Surg Today
Jpn J Surg (1999) 29:16–22

SURGERY TODAY

The Prognostic Significance of Lymph Node Metastasis and Intrapancreatic Perineural Invasion in Pancreatic Cancer After Curative Resection

HIDEO OZAKI[1], TAKEHISA HIRAOKA[2], RYUJI MIZUMOTO[3], SEIKI MATSUNO[4], YOSHIRO MATSUMOTO[5], TOSHIMICHI NAKAYAMA[6], TSUKASA TSUNODA[7], TAKASHI SUZUKI[8], MORITO MONDEN[9], YOICHI SAITOH[10], HIDEMI YAMAUCHI[11], and YOSHIRO OGATA[12]

[1] Department of Surgery, National Cancer Center Hospital, 1-1 Tsukiji 5-Chome, Chuo-ku, Tokyo 104, Japan
[2] First Department of Surgery, Kumamoto University School of Medicine, 1-1-1 Honjo, Kumamoto 860, Japan
[3] First Department of Surgery, Mie University Faculty of Medicine, 2-174 Edobashi, Tsu 514, Japan
[4] First Department of Surgery, Tohoku University School of Medicine, 1-1 Seiryo-cho, Aoba-ku, Sendai 980, Japan
[5] First Department of Surgery, Yamanashi Medical University, 1110 Tamaho, Yamanashi 409-38, Japan
[6] Second Department of Surgery, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830, Japan
[7] Second Department of Surgery, Nagasaki University School of Medicine, 7-1 Sakamoto-machi, Nagasaki 852, Japan
[8] Second Department of Surgery, Yamaguchi University School of Medicine, 1144 Kogushi, Nishi-ku, Ube 755, Japan
[9] Second Department of Surgery, Osaka University Medical School, 2-2 Yamadaoka, Suita 565, Japan
[10] First Department of Surgery, Kobe University School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650, Japan
[11] Department of Surgery, Sendai National Hospital, 2-8-8 Miyagino, Miyagino-ku, Sendai 983, Japan
[12] Department of Surgery, Tochigi Cancer Center, 4-9-13 Yonan, Utsunomiya 320, Japan

Abstract: To investigate the prognostic factors of pancreatic cancer, a retrospective analysis of 193 patients who underwent curative resection was conducted. Of the 193 patients, 38 (20%) survived for more than 5 years, the 5-year survival rates for stages I, II, III, and IV disease being 41%, 17%, 11%, and 6%, respectively. According to a multivariate analysis, lymph node metastasis, intrapancreatic perineural invasion, and portal vein invasion were significant prognostic factors. Subsequently, a subgroup analysis concerning nodal metastasis and intrapancreatic perineural invasion was performed in 126 patients with records of these histological findings. In the group of patients without nodal metastasis, the 5-year survival rate for those without perineural invasion was 75%, whereas that for those with perineural invasion was 29%, the difference in survival of these subgroups being significant ($P < 0.02$). In the group of patients with nodal metastasis, the 5-year survival rate for those without perineural invasion was 17%, while that for those with perineural invasion was 10%. The most favorable 5-year survival of 89% was observed in the subgroup of patients with stage I disease without perineural invasion. Thus, pancreatic adenocarcinoma categorized by the combination of these independent types of biological behavior showed 5-year survival rates ranging from very high to low, indicating that these two factors play an important role in the prognosis of this disease.

Key Words: pancreatic adenocarcinoma, pancreatectomy, prognostic factor, lymph node metastasis, perineural invasion

Reprint requests to: H. Ozaki
(Received for publication on July 18, 1997; accepted on May 15, 1998)

Introduction

The outcome of patients who undergo curative resection of pancreatic ductal adenocarcinoma is generally poor unless they have early stage disease. However, some recent studies have reported an improvement in the survival of patients with advanced pancreatic cancer. To investigate the malignancy of this disease, the records of patients who underwent pancreatectomy for pancreatic adenocarcinoma were collected from 12 institutions in Japan, and the preliminary results of survival were reported in 1993 in Japanese.[1] After a 5-year follow-up of all these patients, the prognostic factors in the inherently malignant biology of this disease, especially lymph node metastasis and perineural invasion, were studied, and the results are presented in this paper.

