, 17.0 months; 5-year survival rate, 26.1%), mucinous carcinoma (MST, 32.2 months; 5-year survival rate, 44.8%), and acinar cell carcinoma (MST, 28.4%; 5-year survival rate, 37.2%) is significantly better than that of patients with tubular adenocarcinoma (MST, 11.3 months; 5-year survival rate, 10.7%). Survival of the patients with adenosquamous carcinoma, anaplastic carcinoma, and undifferentiated carcinoma is extremely poor, with an MST of 7.6, 6.6, and 4.4 months, respectively. Figure 7 shows survival after pancreatectomy according to the differentiation of tubular adenocarcinoma. The difference of MST between well- and moderately differentiated types is 4.3 months, while the difference between moderately and poorly differentiated types is 2.9 months. If a Japanese pathologist diagnosed a tumor as tubular adenocarcinoma without any description of differentiation, the prognosis of these patients may fall somewhere between the well- and moderately differentiated types.

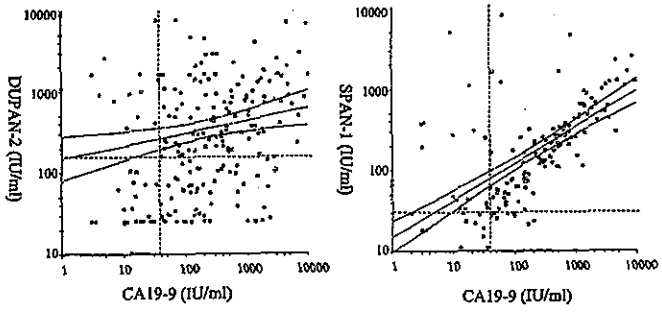

FIGURE 10. Correlation of DUPAN-2 and SPAN-1 with CA19-9 (from cases in 2001 and 2002). The real values of CA19-9 were plotted against DUPAN-2 and SPAN-1. Pearson's correlation coefficient is 0.009 for DUPAN2 (not significant) and 0.714 for SPAN-1 ($P < 0.0001$).

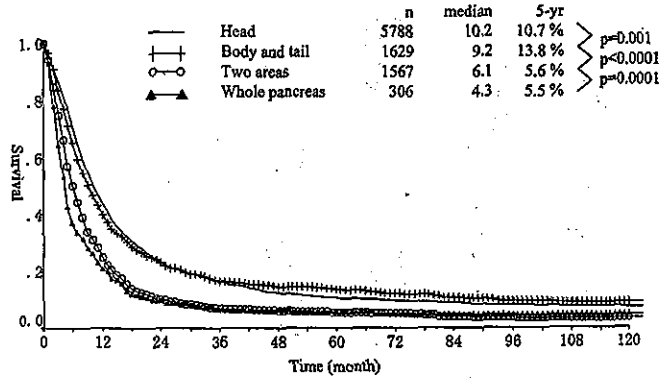

FIGURE 11. Locus of invasive carcinoma and survival. Survival according to the tumor locus is shown. Two areas: the tumor occupies the head and body or body and tail.

Diagnosis of Invasive Cancer

The most frequent reason that patients with invasive cancer visit their physicians is because of the symptoms (83.2%), while 9.7% of such patients went only for health checkups.

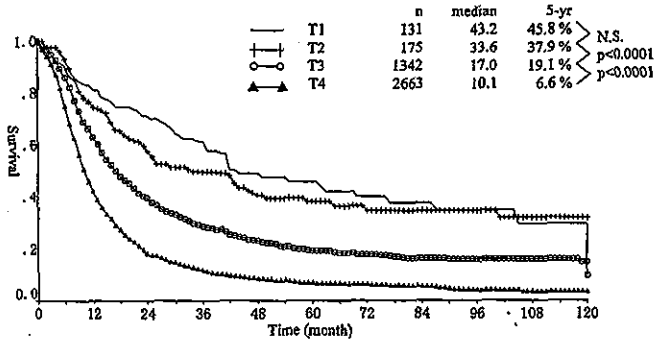

FIGURE 12. JPS T factor of invasive cancer in the head of the pancreas and survival after pancreatectomy. T1, tumor limited to the pancreas; ≤2 cm in greatest dimension; T2, tumor limited to the pancreas, >2 cm in greatest dimension; T3, tumor that has extended into any of the following: bile duct (CH), duodenum (DU), peripancreatic tissue (S, RP); T4, tumor that has extended into any of the following: adjacent large vessels (PV, A), extrapancreatic nerve plexus (PL), other organs (OO). N.S., not significant.

