without IORT (n=36) were calculated and compared. There was no significant difference in survival (p=0.86) between the groups. The 1-, 3-, and 5-year survival rates for patients with (n=44) and without intraoperative radiotherapy (n=61) were 43%, 11%, 5% and 61%, 18%, 18%, respectively **(Figure 3)**, showing no significant difference in survival (p=0.053). There were no significant differences in both MST and RFST between patients with IORT (MST: 10 months, RFST: 7 months) and patients without IORT (MST: 17 months, RFST: 11 months). There was no significant difference (p=0.13) between patients receiving both extended lymphadenectomy and IORT (n=40) and patients receiving lymphadenectomy alone (n=36).

The 1-, 3-, and 5-year survival rates for patients with (n=89) and without lymph node involvement (n=16) were 48%, 11%, 8%, and 85%, 67%, 0%, respectively **(Figure 4)**, showing a significant difference between the groups (p=0.0015). The median survival of patients with and without nodal involvement was 12 and 38 months, respectively. The 5-year survival rate for patients with a positive margin (n=26) and those with a negative margin (n=79) was 0% and 9%, respectively **(Figure 4)**, showing no significant difference (p=0.29).

The numbers of cases of disease recurrence and deaths after surgical resection are shown in **Table 3**. Six patients with invasive ductal cancer had in-hospital deaths, including 3 operative deaths. Recurrent disease occurred in 75 patients. Recurrence sites were as follows; locoregional (n=57), liver (n=47), peritoneum (n=29), lung (n=10), bone (n=2), pleura (n=1), remnant pancreas (n=1), skin (n=1), rectum (n=1), and cervical lymph nodes (n=1). Forty-five percent (13/29) of patients had locoregional recurrence after standard lymphadenectomy, *versus* 58% (44/76) of patients after extended lymphadenectomy. Fifty-five percent (24/44) of patients with intraoperative radiotherapy had locoregional recurrence, *versus* 54% (33/61) of patients without intraoperative radiotherapy. There was no significant difference in the frequency of locoregional recurrence between patients with or without extended lymphadenectomy, and those with or without intraoperative radiotherapy. Six patients underwent secondary resection for liver metastasis (n=3), inferior pyloric node metastasis (n=1), remnant pancreatic recurrence (n=1), or rectal metastasis (n=1). However, recurrent disease occurred in four of these patients after secondary resection.

TABLE 3 Numbers of Disease Recurrence and Death after Surgical Resection

		Standard (n=29)	Extended (n=76)	IORT (+) (n=44)	IORT (-) (n=61)
Death (no.)		18	61	43	36
In-hospital death (no.)		2	4	4	2
Death due to recurrence (no.)		16	49	36	29
Recurrent patients (no.)		20	58	36	42
Recurrence site (no.)	Locoregional	13	44	24	33
	Liver	9	38	22	25
	Peritoneum	7	22	20	9
	Lung	1	9	8	2
	Bone	0	2	0	2
Recurrence free survival time (months)		9	9	7	11

Standard: standard lymphadenectomy; Extended: extended lymphadenectomy; IORT: intraoperative radiotherapy.

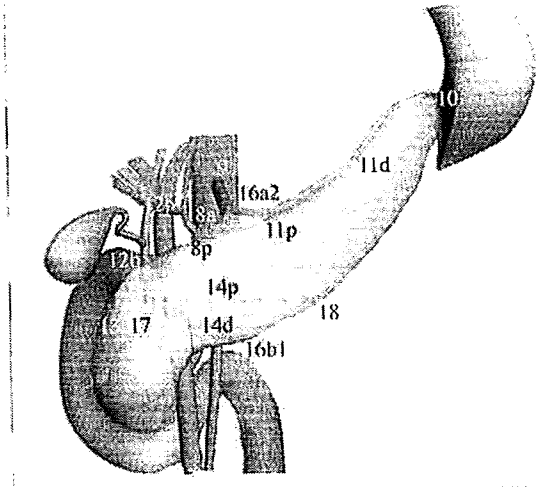

FIGURE 5
A diagram of lymph node station for extended lymphadenectomy following Japanese Classification

DISCUSSION

The main conclusion of this retrospective analysis was that extended lymphadenectomy did not provide any survival benefit in patients with resectable pancreatic adenocarcinoma. Extended removal of lymph nodes is based on the assumption that it could lead to a reduction in the incidence of locoregional recurrence, which is one of the most common causes of death after surgical resection (7-9). However, Yeo *et al.* reported that there were no significant differences in 1-, 3-, 5-year and median survival when comparing standard resection and radical resection (standard resection plus distal gastrectomy and retroperitoneal lymphadenectomy) in a prospective randomized trial (14). Our study showed that extended lymphadenectomy did not have any survival advantage as compared with standard lymphadenectomy, because locoregional recurrence occurred frequently after extended lymphadenectomy. These results suggest that extended lymph node dissection for pancreatic adenocarcinoma does not appear to improve the prognosis (14,15). However, no patients survived more than 3 years after standard lymphadenectomy in this study. Thus, margin negativity in the extended lymphadenectomy group may have a survival benefit that becomes apparent only after long-term follow-up, while this suggestion is not supported by the statistical analyses.

Some randomized controlled trials have demonstrated that adjuvant chemoradiation therapy resulted in significantly better survival than surgery alone (19). Lim reported that although biologic characteristics remained important predictors of survival for patients with resected pancreatic caner, the most powerful determinant was postoperative adjuvant chemoradiation therapy in a retrospective cohort

study (20). Survival was significantly better (p=0.0003) for patients who received adjuvant chemotherapy and/or radiation therapy (n=185) than those who did not receive adjuvant therapy (n=208). However, a recent European Study Group for Pancreatic Cancer (ESPAC) randomized controlled trial showed no benefit of adjuvant chemoradiotherapy (median survival 15.5 months in 175 patients with chemoradiotherapy *versus* 16.1 months in 178 patients without) (17). Regarding intraoperative radiotherapy, Reni *et al.* reported that intraoperative radiotherapy achieved a significant improvement in local control and outcome in patients with locally limited pancreatic cancer (stage 1-2) (11). In patients with locally advanced disease (stage 3-4), a beam energy greater than 6 MeV prolonged the time to local failure, whereas no effect on the time to failure and overall survival was observed. Hishinuma *et al.* reported that they did not find any survival advantage of intraoperative radiotherapy and/or postoperative radiotherapy; however, autopsies revealed a suppressive effect of radiation on cancer growth (13). However, there has been no randomized controlled trial demonstrating the efficacy of intraoperative radiotherapy for resectable pancreatic cancer. Further confirmatory studies are needed to evaluate intraoperative radiotherapy for resectable pancreatic cancer.

Intraductal papillary mucinous tumor of the pancreas is a recently established clinical entity which includes a spectrum of lesions ranging from benign adenoma to malignant infiltrating tumors. The prognosis of this neoplasm is not fully understood. Cuillerier reported that 65% of patients with invasive intraductal papillary carcinoma developed recurrent disease (21). Fukushima also reported that invasive carcinoma derived from intraductal papillary mucinous carcinoma with extrapancreatic invasion should be treated as ductal carcinoma because of its aggressive behavior after resection (22). In this study, patients with invasive intraductal papillary mucinous adenocarcinoma had a similar prognosis to those with invasive ductal adenocarcinoma. However, invasive intraductal papillary mucinous adenocarcinoma had positive surgical margin (35%) more frequently than did invasive ductal adenocarcinoma. Intraductal papillary mucinous tumor is characterized by proliferation of ductal epithelium associated with ductal dilatation. Thus, the difference in nature of intraductal papillary mucinous adenocarcinoma and invasive ductal adenocarcinoma should be considered carefully. In contrast, noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma had a favorable prognosis after surgical treatment (23). Precise differential diagnosis between invasive and noninvasive intraductal papillary mucinous adenocarcinoma is crucial for surgical treatment.

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Surgical Outcome of Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Objective: An increasing number of intraductal papillary mucinous neoplasms of the pancreas have been reported in recent years. However, the clinicopathologic features and surgical outcome of this neoplasm are not fully understood because of the limited number of cases. The objective of this study is to clarify the clinicopathologic features of intraductal papillary mucinous neoplasm of the pancreas and evaluate prognostic factors influencing survival.

Methods: Eighty-two patients with intraductal papillary mucinous neoplasm undergoing surgical resection at the National Cancer Center Hospital East between April 1994 and October 2006 were retrospectively analyzed.

Results: There were 31 patients with adenoma and 51 patients with carcinoma. Carcinomas were subdivided into noninvasive carcinoma (n = 14), minimally invasive carcinoma (n = 6), and invasive carcinoma (n = 31). The postoperative mortality rate was 0%. The 5-year survival rate for patients with intraductal papillary mucinous adenoma, noninvasive carcinoma, minimally invasive carcinoma, and invasive carcinoma was 80%, 78%, 83%, and 24%, respectively. Regardless of the margin status, no patient with adenoma developed recurrent disease. There were significant differences in survival between noninvasive carcinoma and invasive carcinoma (P = .016) and between minimally invasive carcinoma and invasive carcinoma (P = .030). Multivariate analysis confirmed that lymph node metastasis (P = .004) and age (P = .015) were significant prognostic factors after surgical resection of these neoplasms.

