Because of the limited extent of operation and the lack of sufficient lymph node dissection, MP renders the operation noncurative for the patients suffering from invasive adenocarcinoma. Middle pancreatectomy is an adequate option only among patients with benign or low-grade malignant tumors of the pancreas or with pancreatic metastases from other tumors. The lesion and the resection margins should therefore be examined using frozen sections during the operation.[43] Such procedure may result in dissemination of cancer cells when the lesion in fact was adenocarcinoma. Thus, MP should not be considered when there is even a remote suspicion that the lesion may be adenocarcinoma. Fortunately, we came across no case of adenocarcinoma in the current series. The extent of resection in patients with benign cystic neoplasms, such as serous and mucinous cystadenomas, is dependent on the size of these lesions, as only a small segment of tumor free margin is necessary to prevent a recurrence.[44] Of the 26 patients in our series, only 1 with IPMC developed a tumor recurrence in the 68th postoperative month. In this patient, the intra-operative frozen sections did not suggest a malignancy, and the final diagnosis of adenocarcinoma was established only with paraffin-embedded tissue sections. Because MP is not considered an adequate oncologic procedure in ductal adenocarcinoma, the patient was carefully followed after informed consent and eventually underwent further operation. Thus far, 7 cases of tumor recurrence after MP have been reported in the literature for non-adenocarcinoma tumors of the pancreas (Table V). Because of insufficient data, one should refrain from routinely applying this technique to treat malignant primary pancreatic tumors at this time.

In conclusion, MP is a reasonable technique in experienced hands. It is indicated for selected patients with benign tumors or lesions of low malignant potential in the neck and body of the pancreas. Although the incidence of pancreatic fistula formation may be somewhat higher compared with traditional pancreatectomies, MP offers better preservation of exocrine and endocrine function, as well as good postoperative nutritional status.

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Prognostic Factors for Survival After Extended Pancreatectomy for Pancreatic Head Cancer

Influence of Resection Margin Status on Survival

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Objectives: Although a positive resection margin has been reported to be a strong prognostic factor after resection for pancreatic cancer, several studies indicated that resection status did not independently affect survival. The aim of this study was to examine the influence of resection margin status on survival after extended radical resection for pancreatic head cancer.

Methods: One hundred thirty-eight cases of pancreatoduodenectomy and 38 cases of pylorus-preserving pancreatoduodenectomy for invasive ductal carcinoma of the pancreas were retrospectively analyzed.

Results: The resection margins were negative (R0) in 115 patients (65.3%), microscopically positive (R1) in 38 patients (21.6%), and grossly positive (R2) in 23 patients (13.1%). Patients with R1 resection survived significantly shorter (median survival time [MST], 9.4 months) than R0 resection patients (MST, 15.2 months) but survived longer than R2 resection patients (MST, 6.2 months). By multivariate analysis, R2 resection, together with lymph node metastasis, portal venous system, and extrapancreatic nerve plexus invasions, independently affected the overall survival, but R1 resection was not significantly influential.

Conclusions: R2 resection was an independent predictor of poor prognosis after pancreatoduodenectomy/pylorus-preserving pancreatoduodenectomy, whereas R1 resection did not independently affect the survival.

Key Words: pancreatic cancer, pancreaticoduodenectomy, pancreatectomy, extended resection, resection status, margin

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Pancreatic cancer is one of the most difficult diseases to cure by surgical resection. According to the Japanese nationwide surveillance, 5-year survival of patients with cancer in the pancreatic head and body/tail after resection is only 13.0% and 18.2%, respectively.[1] The poor prognosis after resection is mainly due to the rapid progression of metastatic disease or local residual disease. Because pancreatic cancer, especially cancer in the pancreatic head, frequently invades the portal vein and the extrapancreatic nerve plexus, resection of the portal vein and dissection of the nerve plexus are often necessary to obtain a negative resection margin.[2,3]

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Our department has been performing extended radical resection, the so-called isolated pancreatectomy, as a standardized procedure for pancreatic head cancer with suspected portal vein invasion, with the goal of obtaining negative resection margins.[4] This procedure is characterized by a non-touch isolation technique consisting of mesenteric excision, extrapancreatic nerve plexus dissection, simultaneous resection of the superior mesenteric vein (SMV), and the portal vein, if necessary, using an antithrombogenic portal vein bypass catheter.[5]

The resection margin status has been reported to be a powerful pathologic predictor of survival after surgery in addition to the stage, grade, and size of tumor[6–11]; however, several reports have shown that resection status did not independently affect survival.[12–14] The purpose of this study was to examine the significance of resection margin status as a prognostic factor for survival among patients who underwent pancreatoduodenectomy (PD) or pylorus-preserving pancreatoduodenectomy (PPPD) for pancreatic cancer.