Only 1.7% of these patients were diagnosed because of worsening diabetes mellitus. The initial symptoms of patients with invasive cancer are abdominal pain (32.0%) and jaundice (18.1%). If the patient has a tumor in the head of the pancreas, the rate of jaundice increases to 26.3% and there is abdominal pain as well. The enthusiastic screening and progress of the imaging modalities enabled Japanese physicians to find the disease in the early stage, as shown in Figure 8. Since most of the patients are JPS stage III or more, the innovation of early diagnosis is eagerly awaited.

Using the latest data from 949 patients with invasive cancer registered in 2001 and 2002, the clinical significance of tumor markers was assessed. The correlation of CA19-9 with JPS stage and the treatment categories in stage IVa disease are shown in Figure 9. Even though there are exceptional cases, the median CA19-9 value correlates well with the JPS stage. In JPS stage IVa disease, the median CA19-9 value is 262.1 IU/mL and 412.8 IU/mL in stage IVb disease. The median CA19-9 value was significantly lower in patients who underwent pancreatectomy than in the other treatment categories. The value of CEA did not differ significantly between the stages, though there is an increasing tendency (data not shown). DUPAN-2 epitope is a syalylated mucin oligosaccharide but is distinct from Lewis antigen. So, DUPAN-2 may reflect the tumor volume in Lewis antigen–negative patients.[10] SPAN-1 is known to improve sensitivity if combined with CA19-9.[11,12] Median DUPAN-2 and SPAN-1 values were not different in the pancreatectomy group and palliative operation group. The correlation between DUPAN-2 and SPAN-1 with CA19-9 is shown in Figure 10, where the DUPAN-2 can detect the Lewis antigen–negative tumor, and SPAN-1 correlates well with CA19-9, with some exceptions. The relationship of survival and the tumor marker value will be reported shortly.

Staging of Invasive Cancer

If the tumor is localized in the head or body/tail, the MST of the patients is 10.2 and 9.2 months and the 5-year survival rate is 10.7% and 13.8%, respectively (Fig. 11). If the tumor is

TABLE 2. Lymph Node Metastases in the Resected Cases of Invasive Cancer of the Pancreatic Head

	Group	No Metastasis	Metastasis	Unknown	Metastatic Rate (%)	Total
Right cardial	3	2962	12	1936	0.2	
Left cardial	3	2760	8	2142	0.2	
Lesser curvature of the stomach	3	3748	48	1114	1.0	
Greater curvature of the stomach	3	3871	57	982	1.2	
Suprapyloric	3	3901	72	937	1.5	
Inflapyloric	2	3869	298	743	6.1	
Left gastric	3	3627	70	1213	1.4	
Anterosuperior common hepatic	2	3695	523	692	10.7	
Posterior common hepatic	2	3030	205	1675	4.2	
Celiac	3	3567	130	1213	2.6	
Splenic hilum	3	2736	23	2151	0.5	
Proximal splenic	3	3229	121	1560	2.5	
Distal splenic	3	4910	0	0	0.0	4913
Proper hepatic	2	3887	180	843	3.7	
Portal venous	2	3808	257	845	5.2	
Bile duct	2	3784	484	642	9.9	
Superior posterior pancreatic head	1	2830	1490	590	30.3	
Inferior posterior pancreatic head	1	3085	1098	727	22.4	
Proximal superior mesenteric	2	3432	526	952	10.7	
Distal superior mesenteric	2	3348	656	906	13.4	
Middle colic	3	3267	97	1546	2.0	
Abdominal aortic a2	3	3144	318	1448	6.5	
Abdominal aortic b1	3	1489	183	3238	3.7	
Superior anterior pancreatic head	1	3282	764	864	15.6	
Inferior anterior pancreatic head	1	3342	760	808	15.5	
Inferior margin of pancreas	3	3182	84	1	1.7	

The names of the lymph nodes are simplified from the original names in reference 2.