Conclusions: Patients with intraductal papillary mucinous adenoma, noninvasive carcinoma, and minimally invasive carcinoma showed favorable survival. In contrast, invasive intraductal papillary mucinous carcinoma was associated with poor survival regardless of the margin status. Nodal involvement was the strongest predictor of poor survival.

Key Words: Intraductal papillary mucinous neoplasm—Pancreatic resection—Nodal involvement—Invasive carcinoma—Noninvasive carcinoma.

An increasing number of intraductal papillary mucinous neoplasms of the pancreas have been reported in recent years.[1–8] However, the clinicopathologic features and surgical outcome of intraductal papillary mucinous neoplasm of the pancreas are not fully understood because of the limited number of cases. Histopathologic studies have revealed that intraductal papillary mucinous neoplasms show a spectrum of epithelial dysplasia ranging from adenoma to invasive carcinoma. Patients with a noninvasive neoplasm, such as adenoma or noninvasive carcinoma, have a favorable prognosis after surgical resection.[9–12] In contrast, the presence of an invasive component is strongly associated with poor survival

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after surgical resection.[13–15] It has been reported that invasive intraductal papillary mucinous neoplasms recur frequently even after complete curative resection.[16] However, prognostic factors influencing survival after surgical resection of this neoplasm have not been well defined, partly because longer follow-up is required to ensure cure. The present single-institution study examined the clinicopathologic features of intraductal papillary mucinous neoplasm of the pancreas and evaluated prognostic factors predicting survival after surgical resection.

PATIENTS AND METHODS

Eighty-two consecutive patients with intraductal papillary mucinous neoplasm of the pancreas who underwent surgical resection at the National Cancer Center Hospital East between April 1994 and October 2006 were retrospectively analyzed. Patient follow-up ranged from 1 to 153 months (median 28 months). Overall survival analysis included all deaths, including deaths due to an unrelated cause. Intraductal papillary mucinous neoplasms were histologically classified as adenoma (n = 31) and carcinoma (n = 51). Carcinomas were subdivided into noninvasive carcinoma (n = 14), minimally invasive carcinoma (n = 6), and invasive carcinoma originating in an intraductal tumor (n = 31) according to the Classification of Pancreatic Carcinoma proposed by the Japan Pancreas Society.[17] Adenoma is defined as a benign epithelial dysplasia including mild, moderate, or severe dysplasia. Noninvasive carcinoma is defined as a carcinoma limited to the pancreatic duct, and minimally invasive carcinoma is defined as a carcinoma having invaded slightly beyond the duct wall. Invasive carcinoma is defined as a definitely invasive cancer (more than minimally invasive) originating in an intraductal papillary mucinous neoplasm. Intraductal papillary mucinous neoplasms were classified as branch duct type (n = 61) and main duct type (n = 21) according to the predominant location of the tumor. Histopathologic findings were reviewed according to the Classification of Pancreatic Carcinoma.

The following 13 factors were analyzed by Kaplan-Meier survival analysis and multivariate analysis: age (≤65 vs > 65 years), sex, tumor type (main duct type vs branch duct type), tumor size (≤4.0 vs > 4.0 cm), maximum diameter of the main pancreatic duct (< 5.0 vs ≥5.0 mm), histology (adenoma vs carcinoma), retroperitoneal invasion, intrapancreatic nerve invasion, microscopic venous invasion, lymph node metastasis, margin status (R0 vs R1 resection), serum carcinoembryonic antigen (< 5.0 vs ≥5.0 ng/mL), and serum carbohydrate antigen19-9 (< 37 vs ≥37 U/mL).

Statistical analysis was performed by chi-square test and t test, when appropriate. Cumulative survival rates were generated by the Kaplan-Meier method. The survival curves were compared by log-rank test. Significant factors identified by univariate analysis were further examined by multivariate analysis. Multivariate regression analysis was performed with the Cox hazards model using SPSS software: Dr. SPSS 2 for Windows (SPSS Japan Inc., Tokyo). Differences were considered significant at $P < .05$.

RESULTS

The characteristics of the patients with intraductal papillary mucinous adenoma and carcinoma are shown in Table 1. There were 55 men and 27 women, and the mean age of patients with adenoma and carcinoma was 63 and 66 years, respectively. Of the patients with adenoma, 8 (26%) had abdominal pain and 23 (74%) had no symptoms. Of the patients with carcinoma, 16 (31%) had abdominal pain and 26 (51%) had no symptoms. The mean size of adenomas was 3.4 cm (range 1.3–10) and that of carcinomas was 5.8 cm (range 1.0–12), showing a significant difference ($P < .0001$). The mean diameter of the main pancreatic duct of patients with adenoma and carcinoma was 5.1 mm (range 2.0–20) and 10.9 mm (range 5.0–30), respectively, showing a significant difference ($P < .0001$). Ninety-four percent (29 of 31) of adenomas were classified as branch duct type, whereas 63% (32 of 51) of carcinomas were classified as branch duct type. Intraductal papillary mucinous neoplasms were most frequently located in the pancreatic head. The histologic findings are tabulated in Table 2. The surgical margin for carcinomas was positive in one patient with noninvasive carcinoma and eight patients with invasive carcinoma. A positive margin for adenoma in the pancreatic cut end was observed in five patients with adenoma, one patient with noninvasive carcinoma, two patients with minimally carcinoma, and seven patients with invasive carcinoma. The frequency of lymph node metastasis in patients with invasive carcinoma was 48% (15 of 31). No patient with noninvasive carcinoma or minimally invasive carcinoma had lymph node metastasis.

Patients with intraductal papillary mucinous neoplasms were treated by subtotal stomach-preserving pancreatoduodenectomy (n = 27), distal pancrea-

TABLE 1. *Characteristics of intraductal papillary mucinous adenoma and adenocarcinoma*

	Total (n = 82)	Adenoma (n = 31)	Carcinoma (n = 51)
Age, years (mean)	65	63	66
Gender (male/female)	55/27	23/8	32/19
Symptoms (%)			
Abdominal pain	24 (29%)	8 (26%)	16 (31%)
Jaundice	3 (4%)	1 (3%)	2 (4%)
Weight loss	3 (4%)	0	3 (6%)
No symptom	49 (60%)	23 (74%)	26(51%)
Size, cm (mean)	4.9 (range 1.0–12)	3.4 (range 1.3–10)	5.8 (range 1.0–12)
Diameter of MPD, mm (mean)	8.7 (range 2.0–30)	5.1 (range 2.0–20)	10.9 (range 5.0–30)
Tumor type			
Main duct type	21	2	19
Branch duct type	61	29	32
Location			
Head	55	20	35
Head and body	3	2	1
Head, body, and tail	1	0	1
Body	12	6	6
Tail	4	2	2
Body and tail	7	1	6

TABLE 2. *Histological findings of intraductal papillary mucinous neoplasm*

	Adenoma (n = 31)	Noninvasive (n = 14)	Minimally (n = 6)	Invasive (n = 31)
Margin status				
Positive for adenoma	5	1	2	7
Positive for carcinoma	0	1	0	8
Tumor type				
Main duct type	2	6	1	12
Branch duct type	29	8	5	19
Serosal invasion	0	0	0	4
Retroperitoneal invasion	0	0	0	26
Extrapancreatic plexus invasion	0	0	0	4
Intrapancreatic nerve invasion	0	0	0	16
Venous invasion	0	0	0	16
Lymph node metastases	0	0	0	15

Noninvasive, noninvasive carcinoma; Minimally, minimally invasive carcinoma; Invasive, invasive carcinoma.

tectomy (n = 20), pylorus-preserving pancreatoduodenectomy (n = 11), duodenum-preserving pancreatic head resection (n = 6), inferior head resection (n = 6), total pancreatectomy (n = 4), Kausch Whipple pancreatoduodenectomy (n = 4), segmental resection of the body (n = 3), and partial head resection (n = 1). There was no postoperative death in 82 patients.

The survival curves following surgical treatment are shown in Fig. 1 and 2. The overall 1-, 3-, 5-, and 10-year survival rates for patients with adenoma (n = 31) were 97%, 87%, 80%, and 69%, respectively. Regardless of the margin status, no patient with adenoma developed recurrent disease after surgical resection. The overall 1-, 3-, 5-, and 10-year survival rates for patients with carcinoma (n = 51) were 84%, 52%, 47%, and 47%, respectively. There was a significant difference in survival between patients with adenoma and those with carcinoma (P = .017). The 5-year survival rate for patients with noninvasive carcinoma, minimally invasive carcinoma, and invasive carcinoma was 78%, 83%, and 24%, respectively. There were significant differences in survival between noninvasive carcinoma and invasive carcinoma (P = .016), and between minimally invasive carcinoma and invasive carcinoma (P = .030).