MATERIALS AND METHODS

From July 1981 to July 2007, three hundred forty-seven consecutive pancreatectomies were performed for pancreatic cancer at the Department of Surgery II, Nagoya University. There were 70 cases of total pancreatectomy, 62 cases of distal pancreatectomy, and 1 case of pancreatic head resection with segmental duodenectomy.[15] The remaining 214 cases underwent PD with or without pylorus preservation. Thirty-one surviving cases followed up for less than 3 years were excluded to minimize the censoring cases. One case of acinar cell carcinoma and 1 case of undifferentiated carcinoma, distinguished from the cases of invasive ductal carcinoma, were excluded from the analysis. Furthermore, 3 cases with hepatic metastasis and 2 cases with peritoneal dissemination were excluded from the analysis leaving 176 cases of invasive ductal carcinoma of the pancreas (138 cases of PD and 38 cases of PPPD) included in the present study. The cohort included 115 men and 61 women with a mean age of 63.1 years (range, 37–83 years). All patients were followed up for a mean of 20.6 months or until death.

Extended radical resection was performed for all cases in a standard fashion, as previously described.[4] In cases with portal vein invasion suspected after preoperative evaluations including contrast-enhanced computed tomography (CT) and/or transarterial portography, intraportal endovascular ultrasonography was performed to diagnose whether the cancer had invaded the portal vein.[16] As a result, simultaneous resection of the SMV and/or the portal vein was performed in 131 (74.4%) of the 176 patients. Combined resection with reconstruction of the hepatic artery was needed in 5 cases, and resection without reconstruction of the hepatic artery or the splenic artery was also performed in selected cases.

TABLE 1. Patient Demographics

Clinicopathologic Features	Value
Mean age (range), yr	63.1 (37–83)
Sex, M/F	115/61
Operative procedure	
PD (with portal vein resection)	138 (110)
PPPD (with portal vein resection)	38 (21)
Histopathologic diagnosis	
Tubular adenocarcinoma	
Well differentiated	21
Moderately differentiated	127
Poorly differentiated	11
Undetermined	4
Papillary adenocarcinoma	9
Anaplastic carcinoma	2
Mucinous carcinoma	1
Adenosquamous carcinoma	1
Stage (Union Internationale Contre le Cancer, 6th ed)	
IA	5
IB	3
IIA	40
IIB	80
III	14
IV	34
Resection margin status	
R0	115
R1	38
R2	23
Mortality (%)	5 (2.8)
Mean survival time (range), mo	20.6 (0.2–182)

Each resected specimen was formalin-fixed, serially sectioned parallel to the Kerckring fold line that passed through the aperture of the papilla of Vater at approximately 5-mm intervals by the attending surgeons, and then examined histopathologically by experienced pathologists after being stained with hematoxylin and eosin. A detailed description of the sliced specimens with photos or schemata was attached to the specimens to inform the pathologist about the orientation of the specimens. Pathologic findings were evaluated in accordance with the second English edition of the Classification of Pancreatic Carcinoma proposed by the Japan Pancreas Society (JPS).[17] The extent of local tumor spread was evaluated according to the tumor size and anterior pancreatic tissue (serosal), retropancreatic tissue, distal bile duct, duodenal, portal venous system, arterial system, extrapancreatic nerve plexus, and direct invasions to other organs by this classification scheme. The resection margin status of each case was defined as R0 when no cancer cells were identified microscopically at all of the pancreatic cut-end margin (pcm), the bile duct cut-end margin (bcm), and the dissected peripancreatic tissue margin (dpm). The dpm stands for dissected margin of anterior/retropancreatic tissue, the cut-end margin of extrapancreatic nerve plexus, and the medial margin of the head of pancreas. If cancer cells were recognized by the pathologists at any of these margins (clearance of 0 mm), the resection was deemed R1. R2, defined as macroscopically positive margin(s), was determined by the surgeons when gross cancerous tissue was exposed at the dissected margin(s), raising high suspicion of incomplete resection.

Intraoperative radiation therapy (IORT) was delivered using 30 Gy. Adjuvant chemotherapy included systemic administration of gemcitabine and/or *S*-1 and liver perfusion chemotherapy with 5-fluorouracil alone or in combination. Neither neoadjuvant chemotherapy nor extracorporeal radiation therapy was used.