TABLE 3. Combination of Two Nodes in 743 Patients Who Harbored Only Two Nodal Metastases from Invasive Cancer in the Head

	1	2	3	4	5	6	7	8A	8P	9	10	11P	11D	12A	12P	12B	13A	13B	14P	14D	15	16A2	16B1	17A	17B	18
1	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
2		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3			7	0	0	0	1	0	0	0	1	0	0	1	0	1	1	0	1	0	1	0	0	0	0	0
4				5	0	1	0	1	0	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0
5					3	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
6						38	1	2	0	0	0	0	0	0	1	2	9	0	4	2	0	0	0	11	3	1
7							13	1	1	1	0	0	0	1	0	3	1	1	0	2	0	0	1	0	0	0
8A								76	5	4	0	1	0	4	4	1	15	6	6	4	1	6	2	5	7	0
8P									38	1	0	1	0	1	0	2	3	4	3	1	0	1	0	2	3	0
9										14	0	1	0	0	0	1	2	1	0	0	0	0	0	0	3	0
10											2	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0
11P												47	0	2	0	0	5	2	2	1	0	0	0	0	0	0
11D													0	0	0	0	0	0	0	0	0	0	0	0	0	0
12A														22	0	1	5	3	2	0	1	0	1	0	1	0
12P															21	4	4	0	0	1	0	1	0	4	1	0
12B																32	16	11	5	7	1	2	0	12	11	1
13A																	321	138	15	22	0	9	5	47	23	0
13B																		249	6	17	4	6	5	15	24	1
14P																			30	19	0	5	4	4	3	1
14D																				102	2	3	2	7	11	0
15																					12	1	0	1	1	0
16A2																						45	4	4	1	0
16B1																							34	3	6	0
17A																								162	45	1
17B																									148	0
18																										3

Example: Out of 321 cases with 13A involvement, 138 cases (43.0%) had 13B involvement and 47 cases (14.8%) had 17A involvement.

located in more than 2 areas, the prognosis of the patient is extremely poor.

T Factor

In 6084 patients with invasive cancer in the head of the pancreas, 638 were TS1 (10.6), 2929 were TS2 (48.1%), 1519 were TS3 (25.0%), and 652 were TS4 (10.7%). The positive rate of each factor is as follows: CH, 72.1%; DU, 47.7%; S, 49.5%; RP, 47.6%; PV, 50.8%; A, 24.8%; PL, 17.9%; OO, 16.9%, respectively. As a result, the T factors in this population are as follows: T1, 1407 cases (2.3%); T2, 209 cases (3.4%); T3, 1407 cases (23.1%); T4, 3658 cases (60.1%); and TX, 669 cases (11.0%). Survival according to the T factor after pancreatectomy for invasive cancer in the head of the pancreas is shown in Figure 12. Although the tumor size of T1 is <2 cm, the difference in MST and the 5-year survival rate between T1 and T2 was not statistically significant.

N Factor

The nodal involvement in the patients with invasive cancer in the head of the pancreas is shown in Table 2. The most frequent site is 13a and 13b (posterior pancreatic head), followed by 17a, 17b (anterior pancreatic head), 14d, 14p (superior mesenteric), 12b, 12p (hepatoduodenal ligament), and 6 (infrapyloric) nodes. In patients who had single-node metastasis, the frequencies of 13a and 13b are markedly higher, 32.3%

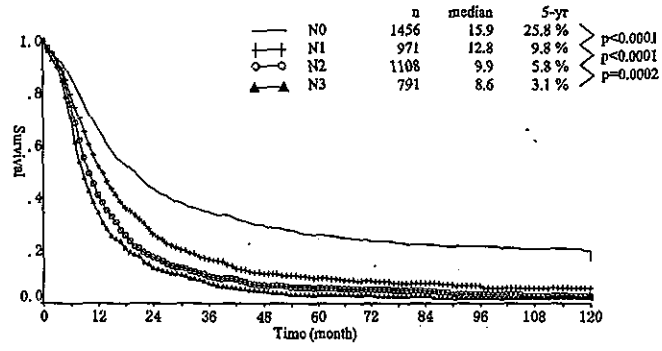

FIGURE 13. JPS N factor of invasive cancer and survival after pancreatectomy. Lymph node grouping is shown in Figure 2.