Numbers of disease recurrence and deaths after surgical resection are shown in Table 3. Recurrent disease occurred in 15 patients with invasive carcinoma, one patient with noninvasive carcinoma, and one patient with minimally invasive carcinoma. Of the nine patients with a carcinoma-positive margin, seven patients died of recurrent disease with a median survival time of 24 months, and one patient died of pneumonia with suspected recurrence. One patient with minimally invasive carcinoma having an adenoma-positive margin died of locoregional recurrence and peritoneal dissemination. Sites of recurrence were

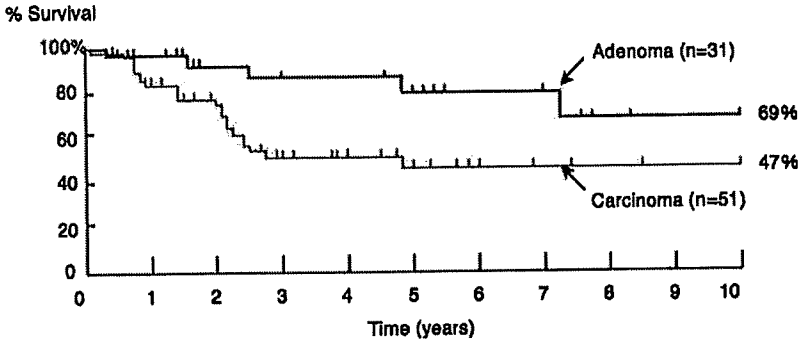

FIG. 1. Survival rates for patients with adenoma (n = 31) and carcinoma (n = 51).

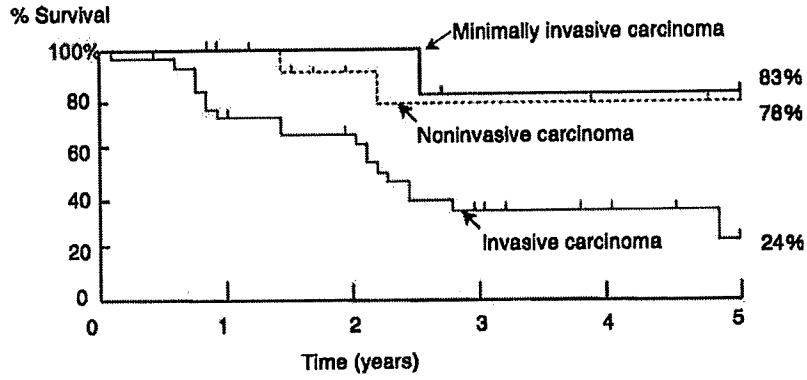

FIG. 2. Survival rates for patients with noninvasive carcinoma (n = 14), minimally invasive carcinoma (n = 6), and invasive carcinoma (n = 31).

TABLE 3. *Numbers of disease recurrence and death after surgical resection*

	Adenoma (n = 31)	Noninvasive (n = 14)	Minimally (n = 6)	Invasive (n = 31)
Numbers of death	5	2	1	19
Death due to recurrence	0	1	1	15
Death from other causes in disease-free patients	5	1	0	4
Numbers of recurrence	0	1	1	16
Recurrent site				
Locoregional	0	0	1	9
Peritoneum	0	1	1	8
Liver	0	0	0	6
Lung	0	0	0	2
Neck lymph node	0	0	0	1

Noninvasive, noninvasive carcinoma; Minimally, minimally invasive carcinoma; Invasive, invasive carcinoma.

as follows: locoregional (n = 10), peritoneum (n = 10), liver (n = 6), lung (n = 2), and neck lymph node (n = 1). Five disease-free patients with adenoma died of unrelated causes, such as lung cancer, gastric cancer, respiratory failure, renal failure, and ischemic heart disease. One disease-free patient with noninvasive carcinoma died of renal failure 17 months after the operation. Four disease-free patients with invasive adenocarcinoma died of unrelated causes, such as esophageal cancer, subarachnoid hemorrhage, pneumonia, and suicide. One patient with invasive carcinoma is alive with disease recurrence.

Clinicopathologic factors likely to influence survival after surgical resection are shown in Table 4. Among 13 factors, 11 were significantly associated with outcome in univariate analysis: age (≤65 vs >65), tumor size (≤4.0 vs >4.0 cm), maximum diameter of the main pancreatic duct (<5.0 vs ≥5.0mm), carcinoma, retroperitoneal invasion, intra-

TABLE 4. *Univariate analysis of potential predictors of overall survival after surgical resection*

Factors	No.	Survival (%) 1 year	3 years	5 years	*P* value
Age (years)					
≤65	41	95	84	79	.004
>65	41	82	45	40	
Gender					
Male	55	87	59	56	.26
Female	27	92	72	63	
Tumor size (cm)					
≤4.0	41	100	78	72	.033
>4.0	41	78	51	47	
Diameter of the MPD (mm)					
<5	24	95	89	81	.03
≥5	58	86	54	50	
Tumor type					
Main duct type	21	95	58	48	.74
Branch duct type	61	86	65	62	
Histology					
Adenoma	31	97	87	80	.017
Carcinoma	51	84	52	47	
Retroperitoneal invasion					
Negative	56	98	83	76	<.0001
Positive	26	68	26	26	
Intrapancreatic nerve invasion					
Negative	66	98	76	70	<.0001
Positive	16	50	16	0	
Venous invasion					
Negative	66	98	76	73	<.0001
Positive	16	47	10	0	
Lymph node metastases					
Negative	67	97	78	72	<.0001
Positive	15	53	10	0	
Margin status					
R0	73	90	73	67	<.0001
R1	9	78	0	0	
Serum CEA (ng/mL)					
<5.0	55	90	74	74	.0053
≥5.0	27	85	44	30	
Serum CA19-9 (U/mL)					
<37	52	98	78	71	.0007
≥37	30	73	35	35	

pancreatic nerve invasion, microscopic venous invasion, lymph node metastases, margin status, carcinoembryonic antigen (<5.0 vs ≥5.0 ng/mL), and carbohydrate antigen 19-9 (<37 vs ≥37 U/mL). Multivariate analysis using the Cox proportional hazards model was completed for 11 factors with a *P* value <.05 in univariate analysis. Multivariate analysis confirmed that lymph node metastasis ($P = .004$) and older age ($P = .015$) were significant and independent prognostic indicators after pancreatic resection for intraductal papillary mucinous neoplasms of the pancreas (Table 5). The overall 1-, 3-, and 5-year survival rates for patients with node-positive intraductal papillary mucinous carcinoma ($n = 15$) were 53%, 10%, and 0%, respectively. The overall 1-, 3-, and 5-year survival rates for patients with node-negative intraductal papillary mucinous neoplasm ($n = 67$) were 97%, 78%, and 72%, respectively. There was a significant difference in survival between patients with node-positive intraductal papillary mucinous neoplasm and those with a node-negative neoplasm ($P < .0001$).

DISCUSSION

The clinicopathologic features and surgical outcome of intraductal papillary mucinous neoplasm have not been fully clarified because this neoplasm is uncommon compared with pancreatic ductal carcinoma. Intraductal papillary mucinous neoplasms are frequently classified as noninvasive neoplasms and invasive neoplasms.[9,13,16] An indolent character and favorable outcome for noninvasive neoplasm have been described.[13,16,18] Conversely, poor survival results have been reported for invasive intraductal papillary mucinous neoplasm. In this study, the 5-year survival rate for invasive intraductal papillary mucinous carcinoma was 24%. Wada et al. reported that survival curves were not different between cases with invasive intraductal papillary mucinous neoplasm cases versus cases with ductal adenocarcinoma matched by stage.[18] Maire et al. reported that the overall 5-year survival rate was higher in patients with malignant invasive intraductal papillary mucinous neoplasm than in those with pancreatic ductal carcinoma, but was similar in the subset of stage II/III tumors.[19] These results suggest that invasive intraductal papillary mucinous neoplasm has a similar survival outcome to pancreatic ductal carcinoma. However, other authors reported that patients with invasive intraductal papillary mucinous neoplasm had a better outcome compared with those with pancreatic ductal carcinoma.[20–22] Salvia et al. reported that invasive intraductal papillary mucinous neoplasm had markedly favorable survival (60% at 5 years)[20]. Shimada et al. reported that the 5-year survival rate of invasive intraductal papillary mucinous neoplasm was significantly higher than that of common-type invasive ductal carcinoma (42% vs 20%).[21] Thus, further studies are needed to clarify the long-term survival of invasive intraductal papillary mucinous neoplasms.

It is difficult to accurately predict the outcome after surgical resection for invasive intraductal papillary mucinous neoplasm. Margin status might be an influential prognostic factor in patients with invasive carcinoma. This study showed that seven of nine patients with a carcinoma-positive margin died of

TABLE 5. *Multivariate Cox regression analysis of prognostic factors after surgical resection*

Factors	Relative risk	(95% CI)	*P* value
Lymph node metastases	5.53	(1.70–18.0)	.004
Age (> 65 years)	3.28	(1.26–8.53)	.015
Tumor size (> 4.0 cm)	0.99	(0.32–3.00)	.99
Diameter of the MPD (≥5 mm)	1	(0.24–4.26)	1
Histology (carcinoma)	0.76	(0.19–3.00)	.7
Retroperitoneal invasion	1.49	(0.28–7.89)	.64
Intrapancreatic nerve invasion	1.6	(0.13–19.5)	.71
Venous invasion	1.09	(0.09–13.2)	.94
Margin status (R1)	2.17	(0.70–6.71)	.18
Serum CEA (≥5.0 ng/mL)	1.78	(0.60–5.24)	.3
Serum CA19-9 (≥37 U/mL)	1.32	(0.50–3.54)	.58

recurrent disease, with a median survival time of 24 months. Sohn et al. reported that the 2-year survival rate for patients with invasive intraductal papillary mucinous neoplasm was only 40% when the margin was positive.[22] Thus, curative resection with a negative margin for carcinoma is essential for treating invasive neoplasm. In contrast, only a few patients with a positive margin for adenoma developed recurrent disease. In this study, 15 patients (five with adenoma, one with noninvasive carcinoma, two with minimally invasive carcinoma, and seven with invasive carcinoma) had a positive margin for adenoma. Of these 15 patients, recurrence occurred in four with invasive carcinoma and one with minimally invasive carcinoma. However, no recurrence occurred in five patients with intraductal papillary mucinous adenoma with a positive margin for adenoma. Chari et al. also reported that noninvasive intraductal papillary mucinous neoplasm recurs infrequently after resection, and survival is excellent regardless of the degree of epithelial dysplasia in the tumor.[16] D'Angelica et al. reported that the presence of atypia or carcinoma in situ at the ductal resection margin was not associated with a poor outcome.[14] These results suggest that a positive margin for adenoma is not associated with disease recurrence.