Patients and Methods

The records of patients with pancreatic cancer who underwent pancreatectomy between 1980 and 1989 were collected. After patients with cystadenocarcinoma, mucin-hypersecreting papillary carcinoma in the pancreatic duct,[2] acinar cell carcinoma, islet cell tumors, ampullary carcinoma, and intrapancreatic bile duct carcinoma had been excluded, 357 patients with ductal adenocarcinoma of the pancreas were enrolled. Among these 357 patients, 164 (46%) were excluded from the analysis for the following reasons: 99 (28%) had undergone noncurative resection because of local residual

tumor or histological evidence of cancer cells in the surgical margins; 28 (8%) had had peritoneal, hepatic, pulmonary or renal metastasis; 22 (6%) had died of surgically-related causes within 2 to 68 postoperative days; 11 (3%) had had primary cancer in another site found simultaneously; and 4 (1%) were lost to follow-up or had data missing from their records. The remaining 193 patients who had undergone curative resection with no residual tumor, defined as R0 according to the UICC TNM classification,[3] were included in this analysis. The resected specimens were handled according to the guidelines of the General Rules for Cancer of the Pancreas by the Japan Pancreas Society.[4,5] The pancreas was serially sectioned at 5-mm intervals after formalin fixation, and examined. Tumor size was measured macroscopically on the cut surface. Stage grouping was classified according to the UICC pTNM pathological classification.[3]

In the statistical analysis, deaths from all causes except those related to surgery were included as an event, and all living patients were followed up for over 5 years. Survival rates were calculated by the Kaplan-Meier method,[6] and differences in survival among subsets were compared with the log-rank test. Prognostic factors were examined by a multivariate analysis using Cox's proportional hazards model.[7] Other comparisons were examined by the chi-squared test.

Results

Patient Demographics

The 193 patients comprised 114 men and 79 women, ranging in age from 36 to 81 years, with a mean age of 61.9 years. There were 157 patients with carcinoma of the head of the pancreas, 112 of whom underwent pancreatoduodenectomy and 45 of whom underwent total pancreatectomy. The remaining 36 patients had carcinoma of the body and tail, 34 of whom underwent distal pancreatectomy and 2, total pancreatectomy. The disease was classified as stage I in 54 patients, stage II in 18, stage III in 105, and stage IV in 16 (Table 1). Stage IV was included because of paraaortic nodal metastasis which was "curatively" resected.

Survival

The 5-year survival rate for the 193 patients who underwent curative resection was 20%, with a median survival of 16.2 months, the median follow-up for survivors being 77 months. The patients who underwent curative resection were compared with 99 patients who underwent noncurative resection because of local residual tumor or histological evidence of cancer cells in the surgical margins. The patients who underwent noncurative resection had a 5-year survival rate of 2% and a median survival time of 8.7 months. Thus, survival after curative resection was significantly better ($P < 0.00000001$) (Fig. 1). Among the 193 patients, the 5-year survival rates for patients with stage I, II, III, and IV disease were 41% with a median survival time of 27.6 months, 17% with a median survival time of 14.8 months, 11% with a median survival time of 14.3 months, and 6% with a median survival time of 10.2 months, respectively (Fig. 2). There were 38 patients who survived for more than 5 years, 22 of whom had stage I disease, 3 of whom had stage II disease, 12 of whom had stage III disease, and 1 of whom had stage IV disease. These patients consisted of 17 men and 21 women, ranging in age from 37 to 78 years, with a mean age of 59.2 years. Histologically, there were 3 cases of papillary adenocarcinoma, 10 of well-differentiated adenocarcinoma, 15 of moderately differentiated adenocarcinoma, 2 of poorly differenti-

Table 1. UICC pTNM classification[3] of 193 patients who underwent curative resection

Stage grouping	No. of patients
Stage I (T1, T2, N0, M0)	54
Stage II (T3, N0, M0)	18
Stage III (Any T, N1, M0)	105
Stage IV (Any T, Any N, M1)	16

T1, tumor limited to the pancreas; T2, tumor extension to the duodenum, bile duct, and peripancreatic tissues; T3, tumor extension to the stomach, spleen, colon, and large vessels; N1, regional lymph node metastasis; M1, distant metastasis