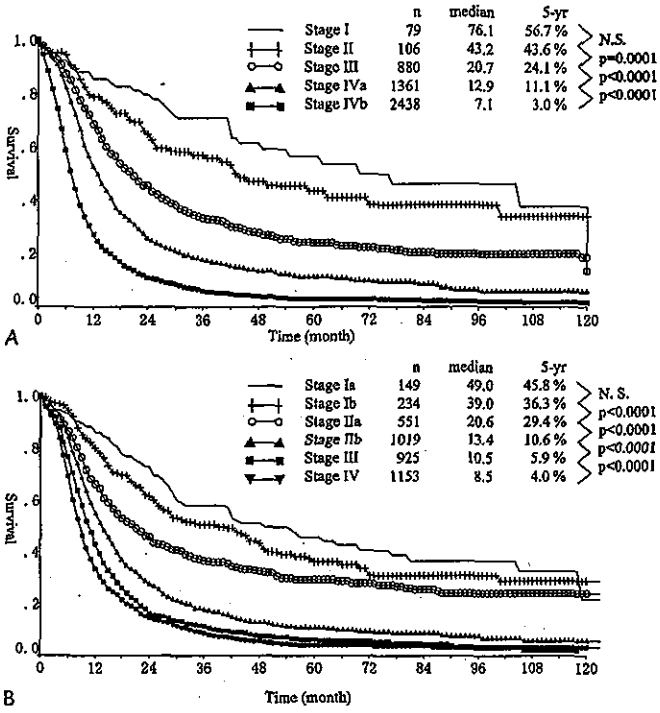

FIGURE 14. (A) JPS stage of invasive cancer and survival after pancreatectomy. (B) UICC stage and survival after pancreatectomy for invasive cancer. Definition of stages in each classification system is shown in Figure 3. N.S., not significant.

and 14.2%, respectively (data not shown). On the other hand, <2% of the patients had single-node metastasis to the paraaortic lymph nodes (16a2 or 16b1). Table 3 shows the combination of the 2 nodes in patients who had only 2-node involvement from the invasive cancer in the pancreas head. Together with the combination pattern in patients with multiple node metastases (data not shown[4]), it may be postulated that 13a and 13b can be sentinel lymph nodes of the lesion in the pancreas head.[13] Survival according to the N factor after pancreatectomy for invasive cancer in the pancreas head is shown in Figure 13. The differences between each N factor are statistically significant, suggesting that dividing the lymph nodes by the distance from the primary lesion is meaningful.

M Factor

Since Japanese surgeons aggressively dissect paraaortic lymph nodes, there are a number of patients who underwent pancreatectomy who were found (histologically or molecularly) to be metastatic to that area. The MST of patients with distant metastasis after pancreatectomy is 8.5 months, while that of the patients with unresected disease is 3.7 months (data not shown[4]).

Comparison of JPS and UICC Staging

In UICC classification, the T category reflects the distinction between potentially resectable (T3) and locally advanced (T4) primary pancreatic tumors, and the stage grouping has been changed to allow stage III to signify unresectable, locally advanced pancreatic cancer, while stage IV is reserved for patients with metastatic disease.[9] There is no definition of plexus invasion, which assigns the tumor to JPS T4 as well as SMA invasion, while it could be either T3 or T4 in the UICC classification. The survival curves of the same patients evaluated in both staging are shown in Figure 14. The JPS classification distinguishes each stage better than does the UICC classification. The 5-year survival rates in JPS stages I and III are 56.7% and 24.1%, respectively, while those of UICC stages Ia and III are 45.8% and 5.9%, respectively. The difference between UICC stage IIa and UICC stage IIb seems to be greater than the difference between IIb and III, thus making UICC stage IIb a very miserable stage. As shown in Table 4, there was no JPS stage III patient falling into the UICC stage III, while UICC stage IIb included patients with JPS stage II–IVb disease.

TABLE 4. JPS Stage and UICC Stage in Patients with Invasive Cancer in the Head of the Pancreas

	UICC							
	IA	**IB**	**IIA**	**IIB**	**III**	**IV**	**Unknown**	**Total**
JPS								
I	58	0	0	0	0	0	0	58
II	0	51	0	14	0	0	0	65
III	61	110	224	321	0	0	3	719
IVA	0	0	224	385	457	0	117	1183
IVB	0	0	0	183	284	991	64	1522
Unknown	0	0	1	1	82	0	348	432
	119	161	449	904	823	991	532	3979

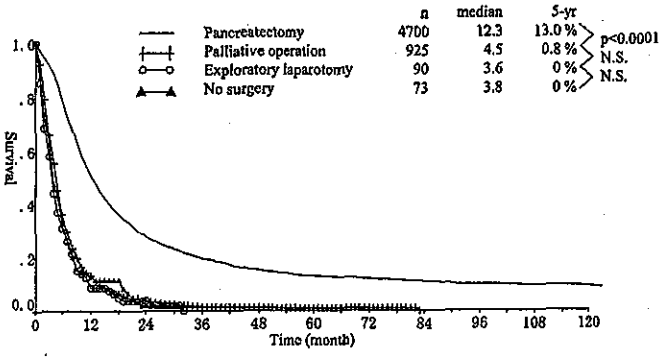

FIGURE 15. Treatment of invasive carcinoma of the head and survival. N.S., not significant.