However, recurrent disease frequently occurred in patients with invasive intraductal papillary mucinous neoplasm even after margin-free resection. Despite a histological negative margin for carcinoma, 52% of patients (16 of 31) with invasive intraductal papillary mucinous neoplasm developed recurrence in our series. Chari et al. reported that invasive intraductal papillary mucinous neoplasm recurred frequently even after complete curative resection.[16] Cuillerier et al. also reported frequent recurrence not only after partial pancreatectomy with involved margins, but also after partial pancreatectomy with disease-free margins in patients with invasive neoplasm.[13] Identification of clinical and pathologic factors influencing survival is useful for the treatment of invasive neoplasms. Previous studies have demonstrated that tumor-associated biological factors, such as lymph node status, vascular invasion, and tumor size, are important in evaluating postoperative prognosis for invasive intraductal papillary mucinous neoplasm.[14,23] This study showed that nodal involvement was the independent predictor of poor survival in patients with intraductal papillary mucinous neoplasm. In this study, the overall 1-, 3-, and 5-year survival rates for patients with nodal involvement (n = 15) were 53%, 9%, and 0%, respectively, and node-positive patients had a significantly worse outcome than node-negative patients. Thus, pancreatectomy with lymph node dissection did not appear to improve survival in node-positive patients with an invasive neoplasm. Of node-positive invasive neoplasms, 93% had retroperitoneal invasion, 80% had intrapancreatic nerve invasion, 73% had microscopic venous invasion, and 33% had a positive margin for carcinoma. These results suggest that node-positive invasive intraductal papillary mucinous neoplasms appear to be in an advanced stage. Thus, resection with lymphadenectomy could not lead to a reduction in the incidence of recurrent disease. Further studies of adjuvant therapy combined with surgical resection are needed to achieve better survival results in invasive intraductal papillary mucinous neoplasm.

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Detail Histologic Analysis of Nerve Plexus Invasion in Invasive Ductal Carcinoma of the Pancreas and Its Prognostic Impact

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Abstract: Nerve plexus invasion is regarded as one of the most important prognostic factors in invasive ductal carcinoma (IDC) of the pancreas, though nerve plexus invasion has not been evaluated in terms of prognostic impact on the basis of detailed histologic investigation. The purpose of this study was to precisely examine morphologic characteristics of nerve plexus invasion and analyze its prognostic predictive power compared with the well-known prognostic parameters of pancreatic IDCs. The outcome and histologic features of 75 patients with pancreatic IDC in the pancreas head were investigated, and 422 lesions of nerve plexus invasion were evaluated. Tumor cells invading nerve plexus showed a duct-forming differentiated feature and predominantly existed in the perineurium and perineural space. Multivariate analyses revealed that the important prognostic factors, in addition to invasive tumor size and tumor necrosis, were at long distances from nerve plexus invasion to pancreatic capsule and perineural invasion in nerve plexus invasion.

Key Words: nerve plexus invasion, pancreatic cancer, perineural space, nerve bundle, perineurium, neural invasion

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Pancreatic nerves converge outside pancreatic parenchyma and form a pancreatic nerve plexus.[25] The pancreatic nerve plexus was classified into the plexus pancreaticus capitalis, branching to pancreas head,[25–27] and the splenic plexus, branching to pancreas body and tail.[1,14] Pancreatic invasive ductal carcinoma (IDC) shows continuous spreading via neural routes.[16] Nerve invasion in pancreatic IDC was classified into intrapancreatic nerve invasion and pancreatic nerve plexus invasion (plx-inv), according to the position on pancreatic neural route.[10] Previous studies reported that intrapancreatic nerve invasion and plx-inv were observed in 90% to 100% and 69% to 81% of pancreatic IDC, and they emphasized the prognostic impact of plx-inv.[17,18] In our previous study,[15] plx-inv was found in 35% of IDCs of the pancreas and was the important prognostic factor, whereas intrapancreatic neural invasion, which was observed in approximately 100%, was not a prognostic factor. We hypothesized that nerve invasion was a common invasion behavior in pancreatic IDC and the level of nerve invasion correlated with survival period. The size of the cancer gland at neural invasion and the diameter of the invaded nerve reportedly had a prognostic impact on prostate cancer[13] and in oral squamous cell cancer.[4] Despite the high frequency of plx-inv in pancreatic IDCs, there are no systematic clinicopathologic studies investigating the detail histologic analysis and its prognostic impact of plx-inv. To identify a useful prognostic factor showing the malignant degree of nerve invasion, we planned to investigate the morphologic details of plx-inv.

The purpose of this study was to examine the histologic characteristics of plx-inv in IDC of the pancreas head in detail and further evaluate the prognostic value in patients with pancreatic IDC.

MATERIALS AND METHODS

Patients

Between September 1992 and January 2004, 75 patients who received a curative pancreaticoduodenectomy at our institution with a pathologic diagnose of pancreatic IDC were investigated. The median patient age was 65 years, where 32 patients were women. None of the patients received neo-adjuvant therapy before their initial operation. Regional lymph node dissection was performed in all patients, and portal vein resections were done in 34 patients. None of the 75 patients received adjuvant treatment.

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Histologic Examination

The resected specimens were fixed in 10% formalin at room temperature, and the size and gross appearance of the tumors were recorded. The specimens obtained through pancreaticoduodenectomy were sectioned along the long axis of the plexus pancreaticus capitalis[10,25–27] to precisely measure the distance of plx-inv (Figs. 1A–E). The entire tumor was sectioned at intervals of 0.5 to 0.7 cm, and all the tumor-containing sections were routinely processed and embedded in paraffin histologic examination. Serial sections (3 μm) of each tumor were cut. One section was stained with hematoxylin and eosin, and then examined pathologically to confirm the diagnosis.

One investigator (S.M.) assessed all the histologic parameters in this study, and another author (T.H.) identified the histologic characteristics of IDC to confirm the tumor cell characteristics assessed by S.M. Whenever a discrepancy occurred, both investigators reexamined the slides to reach a consensus.

Definition of plx-inv Evaluation

Criteria of plx-inv in this study were defined as follows: (A) nerve invasion at the plexus pancreaticus capitalis and (B) nerve invasion with isolation from main tumor and pancreatic tissue. Although perineural invasion was regarded as morphologic characteristics of nerve invasion in pancreatic IDC, intraneural IDC reportedly invaded another neural component, the nerve bundle.[9] The pancreatic nerve consisted of a nerve bundle, perineural space, perineurium, and epineurium.[2,5,12,21] In this study, the following 3 structures were evaluated: (1) nerve bundle where myelinated and unmyelinated nerve fibers consisting of an axon, Schwann cell, and endoneurium; (2) perineurium, which was one or several layers forming continuous epithelioid sheets consisting of spindle-shaped and flattened cells; and (3) perineural space, the internal space between nerve bundle and perineurium (Figs. 2A, B). On the basis of the above nerve structure definitions, IDC position in invaded nerves was classified into the following 3 categories: (1) nerve bundle invasion, and cancer cells clearly invading or irregularly compressed nerve bundles (Figs. 2C, D); (2) perineural space invasion, cancer cells existed in perineural space, and not showing any evidence of nerve bundle invasion (Figs. 2E, F); and (3) neurium invasion, cancer cells existed outer from perineural space, and attached to perineurium (Figs. 2G, H).

Parameters in the plx-inv Findings

Eight histopathologic parameters were evaluated in each of plx-inv, and are summarized in Table 1. The intraneural sites of IDCs in invaded nerves were morphologically evaluated as (1) predominant site, (2) deepest site, and (3) number of invaded sites. According to WHO classification[8] (4) predominant differentiation of IDCs in plx-inv was evaluated. (5) Nerve thickness and (6) cancer thickness were measured at plx-inv. (7) Distance from plx-inv to main tumor and (8) to pancreatic capsule were measured from the midpoint of short axis of nerve bundle in a plx-inv to the nearest main tumor and to the nearest pancreatic capsule. Pancreatic capsule was defined as the dense fibrotic layer outside the pancreas (Fig. 1D)

Parameters of plx-inv in Survival Analysis

The 9 parameters of plx-inv in each patient used for survival analysis were summarized in Table 1. (1) Predominant mode per patient, (2) deepest mode per patient, and (3) number of invaded mode per patient were evaluated as the most frequently observed predominant site of IDCs, deepest site of IDCs, and number of invaded sites of plx-inv in a patient. (4) Predominant differentiation per patient was defined as the most frequently observed differentiation of IDC of plx-inv in a patient. To analyze nerve thickness, cancer thickness, distance to main tumor and distance to pancreatic capsule in a patient, the actual values were evaluated based on amount beyond median value in 50% or more of plx-invs. Subsequently, the following 4 factors were categorized into low (< median) and high (≥ median, which was calculated on the data of 422 plx-invs): (5) nerve thickness per patient, (6) cancer thickness per patient, (7) distance to main tumor per patient, and (8) distance to pancreatic capsule per patient.