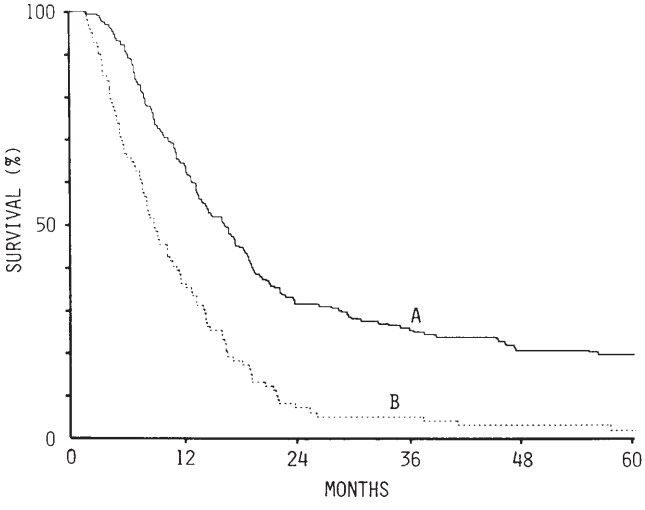

Fig. 1. Survival curves of patients who underwent pancreatic resection. *A*, patients who underwent curative resection ($n = 193$); *B*, patients who underwent noncurative resection because of local residual tumor or histological evidence of cancer cells in the surgical margins ($n = 99$)

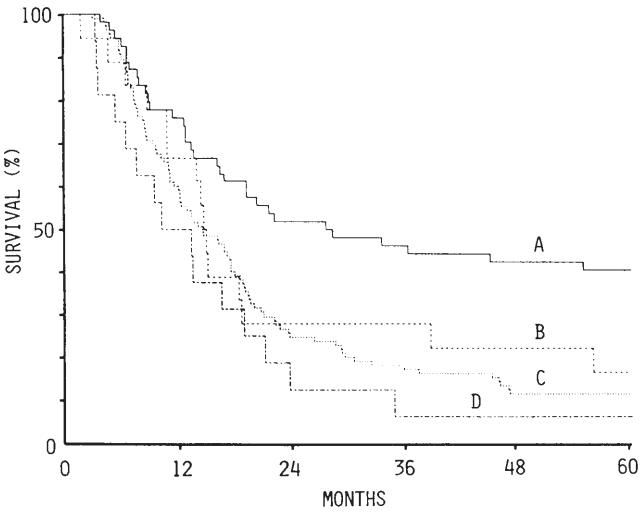

Fig. 2. Survival curves of the 193 patients who underwent curative resection by disease stage. *A*, stage I ($n = 54$); *B*, stage II ($n = 18$); *C*, stage III ($n = 105$); *D*, stage IV ($n = 16$)

ated adenocarcinoma, 3 of mucinous carcinoma, 2 of adenosquamous carcinoma, 2 of undifferentiated carcinoma, and 1 of microadenocarcinoma, which was diagnosed as duct cell origin according to the description of Cubilla and Fitzgerald.[8] In this case, no evidence of any neuroendocrine or acinar component was found by the aid of immunocytochemical markers (Table 2). Moreover, two other patients with stage I disease who underwent noncurative resection because cancer cells were found postoperatively at the cut stump of the pancreas survived for more than 5 years.