Treatment of Invasive Cancer

Surgical Resection

Japanese surgeons have challenged the resection of advanced pancreatic cancer and proved that surgery can be performed safely.[14] Many aggressive surgeons performed extended radical surgeries for various stages of pancreatic cancer, and this registry collected the resulting nationwide survival data. As shown in Figure 15, surgical resection offers the only chance of long-term survival. A number of Japanese investigators have examined pathologic factors of the resected tumor in an effort to establish reliable prognostic variables associated with decreased survival.

Vessels and Plexus Resection

Figure 16 shows the 20-year trends of the vessels and the plexus resection combined with pancreaticoduodenectomy for invasive cancer in the head of the pancreas in Japan. Portal vein resection (PVR) was performed in 17.6% cases in 1981, which increased to 33.6% in 2000. On the other hand, resection of the arteries was performed in 3.0% of all patients, which increased to 5.0% in the early 1990s. Recently, only 1.5%–2.5% of patients underwent arterial resection. Resection of the peripancreatic plexus was performed in 38.3% of patients registered after 1993, when this parameter was first recorded. These trends suggest that surgeons do not go further if the tumor involves the arterial wall and that they frequently resect the plexus to make the surgical margin negative. Survival in patients with invasive cancer in the head of the pancreas is summarized in Table 5. PVR was performed in 91 patients who were finally defined as being without portal vein invasion. The MST of these 91 patients was 13.0 months and the 5-year survival was 8.3%, while the MST of the 1656 patients without PVR was 15.9 months and the 5-year survival rate was 19.2%. PVR did not affect positively or negatively the survival of the patients without portal vein invasion. In the patients with portal vein invasion, PVR was performed in 1219 patients whose MST was 10.2 months and 5-year survival rate was 7.4%. PVR was not performed in 761 patients who underwent pancreaticoduodenectomy though they had portal vein invasion. The difference in survival in each group was not statistically significant. Similarly, resection of the arterial system and peripancreatic plexus did not increase or decrease the improvement of MST or 5-year survival, even though the resection procedure was performed on patients without the specific organ invasion.

Lymph Node Dissection

Due to the modification in lymph node grouping, most patients with invasive cancer underwent pancreatectomy with lymph node dissection of group 3. Survival in patients who underwent each extent of dissection did not differ significantly as shown in Table 6. This fact was confirmed with a stricter algorithm to calculate the D factor in which all the lymph nodes in the group should be removed (data not shown).

Radicality

One prognostic factor of greatest significance in patients who undergo pancreaticoduodenectomy is considered to be incomplete resection.[9] Incomplete resection resulting in a grossly positive retroperitoneal margin is thought to be of no survival advantage compared with those patients who receive chemoradiation and no surgery.[9] The radicality and survival of patients with UICC stage III disease (locally advanced with arterial invasion) in the head of the pancreas are shown in Figure 17. Performing R0 surgery for the disease at this stage is controversial, because correct intraoperative judgment of the disease extent is difficult, even in experienced hands. The survival rate of patients who underwent R0 surgery was signifi-

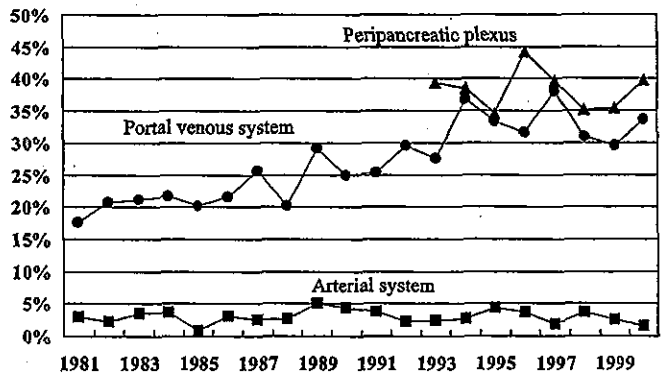

FIGURE 16. Trends of resected vessels and plexus with pancreaticoduodenectomy. Proportion of the patients with the target organ resection combined with pancreaticoduodenectomy is plotted against the registered year. The proportion includes any resection of arterial system: celiac artery, common hepatic artery, superior mesenteric artery, and splenic artery; the portal venous system: superior mesenteric vein, portal vein and splenic vein; extrapancreatic plexus: pancreatic head plexus I and II, superior mesenteric arterial plexus, plexus within the hepatoduodenal ligament, celiac plexus, common hepatic arterial plexus, and splenic plexus.