Clinicopathologic Parameters

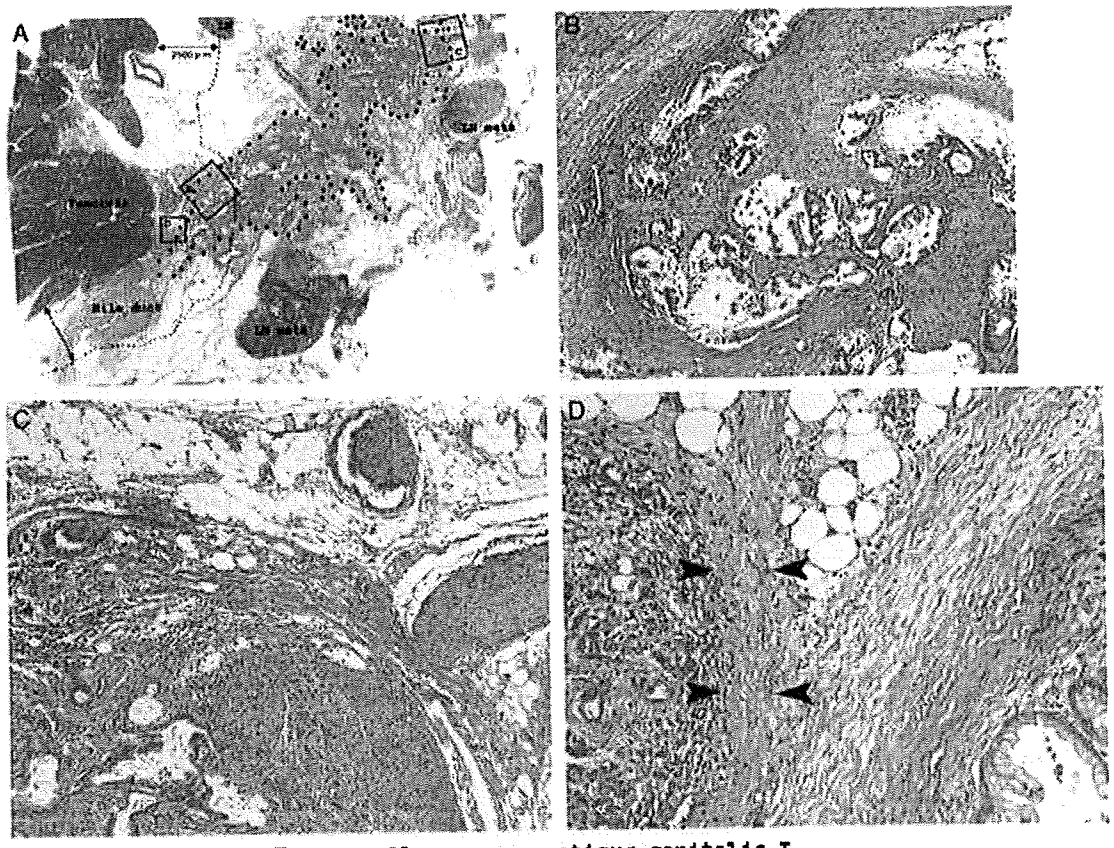
Our previous report[15] precisely described the methods of the evaluation for the histologic parameters in this study. Fourteen histologic parameters were evaluated in this study according to WHO,[8] UICC,[22] and the Japan Pancreas Society[10] as follows: (a) invasive tumor size, (b) predominant differentiation, (c) least differentiation, (d) retroperitoneal invasion, (e) lymph vessel invasion, (f) blood vessel invasion, (g) intrapancreatic neural invasion, (h) UICC pT, (i) UICC pN, (j) UICC pStage, (k) tumor necrosis,[15,19] (l) fibrotic focus,[15,24] (m) portal vein invasion, and (n) portal vein resection.

Outcome

Seventy-five patients were followed for survival, and the follow-up period was calculated from the date of surgery until November 29, 2004. The median follow-up period was 1755 days (95% CI: 1566–2213). Overall, 62 patients died of their disease within the follow-up period.

Statistical Analysis

In a factor having 3 or more categories, for example predominant mode per patient, significant difference of survival between each categorical group was examined by Cox regression hazard model[7] between nerve bundle invasion and perineural space invasion, and between perineural space invasion and neurium invasion. These parameters were classified into 2 groups according to the most prognostic cut off that showed the most significant impact on survival in univariate analyses (data not shown). The reference arm in univariate analysis for plx-inv was the group without plx-inv. The cut off of actual data was determined as median value.



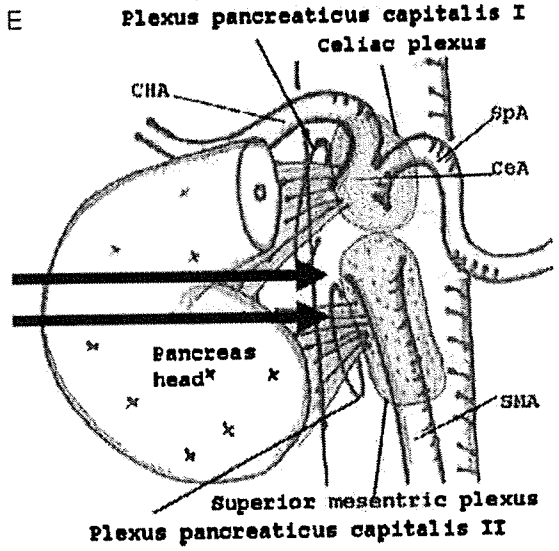


FIGURE 1. Shown is the demonstrable plexus invasion, a distance of 2500 μm from the pancreatic capsule, and the schema of nerve plexus network in the pancreas head. A Massive plexus invasion continuously existed in the plexus pancreaticus capitalis II (the area surrounded by the bold dots). A, distance of 2500 μm from the pancreatic capsule is shown (broken line). The right side of the nerve plexus was in close approximation to the superior mesenteric ganglion (the digital processed image using an objective lens magnification of 5 ×). B, The left side of plexus invasion near the pancreas (at an objective lens magnification of 4 ×). C, The right side of plexus invasion near the superior mesenteric ganglion (at an objective lens magnification of 4 ×). D, The densest layer of pancreatic capsule (at an objective lens magnification of 4 ×). E, Pancreatic nerves in pancreas head converge on plexus pancreaticus capitalis I or II, and achieve celiac plexus or superior mesenteric plexus. The pancreas head is sectioned approximately along the long axis of plexus pancreaticus capitalis (bold arrow). Ao indicates abdominal aorta; CeA, celiac artery; CHA, common hepatic artery; SpA, splenic artery; SMA, superior mesenteric artery.

