

# Prognostic Factors in Patients With Recurrent Pancreatic Cancer: A Multicenter Database Analysis

KENEI FURUKAWA<sup>1</sup>, HIROAKI SHIBA<sup>1</sup>, RYOGA HAMURA<sup>1</sup>, KOICHIRO HARUKI<sup>1</sup>,  
YUKI FUJIWARA<sup>1</sup>, TERUYUKI USUBA<sup>2</sup>, YUKIO NAKABAYASHI<sup>3</sup>, TAKEYUKI MISAWA<sup>4</sup>,  
TOMOYOSHI OKAMOTO<sup>5</sup> and KATSUHIKO YANAGA<sup>1</sup>

<sup>1</sup>Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan;

<sup>2</sup>Department of Surgery, The Jikei University Katsushika Medical Center, Tokyo, Japan;

<sup>3</sup>Department of Surgery, The Kawaguchi Municipal Medical Center, Saitama, Japan;

<sup>4</sup>Department of Surgery, The Jikei University Kashiwa Hospital, Chiba, Japan;

<sup>5</sup>Department of Surgery, The Jikei University Daisan Hospital, Tokyo, Japan

**Abstract.** *Background/Aim:* The prognosis of pancreatic cancer remains poor with a high incidence of recurrence even after curative resection. The aim of this study was to investigate prognostic factors in patients with recurrent pancreatic cancer using the multicenter database. *Patients and Methods:* The subjects were 196 patients with recurrent pancreatic cancer who underwent resection between 2008 and 2015. We retrospectively investigated the relation between clinicopathological characteristics of the patients and overall survival from recurrence using univariate and multivariate analyses. *Results:* In univariate analysis, the positive lymphatic invasion ( $p=0.0240$ ), time to recurrence from resection <1 year ( $p<0.0001$ ), sites of recurrence except for local or lymph node ( $p=0.0273$ ), liver recurrence ( $p=0.0389$ ) and peritoneal recurrence ( $p<0.0001$ ) were significantly associated with poor overall survival from recurrence. In multivariate analysis, time to recurrence from resection <1 year ( $p<0.0001$ ) and peritoneal recurrence ( $p<0.0001$ ) were independently associated with poor overall survival from recurrence. *Conclusion:* Time to recurrence from resection <1 year and peritoneal recurrence were significant independent predictors of poor overall survival from recurrence in patients with recurrent pancreatic cancer.

Pancreatic cancer is currently the fourth leading cause of cancer death worldwide (1). Despite improvements in

*Correspondence to:* Kenei Furukawa, The Jikei University School of Medicine, 3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo 105-8461, Japan. Tel: +81 334331111 ext.3401, Fax: +81 334358677, e-mail: k-furukawa@jikei.ac.jp

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surgical techniques, chemotherapy and follow-up methodology, pancreatic cancer remains a fatal disease, with a global 5-year survival rate of less than 10% (1). The majority of patients with pancreatic cancer present with locally advanced or metastatic disease, and less than 20% of patients are fit for resection at the time of diagnosis (2). Surgical resection is still considered the only potentially curative treatment for pancreatic cancer, but approximately 80% of surgically resected pancreatic cancer recur within 5 years, and over 60% of patients develop recurrences within 2 years (3). Therefore, identifying poor prognostic factors that may predict the tumor recurrence and prognosis of patients is important for selecting appropriate treatment.

There have been reports identifying prognostic factors for pancreatic cancer (4), but most previous studies were based on surgically resected or heterogeneous unresectable including metastatic and recurrent pancreatic cancer. It is therefore worthy to identify prognostic factors in patients who developed recurrent pancreatic cancer.

Here, we retrospectively performed a prognostic factor analysis using a multicenter database in patients with recurrence after surgical resection for pancreatic cancer.

## Patients and Methods

Between 2008 and 2015, a total of 332 patients with pancreatic cancer underwent pancreatic resection at four university hospitals (The Jikei University Hospital, Katsushika Medical Center, Daisan Hospital and Kashiwa Hospital) and an associated facility (The Kawaguchi Municipal Medical Center). Of these, recurrence was observed in 236 patients. We excluded 40 patients from the analysis for the following reasons: 2 with anaplastic cancer and 38 due to lack of data. Finally, 196 patients were included in the final analysis.