TABLE 5. Survival and the Combined Resection for Invasive Cancer in the Head of the Pancreas

		No Combined Resection			Combined Resection			
Organ	Invasion	n	MST	5-Year Survival (%)	n	MST	5-Year Survival (%)	Wilcoxon Test (A vs. B)
Portal venous system	No	1656	15.9	19.2	91	13.0	8.3	N.S.
	Yes	761	9.7	5.9	1219	10.2	7.4	N.S.
Arterial system	No	2817	13.4	14.9	37	10.3	0.0	N.S.
	Yes	636	8.6	3.8	107	8.1	3.4	N.S.
Peripancreatic plexus	No	803	15.5	18.3	571	16.8	16.9	N.S.
	Yes	264	9.1	3.5	261	9.8	7.4	N.S.

N.S., not significant.

cantly better than that of the patients who underwent R1 or R2 surgery. R1 resection did not give the same superior result as the R2 resection. However, the survival rate of patients with UICC stage III disease who underwent pancreatectomy with grossly residual tumor was significantly better than that of patients at the same stage whose tumors were not resected. Taken together, there may be a possible role of mass-reduction surgery for certain patients with locally advanced tumors.

Chemotherapy and Radiation Therapy

Postoperative chemotherapy in patients who underwent pancreatectomy for JPS stages I and II disease did not positively affect survival (data not shown[4]). In patients who underwent pancreatectomy for JPS stage III or advanced disease, postoperative chemotherapy (no specified protocol, retrospective yes or no) had a significant positive effect on survival. MST in patients who underwent pancreatectomy for JPS stages III, IVa, and IVb disease was increased by 5.4, 3.1, and 2.3 months, respectively. Currently, the Ministry of Health, Labor, and Welfare of Japan is hosting a randomized, controlled trial to examine the effectiveness of adjuvant postoperative administration of gemcitabine for patients who underwent pancreatectomy.

Patients who did not undergo pancreatectomy because of stage IV disease were subdivided into 4 categories, as shown in Table 7. Postoperative chemotherapy and radiation therapy for patients with distant lymph node metastasis but without liver metastasis or peritoneal dissemination, positively affected MST, adding 3 and 2 months, respectively. Again, these results are retrospectively archived and with no specific protocol. Conventional treatments for unresectable disease, however, are not satisfactory at all.

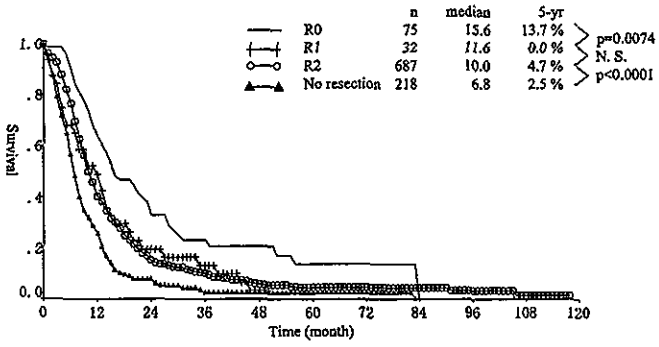

FIGURE 17. Declared radicality and survival of patients with UICC stage III invasive cancer in the head of the pancreas. R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor. N.S., not significant.

SUMMARY

In the past 20 years, Japanese physicians and surgeons have been aggressively fighting this tough disease. Thanks to improvements in perioperative management, the mortality and morbidity of pancreatectomy have been greatly reduced, even though the portal vein, peripancreatic plexus, artery, and/or retroperitoneal connective tissue was resected. However, the biology of pancreatic cancer, not the extent of resection, has been the key to defining survival so far. Improvement of im-

TABLE 6. Radicality of Lymph Node Dissection and Survival After Pancreatectomy in Patients with Invasive Cancer in the Head of the Pancreas

Dissection	n	MST	5-Year Survival Rate (%)	Wilcoxon Test
D0	106	14.4	15.6	
D1	49	12.4	19.1	N.S.
D2	231	13.8	19.7	N.S.
D3	3783	12.4	12.8	N.S.

No significant difference between D0 and D2, and D0 and D3.