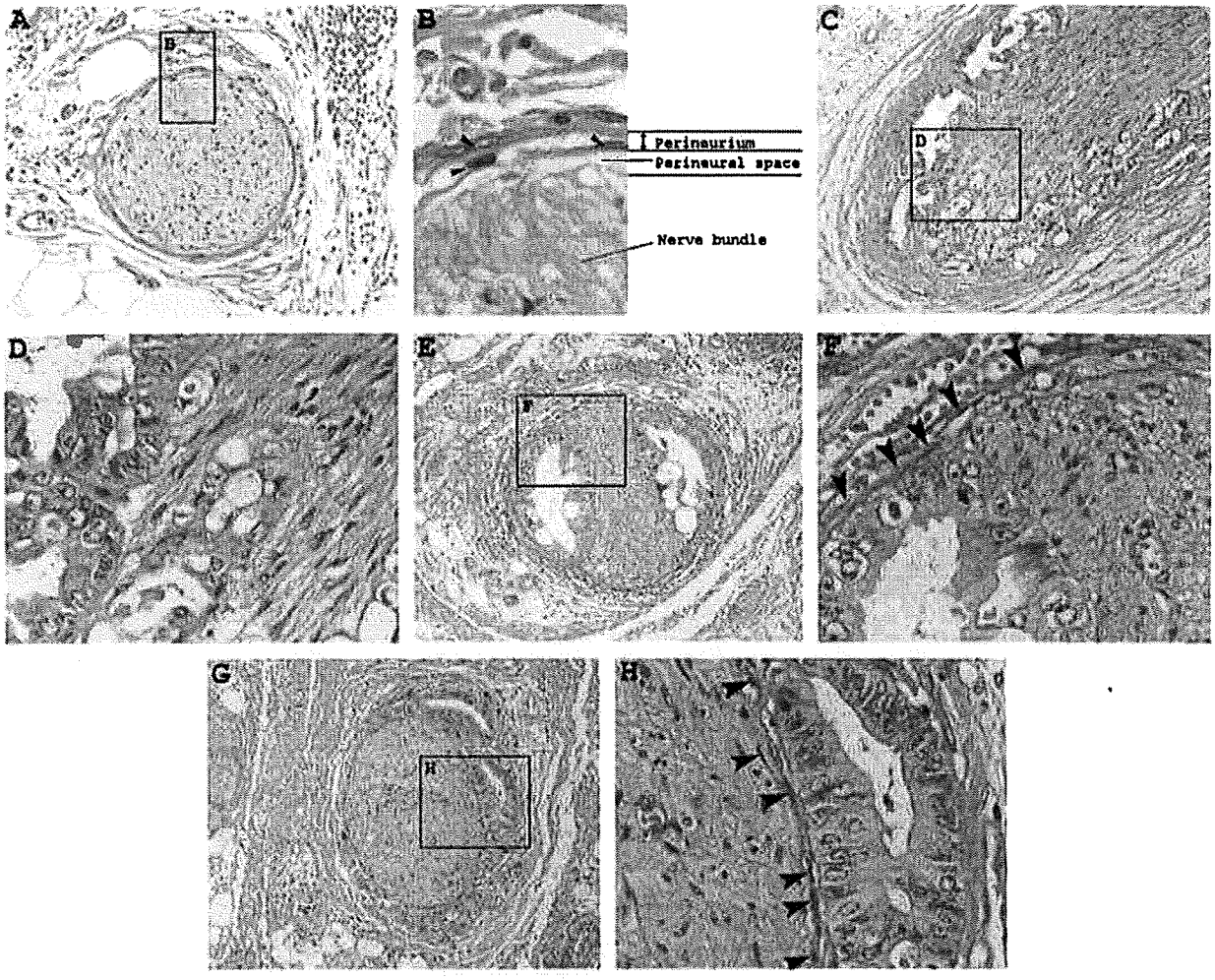


FIGURE 2. The structures of nerve (A, B) and the invaded neural structure classification (C–H). A, A nerve bundle was surrounded by the continuous layer like epithelioid sheets called the perineurium (at an objective lens magnification of 10 ×). B, Perineurium was one or several layers of continuous epithelioid sheets consisting of spindle shaped and flattened cells, called the perineurial cell (arrow head). The internal space between nerve bundle and perineurium was perineural space (at an objective lens magnification of 40 ×). C, Cancer cells clearly invaded the nerve bundle termed nerve bundle invasion. Cancer cells irregularly compressed the nerve bundle, and as seen on the left side, clearly invaded between nerve fibers (at an objective lens magnification of 10 ×). D, Invasive cancer cells clearly seen between nerve fibers. Cancer cells in nerve fibers tended to acquire low differentiation (at an objective lens magnification of 40 ×). E, Perineural space invasion seen as cancer cells in the perineural space. Almost all the cancer glands in perineural space invasion showed well-defined glandular shapes along the perineural space (at an objective lens magnification of 10 ×). F, Cancer glands invading the perineural space compressed the nerve bundle smoothly. The border between cancer cells and nerve bundles did not contain perineurial cells or perineurium. Perineurial cells (arrow head) consisting of perineurium are seen located at the outer aspect of the cancer gland (at an objective lens magnification of 40 ×). G, Neurium invasion was seen as cancer cells in the outer perineural space and attached to perineurium. Cancer glands in neurium invasion kept the well-defined glandular shape, and did not compress nerve bundle (at an objective lens magnification of 10 ×). H, Well-differentiated cancer cells in neurium invasion. Perineurial cells (arrow head) consisting of perineurium were between the nerve bundle and cancer gland (at an objective lens magnification of 40 ×).

The predictive parameters for survival in univariate analyses were analyzed in multivariate analyses using the Cox proportional hazard regression model. This initial multivariate analysis was performed and dealt only with plx-inv parameters or histologic parameters. The prognostic parameters in the initial multivariate analysis were analyzed together in multivariate analysis again to identify the strongest prognostic parameters. Overall survival curves were drawn using the Kaplan-Meier method.[11] Noncategorical data were compared using Mann-Whitney U test. All P values were 2-sided, and the significance level was set at $P < 0.05$. All analyses were performed using the Statview-J 5.0 package, Windows version (SAS, Inc, Cary, NC).

TABLE 1. The Explanation of Parameters to Evaluate the Morphologic Characteristic of Nerve Plx-Inv and Its Prognostic Impact in IDC of the Pancreas

No.	Parameters	Meanings	Variables
Parameters in the findings of plx-inv			
1	Predominant site	The predominant site of plx-inv	nb/pn/neu
2	Deepest site	The deepest site of plx-inv from outer of nerve	nb/pn/neu
3	Number of invaded sites	The numbers of sites of plx-inv	1/2/3
4	Predominant differentiation	Predominant differentiation of IDC in a plx-inv	wel/mod/por
5	Nerve thickness	Short axis of nerve bundle in a plx-inv	Actual (μm)
6	Cancer thickness	Short axis of IDC gland in a plx-inv	Actual (μm)
7	Distance to main tumor	The distance from plx-inv to the nearest main tumor	Actual (μm)
8	Distance to pancreatic capsule	The distance from plx-inv to the nearest pancreatic capsule	Actual (μm)
Parameters of plx-inv in survival analysis			
1	Predominant mode per patient	The most frequently observed predominant site of plx-inv in a patient	nb/pn/neu
2	Deepest mode per patient	The most frequently observed deepest site of plx-inv in a patient	nb/pn/neu
3	Number of invaded mode per patient	The most frequently observed number of sites of plx-inv in a patient	1/2/3
4	Predominant differentiation per patient	The most frequently observed predominant differentiation of IDC in a patient	Wel/mod/por
5	Nerve thickness per patient	Determination whether short axis of nerve bundle in 50% or more of plx-invs was beyond median value or not in a patient	Low/high
6	Cancer thickness per patient	Determination whether short axis of IDC gland in 50% or more of plx-invs was beyond median value or not in a patient	Low/high
7	Distance to main tumor per patient	Determination whether the distance from plx-inv to the nearest main tumor in 50% or more of plx-invs was beyond median value or not in a patient	Low/high
8	Distance to pancreatic capsule per patient	Determination whether the distance from plx-inv to the nearest pancreatic capsule in 50% or more of plx-invs was beyond median value or not in a patient	Low/high
9	Number of plx-inv	Determination whether the number of plx-inv was beyond median value or not in a patient	Low/high

mod indicates moderate differentiated; nb, nerve bundle invasion; neu, neurium invasion; pn, perineural invasion; por, poorly differentiated; wel, well differentiated.

RESULTS

Characteristics of Nerve Plx-Inv Foci

Plx-inv was found in 49 patients (65%). Of all the tumors from these 49 patients, 129 sections contained plx-inv (mean 2.7 ± 1.9 sections per patient). Total and median numbers of plx-inv were 422 and 6. Table 2 shows the morphologic characteristics of plx-inv. Predominant site of plx-inv was observed at perineural space invasion in 34%, at neurium invasion in 48%, and at nerve bundle invasion in 18%. The deepest site of plx-inv was detected evenly in the nerve structures (nerve bundle invasion 35%, perineural space invasion 27%, neurium invasion 38%). Eighty-six percent of IDCs in plx-inv maintained the ductal structure (well differentiation 58%, moderate differentiation 28%), and poorly differentiated IDC was found in 14%. Nerve thickness (thickness of invaded nerve) and the median cancer thickness in plx-inv were 125 and 100 μm, respectively. The median value of the distance from plx-inv to main tumor or pancreatic capsule was 2500 μm.

Survival Outcome

Median survival time in the group without plx-inv, with plx-inv, and all patients were 707, 371, and 400 days, respectively (overall survival curve is shown in Fig. 3A).

Univariate and Multivariate Analyses in Parameters of Nerve Plx-Inv and Orthodox Factors to Identify Important Prognostic Factors

Nine parameters dealing with plx-inv possessed the potential prognostic factors with univariate analysis

TABLE 2. Characteristics of Nerve Plexus Invasion in the Patients Who Received Macroscopic Curative Pancreaticoduodenectomy for IDC of the Pancreas

No.	Parameter	Value
1	Predominant site [plx n.(%)] nb/pn/neu	77(18)/143(34)/202(48)
2	Deepest site [plx n.(%)] nb/pn/neu	147(35)/114(27)/161(38)
3	Number of invaded sites [plx n.(%)] 1/2/3	208(49)/134(32)/80(19)
4	Predominant differentiation [plx n.(%)] well/mod/por	247(58)/119(28)/56(14)
5	Nerve thickness (μm) median (95%CI)	125 (125-150)
6	Cancer thickness (μm) median (95%CI)	100 (87.5-100)
7	Distance to main tumor (μm) median (95%CI)	2500 (2250-2625)
8	Distance to pancreatic capsule (μm) median (95%CI)	2500 (2200-2750)

CI indicates confidential interval; mod, moderately differentiated; nb, nerve bundle invasion; neu, neurium invasion; Plx n, the number of the invaded nerve plexus; pn, perineural space invasion; por, poorly differentiated; well, well differentiated.