Tumor-nodes-metastasis (TNM) staging was based on the eighth edition of the Union for International Cancer Control (UICC) (5). Postoperatively, the patients received adjuvant chemotherapy using

gemcitabine, S-1 or gemcitabine and intra-arterial transfusion of nafamostat mesylate (6), excluding the patients with poor performance status or those who refused treatment. Tumor recurrence was defined as newly detected local or distant metastatic tumors based on the findings of ultrasonography, computed tomography, or magnetic resonance imaging with or without increased serum carcinoembryonic antigen or carbohydrate antigen 19-9 (CA19-9) levels. When multiple sites of recurrence were detected simultaneously, each site was counted. For recurrence, chemotherapy or conversion to another chemotherapy were chosen based on performance status.

At first, we retrospectively investigated the relation between patient characteristics and overall survival from recurrence in patients with recurrent pancreatic cancer by univariate and multivariate analyses. The factors included age, gender, operative time, intraoperative blood loss, tumor position, tumor differentiation, lymphatic invasion, venous invasion, TNM classification, curability, time to recurrence from resection and sites of recurrence.

Next, we compared time to recurrence from resection  $\geq 1$  year and  $< 1$  year using the following factors: age, gender, operative time, intraoperative blood loss, tumor location, tumor differentiation, lymphatic invasion, venous invasion, neural invasion, TNM classification, curability and sites of recurrence. We then analyzed patient characteristics in relation to peritoneal recurrence using the following factors: age, gender, operative time, intraoperative blood loss, tumor location, tumor differentiation, lymphatic invasion, venous invasion, neural invasion, TNM classification, curability and time to recurrence from resection.

This study was approved by the Ethics Committee of the Jikei University School of Medicine (30-322).

**Statistical analysis.** The data were expressed as a mean  $\pm$  standard deviation (SD). Univariate analyses were performed using the log-rank test, non-paired *t*-test and Chi-square test. Multivariate analysis was performed using the Cox proportional regression model. Survival rates were calculated by the Kaplan-Meier method. All *p*-values were considered statistically significant when the associated probability was less than 0.05.

**Results**

**Patient characteristics and overall survival from recurrence by univariate and multivariate analyses.** Characteristics of the patients are summarized in Table I. Tables II and III list the relationship between patient characteristics and overall survival from recurrence in patients that underwent resection for pancreatic cancer. In univariate analysis, the positive lymphatic invasion ( $p=0.0240$ ), time to recurrence from resection  $< 1$  year ( $p<0.0001$ , Figure 1A), sites of recurrence except for local or lymph node ( $p=0.0273$ ), liver recurrence ( $p=0.0389$ ) and peritoneal recurrence ( $p<0.0001$ , Figure 1B) were significantly associated with poor overall survival from recurrence. In multivariate analysis, time to recurrence from resection  $< 1$  year ( $p<0.0001$ ) and peritoneal recurrence ( $p<0.0001$ ) were independently associated with poor overall survival from recurrence.

**Association between patient characteristics and time to recurrence from resection.** Table IV lists the association

Table I. Patient characteristics.

Factor	Median or number	Range or %
Age (years)	69.5	38-87
Gender		
Male	115	59%
Female	81	41%
Tumor location		
Pancreatic head	131	67%
Pancreatic body or tail	65	33%
Operative time (min)	462.5	150-992
Intraoperative blood loss (ml)	758	0-21,080
Tumor differentiation		
Well	61	31%
Moderately	122	62%
Poorly	13	7%
Lymphatic invasion		
Negative	47	24%
Positive	149	76%
Venous invasion		
Negative	72	37%
Positive	124	63%
Neural invasion		
Negative	34	17%
Positive	162	83%
TNM classification		
I	43	22%
II	114	58%
III	33	17%
IV	6	3%
Curability		
R0	149	76%
R1 or 2	47	24%
Time to recurrence from resection (year)		
$\geq 1$	66	34%
$< 1$	130	66%
Site of recurrence		
Local or lymph node	86	44%
Liver	66	34%
Peritoneum	32	16%
Lung	25	13%

TNM: Tumor-nodes-metastasis; R0: microscopic curative resection; R1: microscopic residual tumor; R2: macroscopic residual tumor.

between patient characteristics and time to recurrence from resection. In time to recurrence from resection  $< 1$ -year group, lymphatic invasion and liver recurrence were significantly more frequent than in those in time to recurrence from resection  $\geq 1$ -year group ( $p=0.0038$  and  $0.0085$ , respectively).