TABLE 7. Chemotherapy and Radiation Therapy for Patients with Unresected Stage IV Disease

	Preoperative				Intraoperative				Postoperative			
	Chemotherapy		Radiation		Chemotherapy		Radiation		Chemotherapy		Radiation	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Stage IVa	30	1	30	1	28	3	25	6	13	17	27	2
Stage IVb												
Without M	50	4	52	3	51	5	48	7	23	33	44	11
LYM alone	159	23	175	3	139	34	139	34	71	102	149	20
		−2						**+2**		**+3**		**+2**
HEP or PER	1213	148	1317	39	1054	309	1133	219	661	691	1250	90
								+1		**+1**		**+1**

Number of patients (the bold number under each value indicates the statistically significant difference of MST (months) compared with the respective control). M, distant metastasis; LYM, distant lymph node involvement; HEP, liver metastasis; PER, peritoneal dissemination.

aging modalities has enabled us to detect smaller cancers, but these modalities were not sufficient enough to detect small metastasis to the liver or peritoneal dissemination, which is often found at the time of laparotomy. Histologic diagnosis is not easy, even in the operative cases. These factors make it difficult to expect a realistic prognosis and to define management of these patients. Apparently, management of this disease can be greatly improved. Surgery will still be at the center of management tactics, and conventional chemotherapy and radiation therapy will be employed in both resected and unresected cases. Chemotherapy and radiation therapy protocols are going to be refined in adjuvant or neoadjuvant settings on a randomized, prospective trial basis. Unconventional modalities, such as immunotherapy, gene therapy, and antiangiogenesis therapy, with or without conventional therapies, should be developed.[3] It is critically important to compare the results in a standardized manner. The computerized JPS registry system (http://www.kojin.or.jp/suizou/index.html in English and Japanese) will help mutual comparison and understanding. We strongly hope that the JPS and UICC systems will be revised similarly in the near future.

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Clinical Significance of Intraportal Endovascular Ultrasonography for the Diagnosis of Extrapancreatic Nerve Plexus Invasion by Pancreatic Carcinoma

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Key Words
Intraportal ultrasonography · Pancreatic cancer · Extrapancreatic nerve plexus invasion · Diagnosis

Abstract

Background/Aims: The extrapancreatic nerve plexus (PL) invasion is a common feature of pancreatic cancer and affects the outcome of the patients after surgical resection. IPEUS with high-resolution probes can visualize the PL invasion with high overall accuracy rate. The aim of this study is to evaluate the clinical significance of the PL invasion diagnosed intraoperatively by intraportal endovascular ultrasonography (IPEUS). ***Methods:*** IPEUS was performed in 64 patients who underwent the pancreatic resection. Several clinicopathological factors were studied in patients with or without PL invasion. ***Results:*** There were 18 cases in which PL invasion was confirmed pathologically. IPEUS showed 94% sensitivity, 98% specificity and 97% accuracy for the diagnosis of the PL invasion with the false-positive rate of 5.6%. The 1-, 2- and 3-year survival in 18 patients with PL invasion was 30, 6 and 0% in comparison to 52, 32 and 18% in those 46 patients without PL invasion and the difference was statistically significant ($p = 0.008$). A significant correlation was found between PL invasion and the portal vein invasion, invasion of the margins or pTNM stage. ***Conclusions:*** According to current results, the prognosis of the cases with PL invasion is very poor and indication for resection is doubtful. We conclude that the cases in which PL invasion is diagnosed by IPEUS are not indicated for extended resection and correct diagnosis of PL invasion is important not only to predict the outcome but also to decide the surgical procedure for obtaining negative margins while improving the quality of life after surgery.

Introduction

Pancreatic cancer is deadly and is an increasing public health problem in many countries. In the United States, it causes more than 26,000 deaths every year and has the lowest 5-year survival rate of any cancer [1]. Operative resection provides the only chance for cure or long-term survival if the tumor is localized and resectable at the time of diagnosis. There are many factors such as advanced stage and positive resection margins shown to be responsible for the dismal survival of the patients with pancreatic carcinoma [2, 3]. The extrapancreatic nerve plexus (PL) invasion is a common feature of pancreatic cancer and affects the outcome of patients after surgical resection [3, 4]. Several studies have demonstrated that tumor involve-

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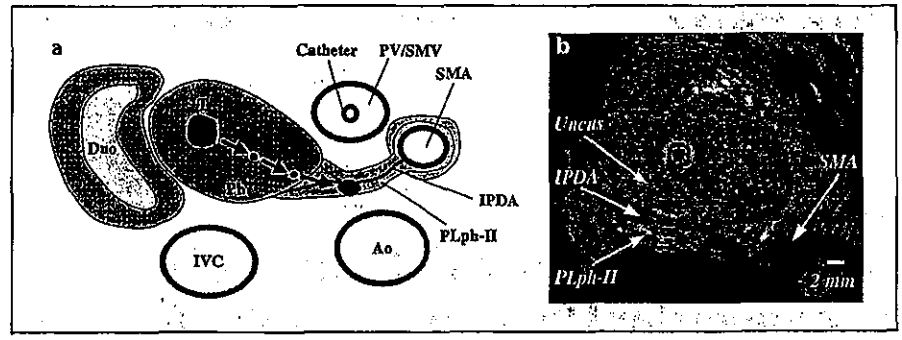