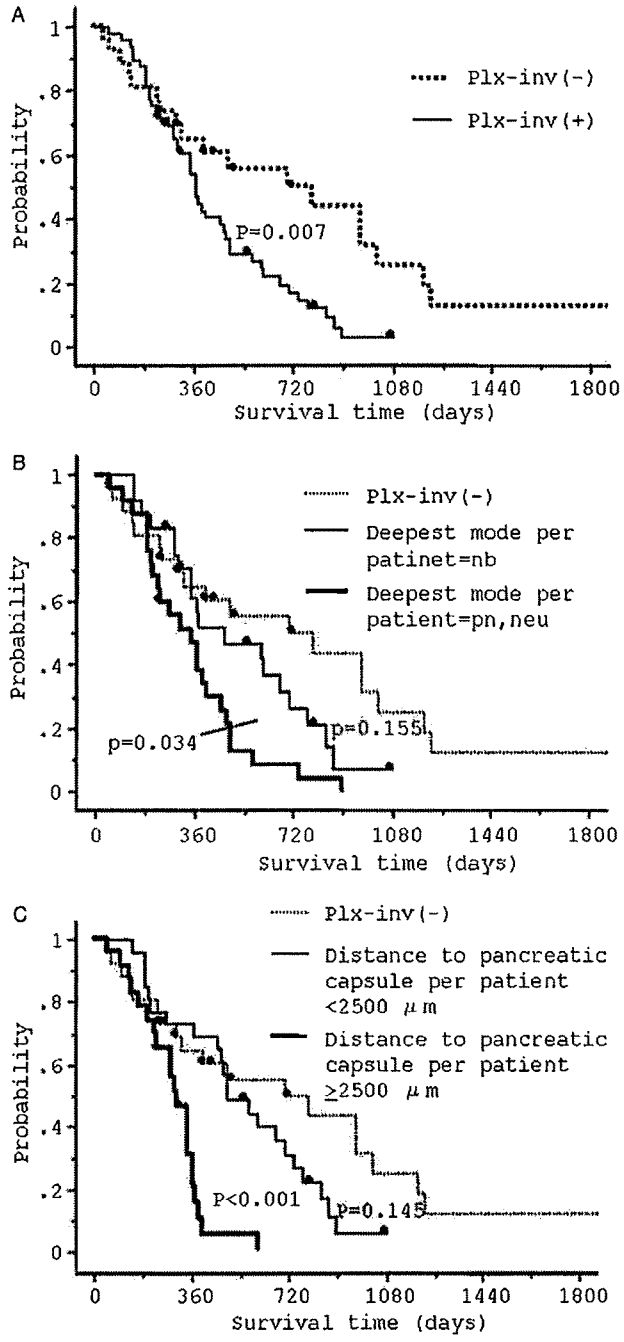


FIGURE 3. The overall survival curves according to the important factors of nerve plexus invasion (plx-inv) in all patients. A, Overall survival curves with or without plx-inv. The patients with nerve plx-inv showed a significantly poor prognosis. B, Survival curves according to deepest mode of plx-inv per patient. The developed manner of plx-inv without nerve bundle invasion significantly influenced poor prognosis. C, Survival curves according to distance from plx-inv to pancreatic capsule per patient. The patients in which plx-inv was predominantly 2500 μm or more away from pancreatic capsule showed a significantly poor prognosis. nb indicates nerve bundle invasion; pn, perineural space invasion; neu, neurium invasion.

(Table 3). Multivariate analysis-revealed independent prognostic factors among the parameters of plx-inv were perineural space invasion or neurium invasion in deepest mode per patient and distance to pancreatic capsule per patient (Table 3, and overall survival curves are shown in

TABLE 3. Univariate and Multivariate Analyses Using the Factors of Nerve Plexus Invasion in the Patients who Underwent Macroscopic Curative Pancreaticoduodenectomy for IDC of the Pancreas

No.	Parameter	n	Death (%)	HR	95% CI	P
Univariate analysis						
	Nerve plexus invasion					
	Absent	26	19 (73)	ref		ref
	Present	49	43 (88)	2.2	1.2-4.1	0.009
1	Predominant mode per patient					
	nb	7	5 (71)	1.5	0.5-4.1	0.469
	pn, neu*	42	38 (90)	2.4	1.3-4.5	0.005
2	Deepest mode per patient					
	Nb	24	19 (79)	1.7	0.9-3.4	0.126
	pn, neu*	25	24 (96)	3.2	1.6-6.3	< 0.001
3	Number of invaded mode per patient					
	< 3	21	21 (100)	2.2	1.1-4.4	0.021
	≥ 3*	28	22 (79)	2.3	1.2-4.4	0.018
4	Predominant differentiation per patient					
	Well	28	23 (82)	1.9	0.9-3.7	0.053
	Mod, por*	21	20 (95)	2.9	1.5-5.9	0.027
5	Nerve thickness per patient (μm)					
	< 125	17	16 (94)	1.8	0.9-3.7	0.103
	≥ 125*	32	27 (84)	2.6	1.4-5.0	0.004
6	Cancer thickness per patient (μm)					
	< 100*	25	23 (92)	2.6	1.3-5.1	0.005
	≥ 100	24	20 (83)	1.9	0.9-3.8	0.055
7	Distance to main tumor per patient (μm)					
	< 2500*	20	19 (95)	2.5	1.2-5.0	0.011
	≥ 2500	29	24 (83)	2.1	1.1-4.0	0.028
8	Distance to pancreatic capsule per patient (μm)					
	< 2500	26	22 (85)	1.6	0.8-3.2	0.149
	≥ 2500*	23	21 (91)	4.8	2.3-10.3	< 0.001
9	Numbers of plx-inv					
	< 6	22	20 (91)	2.1	1.1-4.2	0.030
	≥ 6*	27	23 (85)	2.3	1.2-4.5	0.012
Multivariate analysis						
2	Deepest mode per patient					
	pn, neu	25	24 (96)	2.1	1.2-3.7	< 0.001
8	Distance to pancreatic capsule per patient (μm)					
	≥ 2500	23	21 (91)	3.2	1.7-6.0	< 0.001

Univariate analysis was performed with cox regression hazard model referring to the patients without nerve plexus invasion (n = 26, deaths = 19). The factors with * at the end of a word were used for multivariate analysis in this table. Cox regression hazard model was used in multivariate analysis. Significant level was set at < 0.05.

CI, confidence interval; HR, hazard ratio; mod, moderately differentiated; nb, nerve bundle invasion; neu, neurium invasion; pn, perineural space invasion; por, poorly differentiated; well, well differentiated.

TABLE 4. Univariate and Multivariate Analyses Using the Factors of Main Tumor in the Patients Who Underwent Macroscopic Curative Pancreaticoduodenectomy for Invasive Ductal Carcinoma of the Pancreas

No.	Parameter	n	Deaths	HR	95% CI	P
Univariate analysis						
a	Invasive tumor size					
	≤3.0	38	27 (71)	ref		ref
	> 3.0*	37	35 (95)	2.7	1.6-4.6	< 0.001
b	Predominant differentiation					
	well, mod	65	52 (80)	ref		ref
	por	10	10 (100)	1.6	0.8-3.2	0.199
c	Lowest differentiation					
	well, mod	37	29 (78)	ref		ref
	por	38	33 (87)	1.0	0.6-1.7	0.907
d	Retroperitoneal invasion					
	0, 1	31	25 (81)	ref		ref
	2, 3	44	37 (84)	1.4	0.8-2.3	0.260
e	Lymph vessel invasion					
	0, 1	52	40 (77)	ref		ref
	2, 3*	23	22 (96)	1.8	1.0-3.0	0.038
f	Blood vessel invasion					
	0, 1	8	7 (88)	ref		ref
	2,3	67	55 (82)	1.9	0.9-4.2	0.111
g	Intrapancreatic neural invasion					
	0, 1	21	17 (81)	ref		ref
	2, 3	54	45 (83)	1.4	0.8-2.6	0.243
h	UICC pT					
	Pt3	71	58 (82)	ref		ref
	pT1, pT2	4	4 (100)	5.7	1.9-17.1	0.002
i	UICC pN					
	pN0	12	7 (58)	ref		ref
	pN1*	63	55 (87)	2.6	1.2-5.8	0.018
j	UICC pStage					
	IA, IB, IIA	15	10 (67)	ref		ref
	IIB, III, IV	60	52 (87)	1.8	0.9-3.6	0.095
k	Tumor necrosis					
	Absent	52	39 (75)	ref		ref
	Present*	23	23 (100)	2.2	1.3-3.7	0.004
l	Fibrotic focus					
	Absent	33	24 (73)	ref		ref
	Present	42	38 (90)	1.3	0.8-2.2	0.293
m	Portal vein invasion					
	Absent	57	48 (84)	ref		ref
	Present	18	14 (78)	1.1	0.6-1.9	0.863
n	Portal vein resection					
	Absent	41	35 (85)	ref		ref
	Present	34	27 (79)	0.7	0.4-1.2	0.152
Multivariate analysis						
a	Invasive tumor size					
	> 3.0	37	35 (95)	2.2	1.2-3.8	0.007
e	Lymph vessel invasion					
	2, 3	23	22 (96)	1.6	0.9-2.8	0.116
i	UICC pN					
	pN1	63	55 (87)	2.0	0.9-4.7	0.100
k	Tumor necrosis					
	Present	23	23 (100)	1.9	1.1-3.3	0.027

Univariate analysis was performed with cox regression hazard model. The factors with * at the end of a word were used for multivariate analysis in this table. Cox regression hazard model was used in multivariate analysis. Significant level was set at $P < 0.05$.