Prognostic Factors

The prognostic impact of sex, age, tumor location, tumor size, lymph node metastasis, intrapancreatic perineural invasion (IPNI), portal vein invasion, and adjacent large artery invasion was examined by a univariate analysis (Table 3). The grade of differentiation was not determined because the data are based on records from 12 institutions. A tumor size larger than 2 cm, lymph node metastasis, IPNI, and portal vein invasion were associated with a worse prognosis. Subsequently, a multivariate analysis was performed by the Cox's proportional hazards model to determine independent prognostic factors for long-term survival. Lymph node metastasis, IPNI, and portal vein invasion were found to be significant prognostic factors for survival (Table 4). In 126 patients who had records of the histological finding of IPNI, a subgroup analysis concerning nodal metastasis and IPNI was performed. In the group of patients without nodal metastasis, defined as stage I plus II, the 5-year survival rate for those without IPNI was 75%, while that for those with IPNI was 29%, the median survival time being 19.1 months, as shown in Fig. 3. The survival of patients without IPNI was significantly better than that of those with IPNI ($P < 0.02$). In the group of patients with nodal metastasis, defined as stage III plus IV, the 5-year survival rate for those without IPNI was 17%, the median survival time being 22.3 months, while that for those with IPNI was 10%, the median survival time being 12.8 months. There was no significant difference in survival between patients with or without IPNI ($P = 0.15$). Furthermore, the survival of patients with stage I and III disease according to the presence or absence of IPNI was examined (Fig. 4). In stage I disease, the 5-year survival rate for patients without IPNI was 89%, while that for those with IPNI was 37%, the median survival time being 36.3 months. There was a significant difference in survival between patients with or without IPNI ($P < 0.03$). In stage III disease, the 5-year survival rate for patients without IPNI was 18%, the median survival time being 22.3 months, while that for those with IPNI was 11%, the median survival time being 12.8 months. There was no significant difference in survival between patients with or without IPNI ($P = 0.16$). Because of the small number of patients with stage II and IV disease, their subgroup analyses were not performed.

The other independent prognostic factor was portal vein invasion. Of the 193 patients who underwent curative resection, 49 (25%) also underwent resection of the portal vein, only 4 of whom survived for more than 5 years. Histologically, one patient had PV0 (no invasion to the portal vein) and three had PV1 (invasion to the tunica adventitia or media), but none had PV2 (invasion to the tunica intima).

Regarding the tumor size, the median survival of patients with tumors 2.0 cm or smaller (TS1) was 36.3 months, with a 5-year survival rate of 38%, whereas that of patients with tumors larger than 2.0 cm (TS2–4) was 13.7 months, with a 5-year survival rate of 15%. The survival of patients with TS1 was significantly better than that of those with TS2–4 ($P < 0.01$). As shown in Table 5, the incidence of nodal metastasis and IPNI in patients with TS1 was significantly lower than that in those with TS2–4 (both $P < 0.01$). In contrast, neither nodal metastasis nor IPNI was recognized in 21% of the patients with TS1, but in only 7% of those with TS2–4.

Discussion

A number of recent reports have described the long-term survival of patients who have undergone pancreatectomy for pancreatic adenocarcinoma, with 5-year survival rates of more than 20%.[9–14] Trede et al.[9] stated that the 5-year survival rate for patients after

Table 2. Characteristics of 5-year survivors after pancreatic resection

No.	Sex	Age	Stage	Size	Histology
1.	F	76	I	TS1	Well-differentiated adenocarcinoma
2.	F	60	I	TS1	Well-differentiated adenocarcinoma
3.	M	40	I	TS1	Well-differentiated adenocarcinoma
4.	F	71	I	TS1	Moderately differentiated adenocarcinoma
5.	F	64	I	TS1	Moderately differentiated adenocarcinoma
6.	M	72	I	TS1	Moderately differentiated adenocarcinoma
7.	M	73	I	TS1	Poorly differentiated adenocarcinoma
8.	M	59	I	TS1	Poorly differentiated adenocarcinoma
9.	M	67	I	TS1	Mucinous carcinoma
10.	M	63	I	TS1	Adenosquamous carcinoma
11.	M	68	I	TS2	Papillary adenocarcinoma
12.	F	39	I	TS2	Well-differentiated adenocarcinoma
13.	M	61	I	TS2	Well-differentiated adenocarcinoma
14.	F	78	I	TS2	Well-differentiated adenocarcinoma
15.	F	63	I	TS2	Moderately differentiated adenocarcinoma
16.	F	45	I	TS2	Undifferentiated carcinoma
17.	F	42	I	TS3	Papillary adenocarcinoma
18.	F	72	I	TS3	Moderately differentiated adenocarcinoma
19.	F	48	I	TS3	Moderately differentiated adenocarcinoma
20.	F	37	I	TS3	Moderately differentiated adenocarcinoma
21.	M	41	I	TS3	Mucinous carcinoma
22.	M	55	I	TS4	Well-differentiated adenocarcinoma
23.	M	65	II	TS1	Undifferentiated carcinoma
24.	F	77	II	TS2	Mucinous carcinoma
25.	F	49	II	TS3	Well-differentiated adenocarcinoma
26.	F	56	III	TS1	Well-differentiated adenocarcinoma
27.	F	55	III	TS1	Adenosquamous carcinoma
28.	F	45	III	TS2	Well-differentiated adenocarcinoma
29.	M	65	III	TS2	Moderately differentiated adenocarcinoma
30.	F	56	III	TS2	Moderately differentiated adenocarcinoma
31.	M	58	III	TS2	Moderately differentiated adenocarcinoma
32.	M	45	III	TS2	Moderately differentiated adenocarcinoma
33.	F	76	III	TS2	Moderately differentiated adenocarcinoma
34.	F	67	III	TS3	Papillary adenocarcinoma
35.	M	66	III	TS3	Moderately differentiated adenocarcinoma
36.	F	63	III	TS4	Moderately differentiated adenocarcinoma
37.	M	63	III	TS4	Microadenocarcinoma[a]
38.	M	51	IV	[b]	Moderately differentiated adenocarcinoma
39.	M	75	I	TS1	Papillary adenocarcinoma
40.	M	77	I	TS2	Moderately differentiated adenocarcinoma