**Association between patient characteristics and peritoneal recurrence.** Table V lists the association between patient characteristics and peritoneal recurrence. In the peritoneal recurrence present group, intraoperative blood loss, well differentiated tumor and venous invasion were significantly more frequent than in those in the peritoneal recurrence absent group ( $p=0.0408$ ,  $0.0033$  and  $0.0211$ , respectively).

Table II. Univariate analysis of overall survival from recurrence for pancreatic cancer.

Factor	N	Overall survival from recurrence	
		Median (years)	p-Value
Age (years)			
≥70	97	0.48	0.5414
<70	99	0.55	
Gender			
Male	115	0.55	0.6372
Female	81	0.45	
Operative time (min)			
≥500	70	0.53	0.4859
<500	126	0.52	
Intraoperative blood loss (mL)			
≥1,000	76	0.43	0.0771
<1,000	120	0.59	
Tumor location			
Pancreatic head	131	0.45	0.0810
Pancreatic body or tail	65	0.57	
Tumor differentiation			
Well	61	0.67	0.1277
Moderately	122	0.45	
Poorly	13	0.51	
Lymphatic invasion			
Negative	47	0.60	0.0240
Positive	149	0.48	
Venous invasion			
Negative	72	0.47	0.4797
Positive	124	0.55	
Neural invasion			
Negative	34	0.38	0.2474
Positive	162	0.56	
TNM classification			
I or II	157	0.48	0.6078
III or IV	39	0.57	
Curability			
R0	149	0.55	0.2401
R1 or 2	47	0.39	
Time to recurrence from resection (year)			
≥1	66	0.89	<0.0001
<1	130	0.42	
Site of recurrence (Local or lymph node)			
Present	86	0.67	0.0273
Absent	110	0.41	
Site of recurrence (Liver)			
Present	66	0.40	0.0389
Absent	130	0.59	
Site of recurrence (Peritoneum)			
Present	32	0.33	<0.0001
Absent	164	0.57	
Site of recurrence (Lung)			
Present	25	0.77	0.5294
Absent	171	0.48	

TNM: Tumor-nodes-metastasis, R0: microscopic curative resection, R1: microscopic residual tumor, R2: macroscopic residual tumor.

Table III. Multivariate analysis of overall survival from recurrence for pancreatic cancer.

Factor	Odds ratio (95%CI)	p-Value
Lymphatic invasion (positive)	1.427 (0.938-2.172)	0.0970
Time to recurrence from resection (<1 year)	2.732 (1.817-4.108)	<0.0001
Site of recurrence (Local or lymph node)	1.227 (0.789-1.908)	0.3645
Site of recurrence (Liver)	1.422 (0.922-2.193)	0.1116
Site of recurrence (Peritoneum)	2.717 (1.649-4.476)	<0.0001

CI: Confidence interval.

### Discussion

We herein demonstrated that time to recurrence from resection <1 year and peritoneal recurrence were independently significant predictors of poor prognosis in patients with recurrence after resection for pancreatic cancer using a multicenter database. To the best of our knowledge, there were only two reports on prognostic factors in patients with recurrent pancreatic cancer. Sakamoto, *et al.* reported that the combination of neutrophil-to-lymphocyte ration (NLR) and serum CA19-9 level were independent prognostic factors in 66 patients with recurrent pancreatic cancer (7). Yamada, *et al.* reported that the performance status, invasion of lymph vessels, kind of treatment for recurrence and initial recurrence were independent significant risk factors for the survival time after recurrence in 85 patients who developed recurrence after curative surgery for pancreatic cancer (8).

Recurrence can develop at various sites including the locoregional area, liver, peritoneum and lung. The prognosis differs according to the site of recurrence because each type of recurrence is caused by different mechanisms and has its own specific characteristics (9). Kim, *et al.* reported that patients with peritoneal recurrence had the shortest survival and patients with lung recurrence had the longest survival (10). In the current study, patients with peritoneal recurrence had the shortest survival after recurrence.