CI indicates confidence interval; HR, hazard ratio; mod, moderately differentiated; por, poorly differentiated; UICC, International union against cancer; well, well differentiated; 0, none; 1, slightly seen; 2, occasionally seen; 3, frequently seen.

TABLE 5. Multivariate Analysis Using the Important Factors of Nerve Plexus Invasion and Main Tumor in Patients Who Underwent Macroscopic Curative Pancreaticoduodenectomy for IDC of the Pancreas

Parameter	n	HR	95% CI	P
Distance to pancreatic capsule per patient				
≥ 2500 μm	23	2.8	1.5-5.3	0.001
Deepest mode per patient				
pn, neu	25	2.1	1.2-3.6	0.008
Invasive tumor size				
> 3.0 cm	48	2.3	1.3-3.9	0.004
Tumor necrosis				
Present	23	2.3	1.3-3.9	0.049

Cox regression hazard model was used in multivariate analysis. Significant level was set at $P < 0.05$.

CI indicates confidential interval; HR, hazard ratio; nb, nerve bundle invasion; neu, neurium invasion; pn, perineural space invasion.

Fig. 3B, C). With regard to histologic factors of main tumor, invasive tumor size and tumor necrosis possessed an independent predictive prognostic power (Table 4). Multivariate analysis of these four independent parameters showed their significant hazard ratio of death (Table 5). Invasive tumor size was recognized as the useful and powerful prognostic factor in oncology; however, the prognostic power of distance from plx-inv to pancreatic capsule exceeded that of invasive tumor size.

Distance to Pancreatic Capsule in the Groups Assigned by Deepest Site

To confirm the independence between the deepest invaded site of plx-inv and the distance from plx-inv to pancreatic capsule, 422 plx-inv were divided into nerve bundle invasion group or not, according to the deepest invaded site of plx-inv, and the distance from plx-inv to pancreatic capsule was compared between these 2 groups. These groups had similar values (nerve bundle invasion, n = 147, 2625 μm; perineural space invasion or neurium invasion, n = 275, 2250 μm) and were not significantly different ($P = 0.360$ in U test).

DISCUSSION

This study clearly demonstrates a long distance between nerve plx-inv and pancreatic capsule is very important in predictive prognosis of patients with pancreatic IDC. In addition, perineural space or neurium invasion as well as invasive tumor size and tumor necrosis are important prognostic factors. This is the first study to evaluate and quantify the morphologic detail and its prognostic impact in nerve invasion of pancreatic IDC.

Long distance (≥ 2500 μm) from plx-inv to pancreatic capsule is significantly associated with a shortened survival period. To discuss the relevance of the distance from plx-inv to pancreatic capsule, it is necessary to mention the relationship between pancreatic neural route, sectioning, and IDC nerve invasion. The nerve plexus of the pancreas head runs from the pancreas to celiac or

superior mesenteric plexus at approximately right angles from the abdominal aorta (Fig. 1A, E).[25–27] The resected specimen after a pancreaticoduodenectomy was sectioned at a right angle from the abdominal aorta.[10] Therefore, the sections are parallel to the nerve plexus route in the pancreas head. This directional alignment indicates the distance from plx-inv to pancreas approximates the extrapancreatic nerve length with invasion. As nerve invasion is continuous from the primary tumor,[20] this length is the developed distance of IDCs in the extrapancreatic nerve. On the basis of the above context, the developed distance of intraneural IDC is approximately equal to the distance from plx-inv to pancreatic capsule, and is considered to be an important prognostic factor. As this long distance of intraneural IDCs may correspond to the high capacity of tumor cells spreading in nerve, intraneural spreading ability of pancreatic IDC should be the focus of future studies. On the other hand, the distance to the main tumor is not a useful prognostic factor, and is considered insufficient when evaluating the developed distance of intraneural IDCs. Thus, the distance from the plx-inv should be assessed with respect to the pancreatic capsule and not the main tumor.

This study also demonstrates the significant prognostic effect of perineural space invasion or neurium invasion of tumor cells, but not nerve bundle invasion of the tumor cells. This result means that perineural invasion is an important prognostic factor. Perineural invasion is characteristic of nerve invasion in pancreatic IDC and its high prevalence is quantified in this study. The morphologic difference between nerve bundle invasion and perineural invasion is the disruption of nerve bundle owing to IDC invasion. According to Sunderland's[23] classification, which arranges peripheral nerve injuries in ascending order of severity from the first to the fifth degree corresponding to injury to myelin, axon, endoneurium, perineurium, and the entire nerve trunk, nerve bundle invasion (the third-degree injury) leads to more severe nerve damage than perineural invasion (the first to second-degree injury). Severe nerve damage results in poor nerve function,[23] and may change the interaction between IDC and nerve system. Anatomically, pancreatic nerve plexus is one of the pancreatic neural networks between pancreas and spine,[6] and connects each other through the nerve bundle. Nerve bundle invasion amputates this neural network, gives severe neural damage, and may lose tumor spreading acceleration via a neural network. On the other hand, perineural invasion leads to mild neural damage, is able to use functional neural network through the preservation of nerve bundle, and may result in local recurrence or other incidence.

Invasive tumor size and tumor necrosis were the important prognostic factors in our previous study,[15] and are reconfirmed in our current study. The distance from plx-inv to pancreatic capsule and perineural invasion shows the independent predictive prognostic power of invasive tumor size and tumor necrosis in multivariate analysis. Furthermore, there is no significant association between the 2 prognostic factors of plx-inv. Therefore, the prognostic value of the 2 plx-inv factors is validated in pancreatic IDC.

The determination of optimal section to evaluate plx-inv will be an important problem in the future. Careful tissue sectioning of pancreatic neural route is necessary considering the findings of this study. Anatomically, pancreatic neural route is elucidated in detail, and the determination of neural route sections may be useful when selecting optimal sections to evaluate plx-inv. The current data are the result of evaluations of entire tumor sections. Thus, the confirmation of the above hypothesis needs further study.

Although the mechanism of plx-inv is still unknown, the 2 prognostic parameters of plx-inv indicate that perineural development ability of tumor cell are worthy of further study of pancreatic IDC. An electron microscopic study reported that perineural pancreatic IDC attaches endoneurium and perineurium.[3] It is speculated that intraneural extracellular matrix is associated with perineural IDCs. Neural extracellular matrix might accelerate motility and/or proliferation of IDCs in the nerve, resulting in high ability of perineural development in pancreatic IDC. The ability of perineural development should be the focus for further study of pancreatic IDC.

In conclusion, 2 prognostic parameters in plx-inv for pancreatic IDC were revealed in this study: (1) the distance from plx-inv to pancreatic capsule was 2500 μm or more and (2) the invasive mode of tumor cells in nerve bundles. These results indicate that the long distance between intraneural IDCs and perineural invasion are important invasive predictors in pancreatic IDC. Pathologists should keep these in mind, along with invasive tumor size and tumor necrosis, in routine histologic examination of pancreatic IDCs.

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CASE REPORT

Adenocarcinoma of the minor duodenal papilla with intraepithelial spread to the pancreatic duct

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Abstract It is extremely rare to encounter tumors arising exclusively in the minor duodenal papilla. We report a 60-year-old male patient with a polypoid type of adenocarcinoma of the minor papilla. Preoperative examinations, including computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP), suggested pancreas divisum and showed a series of stones in the dorsal pancreatic duct. The patient underwent subtotal stomach-preserving pancreaticoduodenectomy (SSpPD). On histology, an adenocarcinoma was located in the minor papilla, which was limited to the mucosa, without invasion of the duodenum, sphincter muscles of the minor papilla, or the underlying pancreas. The carcinoma cells, together with dysplastic and hyperplastic epithelium of the pancreatic duct, extended peripherally within the pancreatic duct. No cystic dilatation of the pancreatic duct was observed. The ventral pancreatic duct was short and narrow; there was evidence of chronic pancreatitis in the dorsal pancreas, whereas the ventral pancreas was almost normal, suggesting the existence of pancreas divisum. Although it is well known that adenocarcinoma of the duodenal papilla is sometimes accompanied by intraepithelial spread in the pancreatic duct, an adenocarcinoma arising in the minor papilla in this case with pancreas divisum was more extended than our thoughts.

Keywords Adenocarcinoma · Minor duodenal papilla · Intraepithelial spread · Pancreas divisum

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Introduction

Tumors of the minor duodenal papilla are rare. Most reported cases have been benign tumors, including carcinoid [12, 15, 19, 22, 23], somatostatinoma [3, 13, 20], adenoma [21], adenomyoma [4], and gangliocytic paraganglioma [11, 14]; only one case of adenocarcinoma has been previously reported [24]. Tumors in the minor papilla may be underestimated because of the difficulty in determining the origin of tumors that involve the papilla because the papilla may be overgrown even by small tumors, and the histological appearance of periampullary tumors is similar [1].

We present a case of primary adenocarcinoma of the minor duodenal papilla that exhibited wide intraepithelial spread in the pancreatic duct. Moreover, the existence of pancreas divisum was also suspected because of the distribution of pancreatitis on microscopic examination.

Clinical history

A 60-year-old male patient complained of transient abdominal pain for 2 months. His general practitioner performed gastroduodenoscopy and found a polypoid tumor of the duodenum. The patient was referred to the Department of Hepatobiliary Pancreatic Surgery at the National Cancer