Nos. 39 and 40 were patients who underwent noncurative resection. TS1, 2.0 cm or less; TS2, 2.1–4.0 cm; TS3, 4.1–6.0 cm; TS4, >6.0 cm

[a] Microadenocarcinoma was diagnosed as duct cell origin according to the description of Cubilla and Fitzgerald[8] (see text)

[b] Multiple tumors in the pancreatic head and body

radical resection with negative surgical margins was 36%, but none of those with non-radical resection with positive surgical margins survived for more than 2 years. Willett et al.[10] also reported that there were no survivors beyond 41 months among patients who underwent resection with residual tumor at the resection margins. On the other hand, Yeo et al.[12] reported that the 5-year survival rate of patients with positive margins was 8%. According to a report by Geer and Brennan,[11] there was no significant difference in survival between positive versus negative resection margins. In the present study, the survival of patients who underwent noncurative resection because of local residual tumor or microscopical evidence of cancer cells in the surgical margins was much worse than that of patients who underwent curative resection associated with negative surgical margins ($P < 0.00000001$). Therefore, all patients who underwent noncurative resection were excluded from the statistical analysis. The 5-year survival rate for the 193 patients receiving curative resection was 20%, being 41% for those with stage I disease, but much lower for those with stage II, III, or IV disease. Thus, the progno-

Table 3. Factors affecting survival after curative resection

Factors	No. of patients	Median survival (months)	*P*-Value
Sex			
male	114	13.5	0.057
female	79	17.4	
Age			
65≧	117	14.8	0.858
65<	76	17.3	
Location			
head	157	16.1	0.417
body & tail	36	16.7	
Tumor size			
TS1 (≤2.0 cm)	34	36.3	0.010
TS2 (2.1–4.0 cm)	105	15.0	
TS3 (4.1–6.0 cm)	40	12.3	
TS4 (6.0 cm<)	14	11.1	
Nodal metastasis			
0 (negative)	72	19.1	0.004
1 (regional[a])	105	14.4	
2 (paraaortic)	16	10.2	
IPNI			
negative	30	38.9	<0.001
positive	96	15.0	
Portal vein invasion[b]			
PV0 (no invasion)	145	17.4	<0.001
PV1 (adventitia, media)	21	11.0	
PV2 (intima)	25	13.5	
Large artery invasion[b]			
A0 (no invasion)	184	16.6	0.121
A1 (adventitia, media)	3	6.4	
A2 (intima)	6	13.5	

IPNI, intrapancreatic perineural invasion. *P*-values were based on the log-rank test

[a] Regional lymph nodes represent those defined in the UICC TNM classification[3]

[b] The grade of invasion was proven histologically. Large artery invasion includes the common hepatic, celiac, and superior mesenteric arteries

Table 4. Multivariate analysis by Cox's proportional hazards model

Variable	Hazard ratio	95% Confidence interval	*P*-Value
Nodal metastasis	2.52	1.57–4.05	<0.001
IPNI	1.83	1.11–3.01	0.018
Portal vein invasion	1.61	1.04–2.49	0.033