Peritoneal recurrence is the most dismal type of recurrence in terms of symptoms and prognosis due to ascites and intestinal obstruction leading to abdominal distension (11, 12). Ariake, *et al.* reported that excessive blood loss, artery invasion, pancreatic nerve plexus invasion and histological grade 3 were risk factors for peritoneal recurrence (12). On the other hand, the current study interestingly showed that a well differentiated tumor was a risk factor for peritoneal recurrence, and an independent predictor for poor overall survival from recurrence. Our previous study reported that well tumor differentiation was an independent predictor for good disease-free and overall survival in patients who underwent pancreaticoduodenectomy for pancreatic cancer

Table IV. Association between patient characteristics and time to recurrence from resection.

Factor	Time to recurrence from resection		p-Value
	≥1 year (n=66)	<1 year (n=130)	
Age (years)	66.9±8.8	69.5±9.1	0.0543
Gender (Male:Female)	41:25	74:56	0.4849
Operative time (min)	475.1±131.9	459.5±133.6	0.4384
Intraoperative blood loss (ml)	1,212.5±1,251.3	1,207.7±2,001.4	0.9858
Tumor position (Pancreatic head:Pancreatic body or tail)	43:23	88:42	0.7210
Tumor differentiation (Well:Others)	24:42	37:93	0.2588
Lymphatic invasion (Negative:Positive)	24:42	23:107	0.0038
Venous invasion (Negative:Positive)	27:39	45:85	0.3877
Neural invasion (Negative:Positive)	12:54	22:108	0.8259
TNM classification (I or II:III or IV)	58:8	99:31	0.0520
Curability (R0:R1 or 2)	52:14	97:33	0.5179
Site of recurrence (Local or lymph node:Others)	35:31	51:79	0.0658
Site of recurrence (Liver:Others)	14:52	52:78	0.0085
Site of recurrence (Peritoneum:Others)	8:58	24:106	0.2564
Site of recurrence (Lung:Others)	8:58	17:113	0.8497

Mean±SD; TNM: Tumor-nodes-metastasis; R0: microscopic curative resection; R1: microscopic residual tumor; R2: macroscopic residual tumor.