Fig. 1. a Schematic drawing of the second portion of the extrapancreatic nerve plexus (PLph-II) shows the anatomical relationship between the pancreatic head (Ph) and the portal vein/superior mesenteric vein (PV/SMV), the superior mesenteric artery (SMA) and the inferior pancreaticoduodenal artery (IPDA). During the IPEUS, the IVUS catheter tip is positioned at the most close part anatomically possible (PV/SMV) to visualize the PLph-II. Arrows indicate the intrapancreatic nerve invasion as a route for the PL invasion. T = Tumor; Duo = duodenum; Ao = aorta; IVC = inferior vena cava. **b** IPEUS finding at the level of uncus. IPEUS shows the IPDA, uncus and PLph-II.

ment of the PL around superior mesenteric artery (SMA) makes it impossible to achieve a negative retroperitoneal margin of excision even with radical resections [3–8]. The diagnosis of PL invasion can still be difficult and there has been no method reported for the accurate diagnosis of the PL invasion except IPEUS by our institution [9, 10]. IPEUS with high-resolution probes can visualize the PL invasion with high overall accuracy rate of 93% [10]. In the current study we retrospectively evaluated the clinical significance of the PL invasion diagnosed peroperatively by IPEUS.

Patients and Methods

Sixty-four patients who underwent the pancreatic resection and IPEUS examination during the operation between February, 1992 and November, 2001 in the Department of Surgery II, Nagoya University Hospital were retrospectively evaluated. There was no patient excluded from the study. There were 19 patients who underwent IPEUS without pancreatic resection. The reasons for unresectability were liver metastases which were not detected in preoperative examinations (10 patients), superior mesenteric arterial invasion (5 patients), para-aortic lymph node metastases (2 patients) and peritoneal dissemination (2 patients). These 19 patients were not included in this study because gold standard for the diagnosis of extrapancreatic nerve plexus invasion was pathology of resected specimen. The resection of choice was partial pancreatectomy with dissection of the regional nerve plexus and lymph nodes. All resected specimens were handled according to the 'General Rules for the Study of Pancreatic Cancer' published by Japan Pancreas Society [11]. The resected specimens were cut into slices perpendicular to the portal vein axis, and relationship between the tumor and the portal vein was studied on histologic examination. The following parameters which were assessed according to the 'Classification of Pancreatic Carcinoma' by the Japan Pancreas Society were studied: histology, tumor size, lymph node invasion, resection margins status, intrapancreatic nerve invasion, extrapancreatic nerve plexus invasion and portal vein invasion. Tumor size was determined on the cut surface of the resected specimen which was fixed in formalin. All patients were classified according to pTNM stage defined by the 'TNM Classification of Malignant Tumors' by UICC [12]. Resection margins of the pancreas, distal common bile duct, retropancreatic tissue, portal/superior mesenteric vein and extrapancreatic nerve plexus were marked and examined in detailed microscopically by experienced pathologist (T.N.).

IPEUS was performed with either an 8-Fr, 20-MHz IVUS catheter with a mirror at 45° that reflects the beam perpendicular to the long axis of the catheter (Boston Scientific, Boston, Mass., USA) or an 8-Fr, 20-MHz IVUS catheter with a rotating transducer on the tip (Aloka, Tokyo, Japan) from a branch of the superior mesenteric vein intraoperatively. After laparotomy, a branch of the superior mesenteric vein was exposed and cut down. An 8.5-Fr introducer was inserted into this vein and fixed. The IVUS catheter was then withdrawn for sequential observation of the cross-sectional images perpendicular to the portal vein axis from the intrahepatic to the intrapancreatic portion. Ultrasound images of the area under investigation were recorded on videotape and individual still frames were recorded with Polaroid film. IPEUS images were evaluated at the time of scanning. IPEUS was performed and diagnosed by an IVUS specialized surgeon (T.K.). IPEUS was done after conventional intraoperative intra-abdominal examination. In cases of obvious liver metastasis, IPEUS was not performed. In cases that involved combined resection of the portal vein, the introducer was replaced by an Anthron tube which bypassed the portal vein blood to the right femoral vein while the portal vein was clamped. In cases not requiring portal vein resection, the introducer was removed and the branch of the portal vein was ligated. Informed consent was obtained from all patients in the study.

The pancreatic head nerve plexus exists behind the portal vein and this anatomical relation permits us to visualize the invasion of the pancreatic carcinoma through the portal vein using the intravas-