Multivariate analysis was performed for 124 patients with adequate records of histological findings. The estimates and *P*-values were based on the maximum likelihood method

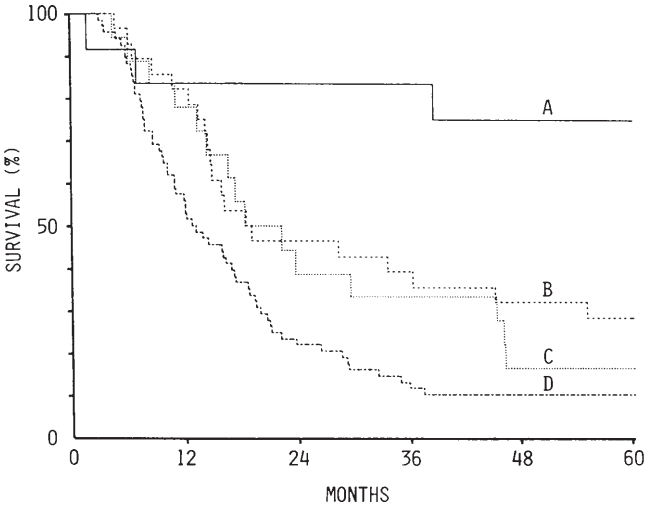

Fig. 3. Survival curves of patients without nodal metastasis (stage I plus II) and those with nodal metastasis (stage III plus IV) according to the presence or absence of intrapancreatic perineural invasion (IPNI). *A*, stage I plus II without IPNI ($n = 12$); *B*, stage I plus II with IPNI ($n = 28$); *C*, stage III plus IV without IPNI ($n = 18$); *D*, stage III plus IV with IPNI ($n = 68$). The survival of patients in curve A was significantly better than that of those in curve B ($P < 0.02$). There was no significant difference between survival curves C and D

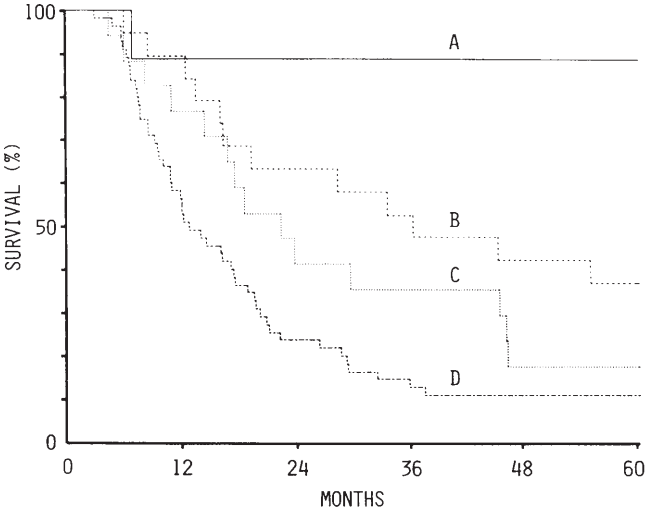

Fig. 4. Survival curves of patients with stage I and stage III diseases according to the presence or absence of IPNI. *A*, stage I without IPNI ($n = 9$); *B*, stage I with IPNI ($n = 19$); *C*, stage III without IPNI ($n = 17$); *D*, stage III with IPNI ($n = 55$). The survival of patients in curve A was significantly better than that of those in curve B ($P < 0.03$). There was no significant difference between survival curves C and D

sis in this study was determined not only by the number of patients who underwent curative resection, but also by the number of patients with stage I disease.

There are three main causes of local recurrence: direct extension to the adjacent structures or the remaining pancreas; lymph node metastasis; and extrapancreatic perineural invasion. When performing radical pancreatectomy, the importance of extended dissection of the lymph nodes and nerve plexus has been emphasized by many Japanese surgeons. While