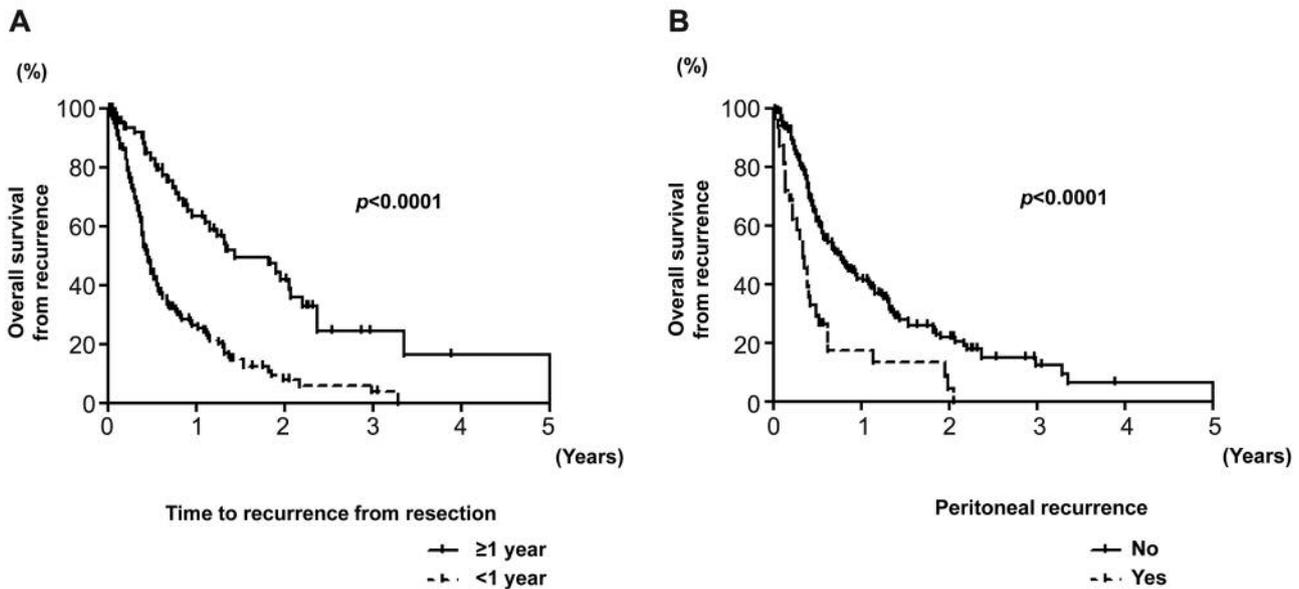


Figure 1. Kaplan-Meier curves of overall survival from recurrence in patients with time to recurrence from resection ≥1 and <1 year (A), and those with and without peritoneal recurrence (B).

(13), which could indicate that the prevention of the peritoneal recurrence in patients with a well differentiated tumor is important for better prognosis. Our multicenter database showed that overall survival rates at 1, 3 and 5-year were 85.3%, 60.0% and 47.1% in 77 patients with well differentiated pancreatic cancer without peritoneal recurrence.

*Nab*-paclitaxel plus gemcitabine is one of the standard first-line systemic chemotherapy regimens for patients with

metastatic pancreatic cancer (14). Paclitaxel has been shown to have a promising efficacy for gastric cancer with peritoneal metastasis (15), and *nab*-paclitaxel was more effective for peritoneal metastasis than paclitaxel in patients with advanced gastric cancer (16). Therefore, *nab*-paclitaxel plus gemcitabine as adjuvant chemotherapy may prevent peritoneal recurrence in patients with resected pancreatic cancer, resulting in better prognosis. A randomized

Table V. Association between patient characteristics and peritoneal recurrence.

Factor	Peritoneal recurrence		p-Value
	Present (n=32)	Absent (n=164)	
Age (years)	69.2±10.5	68.5±8.8	0.7230
Gender (Male:Female)	16:16	99:65	0.2760
Operative time (min)	446.3±160.5	468.3±127.1	0.3928
Intraoperative blood loss (ml)	1,797.6±3,684.4	1,094.5±1,063.7	0.0408
Tumor position (Pancreatic head:Pancreatic body or tail)	22:10	109:55	0.8016
Tumor differentiation (Well:Others)	17:15	44:120	0.0033
Lymphatic invasion (Negative:Positive)	7:25	40:124	0.7605
Venous invasion (Negative:Positive)	6:26	66:98	0.0211
Neural invasion (Negative:Positive)	6:26	28:136	0.8188
TNM classification (I or II:III or IV)	27:5	130:34	0.5080
Curability (R0:R1 or 2)	21:11	128:36	0.1321
Time to recurrence from resection (years)	0.84±0.72	1.04±0.91	0.2387

Mean±SD; TNM: Tumor-nodes-metastasis; R0: microscopic curative resection; R1: microscopic residual tumor; R2: macroscopic residual tumor.

controlled study of adjuvant *nab*-paclitaxel plus gemcitabine for resectable pancreatic cancer is now ongoing (17).

The current study had a retrospective and observational design. Furthermore, the detailed treatment for recurrence was not described due to lack of data. However, a unique strong point was that this was the first report analyzing prognostic factors for recurrent pancreatic cancer using a multicenter database.

In conclusion, time to recurrence from resection <1 year and peritoneal recurrence were the significant independent predictors of poor overall survival from recurrence in patients with recurrence after resection for pancreatic cancer.

### Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

### Authors' Contributions

Kenei Furukawa: Design of the study, collection and analysis of data and drafting of the article; Hiroaki Shiba: Revision of the article; Ryoga Hamura: Collection of data; Koichiro Haruki: Collection of data; Yuki Fujiwara: Collection of data; Teruyuki Usuba: Collection of data; Yukio Nakabayashi: Collection of data; Takeyuki Misawa: Collection of data; Tomoyoshi Okamoto: Collection of data; Katsuhiko Yanaga: Revision of the article and final approval of the article.

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