Table 5. Incidence of nodal metastasis and IPNI according to the tumor size

Tumor size 2 cm or smaller:	
nodal metastasis (+)	38% (13/34)
IPNI (+)	47% (9/19)
nodal metastasis (−) and IPNI (−)	21% (4/19)
Tumor size larger than 2 cm:	
nodal metastasis (+)	68% (108/159)
IPNI (+)	81% (87/107)
nodal metastasis (−) and IPNI (−)	7% (8/107)

some of these surgeons perform aggressive and complete dissection of the nerve plexus, including the pancreatic head nerve plexus named by Yoshioka and Wakabayashi,[15] the superior mesenteric, hepatic, and celiac nerve plexus, and the celiac ganglia, others perform incomplete or partial dissection of these plexuses to avoid the severe diarrhea and malnutrition that frequently occur after complete dissection. In this study, IPNI was intentionally selected for analysis instead of extrapancreatic perineural invasion because IPNI is not influenced by the operative extent. The multivariate analysis showed that the strongest prognostic factors were lymph node metastasis, IPNI, and portal vein invasion, the incidences of nodal metastasis and IPNI being 63% and 76%, respectively.

There are several reports concerning the correlation between the histological malignancy of this disease and the incidence of perineural invasion. Miller et al.[16] and Drapiewski[17] reported that no correlation was found between the grade of malignancy and the incidence of perineural invasion; however, Nagayo et al.[18] stated that perineural invasion was found more frequently in patients with highly differentiated adenocarcinoma than in those with poorly differentiated adenocarcinoma. On the other hand, an experimental study demonstrated that there was no communication between the lymphatic pathway and the perineural space.[19] Moreover, clinicopathologically, there was no distinct correlation between lymph vessel invasion and perineural invasion.[20,21] As shown in Fig. 3, the survival curve of patients with IPNI without nodal metastasis (curve B) had the same trend as that of patients with nodal metastasis without IPNI (curve C), showing the similarity of the malignant biological profiles of these two independent factors. Nitecki et al.[22] reported that 5-year survival rate was most favorable (23%) in the subset of patients with negative nodes and no duodenal or perineural invasion. In the group of patients without nodal metastasis in our series, the 5-year survival rate for those without IPNI was 75% versus only 29% for those with IPNI, while in the group of patients with nodal metastasis, the 5-year survival rate for those without IPNI was 17%, and that for those with IPNI was 10%. The most favorable survival was observed in the group of patients with stage I disease without IPNI, which was associated with an 89% 5-year survival rate. Thus, pancreatic adenocarcinoma categorized by the combination of these two types of biological behavior showed 5-year survival rates ranging from a very high level to a low level, and the two factors seemed to play an important role in the prognosis of this disease. Especially in the stage I UICC pTNM classification, IPNI appears to be an additional independent factor for subclassification.

The other strongest prognostic factor was portal vein invasion. Some recent reports[23,24] pointed out that prognosis after resection of the pancreas with the portal vein tended to be related to the depth of invasion in the wall. Although the outcome was poor in our series, there were three 5-year survivors with PV1 who underwent resection of the portal vein.

Regarding the tumor size, the 5-year survival rate for patients with tumors 2 cm or smaller in diameter was 38%, and the incidence of nodal metastasis and IPNI was significantly lower in these patients than in those with tumors larger than 2 cm in diameter. Although extended surgery is necessary even for patients with tumors 2 cm or smaller because of the high incidence of local extension of cancer cells,[25] in our opinion, this size is a tentative target for early detection.

The prognosis of patients with nodal metastasis and/or IPNI is possibly influenced by the extent of resection of the lymph nodes and the nerve plexus, and by adjuvant radio- and chemotherapy. However, in view of the fact that the data were insufficient in this retrospective study, the influence of these factors might be further elucidated by an analysis of a prospectively randomized controlled clinical trial.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare of Japan.

References

1. Ozaki H, Matsuno S, Yamauchi H, Ogata Y, Matsumoto Y, Mizumoto R, Monden M, Saitoh Y, Suzuki T, Tsunoda T, Nakayama K, Hiraoka T, Tajima K (1993) Retrospective study of resectable pancreatic cancer. Results of cases collected from 12 institutions (in Japanese with English abstract). Suizou (J Jpn Pancr Soc) 8:480–486
2. Ohhashi K, Murakami Y, Maruyama M, Takekoshi T, Ohta H, Ohhashi I, Takagi K, Kato Y (1982) Four cases of mucous-secreting pancreatic cancer (in Japanese with English abstract). Prog Dig Endosc 20:348–351
3. Hermanek P, Sobin LH (eds) (1992) UICC TNM classification of malignant tumors, 4th edn, 2nd rev. Springer, Berlin
4. Japanese Pancreatic Society (1980) General rules for surgical and pathological studies on cancer of the pancreas (in Japanese), 1st edn. Kanehara, Tokyo
5. Japan Pancreas Society (1986) General rules for cancer of the pancreas (in Japanese), 3rd edn. Kanehara, Tokyo

6. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481
7. Cox DR (1972) Regression models and life tables. J R Stat Soc 34:187–220
8. Cubilla AL, Fitzgerald PJ (1984) Tumors of the exocrine pancreas. In: Atlas of tumor pathology, second series, Fasc. 19. Armed Forces Institute of Pathology, Washington, pp 110, 174–176
9. Trede M, Schwall G, Saeger HD (1990) Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. Ann Surg 211:447–458
10. Willett CG, Lewandrowski K, Warshaw AL, Efird J, Compton CC (1993) Resection margins in carcinoma of the head of the pancreas. Implications for radiation therapy. Ann Surg 217:144–148
11. Geer RJ, Brennan MF (1993) Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg 165:68–73
12. Yeo CJ, Cameron JL, Lilemoe KD, Sitzmann JV, Hruban RH, Goodman SN, Dooley WC, Coleman J, Pitt HA (1995) Pancreaticoduodenectomy for cancer of the head of the pancreas: 201 patients. Ann Surg 221:721–733
13. Nagakawa T, Nagamori M, Futakami F, Tsukioka Y, Kayahara M, Ohta T, Ueno K, Miyazaki I (1996) Results of extensive surgery for pancreatic carcinoma. Cancer 77:640–645
14. Ishikawa O, Ohigashi H, Imaoka S, Sasaki Y, Iwanaga T, Matayoshi Y, Inoue T (1994) Is the long-term survival rate improved by preoperative irradiation prior to Whipple's procedure for adenocarcinoma of the pancreatic head? Arch Surg 129:1075–1080
15. Yoshioka H, Wakabayashi T (1958) Therapeutic neurotomy on head of pancreas for relief of pain due to chronic pancreatitis. A new technical procedure and its results. Arch Surg 76:546–554
16. Miller JR, Baggenstoss AH, Comfort MW (1951) Carcinoma of the pancreas. Effect of histological type and grade of malignancy on its behavior. Cancer 4:233–241
17. Drapiewski JF (1944) Carcinoma of the pancreas: a study of neoplastic invasion of nerves and its possible clinical significance. Am J Clin Pathol 14:549–556
18. Nagayo T, Murakami N, Matsuoka Y (1976) Local neural invasion of carcinoma of the gallbladder, bile ducts and pancreas (in Japanese). Gan No Rinsyo (Clin Cancer) 22:1406–1409
19. Larson DL, Robin AE, Roberts DK, O'Steen WK, Rapperport AS, Lewis SR (1966) Perineural lymphatics: myth or fact. Am J Surg 112:488–492
20. Matsuda M, Nimura Y (1983) Perineural invasion of pancreas head carcinoma (in Japanese with English abstract). Nippon Geka Gakkai Zasshi (J Jpn Surg Soc) 84:719–728
21. Nagakawa T, Kayahara M, Ueno K, Ohta T, Konishi I, Ueda N, Miyazaki I (1992) A clinicopathologic study on neural invasion in cancer of the pancreatic head. Cancer 69:930–935
22. Nitecki SS, Sarr MG, Colby TV, van Heerden JA (1995) Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? Ann Surg 221:59–66
23. Takahashi S, Ogata Y, Tsuzuki T (1994) Combined resection of the pancreas and portal vein for pancreatic cancer. Br J Surg 81:1190–1193
24. Nakao A, Harada A, Nonami T, Kaneko T, Inoue S, Takagi H. (1995) Clinical significance of portal invasion by pancreatic head carcinoma. Surgery 117:50–55
25. Tsuchiya R, Noda T, Harada M, Miyamoto T, Tomioka T, Yamamoto K, Yamaguchi T, Izawa K, Tsunoda T, Yoshino R, Eto T (1986) Collective review of small carcinoma of the pancreas. Ann Surg 203:77–81