The significance of correlations between the resection margin status and clinicopathologic features was studied with the Fisher exact test. The logistic regression was used to identify the factors that were independently associated with positive resection margins. Overall survival (OS) rates were estimated using the Kaplan-Meier method. The log-rank test was used to compare differences in survival curves. Potential prognostic factors, including age; sex; tumor size; anterior pancreatic tissue, retropancreatic tissue, bile duct, duodenal, portal venous system, arterial system, extrapancreatic nerve plexus, lymph vessel, venous, and perineural invasions; lymph node status; histological grade; use of adjuvant chemotherapy; intraoperative radiation therapy; and resection margin status were investigated for association with OS. The Cox proportional hazards regression model was used to identify independent prognostic factors. $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

One hundred thirty-eight patients underwent PD, and 38 patients underwent PPPD. Combined resection and reconstruction of the portal vein and/or SMV was performed in 110 PD cases and in 21 PPPD cases. Histopathologic diagnoses based on the classification by the JPS and conclusive stages according to the sixth edition of the Union Internationale Contre le Cancer classification of the 176 cases are shown in Table 1. One hundred sixty-three cases were diagnosed as tubular adenocarcinoma, 9 cases as papillary adenocarcinoma, and 4 cases as others (anaplastic carcinoma, 2; mucinous carcinoma, 1; and adenosquamous carcinoma, 1). Pathological stages according to the TNM classification were IA in 5 cases, IB in 3 cases, IIA in 40 cases, IIB in 80 cases, III in 14 cases, and IV in 34 cases. Operative death (within 30 days after surgery) occurred in 5 patients, giving a mortality rate of 2.8%. The resection margins were histologically negative (R0) in 115 patients (65.3%), histologically positive and macroscopically negative (R1) in 38 patients (21.6%), and macroscopically positive (R2) in 23 cases (13.1 %). Among the 38 cases of R1 resection, the pcm, bcm, and dpm were determined positive for cancer cells in 6, 5, and 29 cases, respectively. Regarding the 23 cases of R2 resection, pcm, bcm, and dpm were diagnosed as positive for cancerous tissue in 4, 0, and 20 cases, respectively.

Clinicopathologic Factors Associated With Positive Resection Margins

The demographic, operative, and pathologic characteristics of patients with negative resection margins (R0, n = 115) and positive resection margins (R1 and R2, n = 61) are shown in Table 2. Tumor size, invasion of cancer cells into the anterior pancreatic tissue, retropancreatic tissue, portal venous system, arterial system, extrapancreatic nerve plexus, lymph vessels, and lymph node metastasis were significantly associated with positive resection margins by Fisher exact test. Using logistic regression, we determined that nerve plexus invasion (odds ratio [OR], 6.14; 95% confidence interval [CI], 2.74–13.73), retropancreatic tissue invasion (OR, 3.00; 95% CI, 1.10–8.15), and

TABLE 2. Factors Associated With Positive Resection Margin (R1 + R2)

	No. Patients		Fisher Exact Test	Multivariate Analysis		
	R0 Resection	R1 + R2 Resections	*P*	OR	95% CI	*P*
Total patients	115	61				
Age						
≥60 yr	76	46	0.232			
<60 yr	39	15				
Sex						
M	77	38	0.618			
F	38	23				
Tumor size						
<2 cm	22	4	0.027*	1.24	0.29–5.26	0.768
≥2 cm	92	56				
Anterior pancreatic tissue invasion						
Negative	81	22	<0.001*	2.50	1.18–5.60	0.026*
Positive	34	39				
Retropancreatic tissue invasion						
Negative	53	7	<0.001*	3.00	1.10–8.15	0.032*
Positive	62	54				
Bile duct invasion						
Negative	32	16	0.861			
Positive	83	45				
Duodenal invasion						
Negative	54	22	0.201			
Positive	61	39				
Portal venous system invasion						
Negative	67	24	0.018*	1.07	0.48–2.38	0.878
Positive	48	37				
Arterial system invasion						
Negative	107	52	0.112			
Positive	8	9				
Extrapancreatic nerve plexus invasion						
Negative	97	23	<0.001*	6.14	2.74–13.73	<0.001*
Positive	18	38				
Lymph vessel invasion						
Negative	17	2	0.021*	1.10	0.17–7.11	0.919
Positive	95	56				
Venous invasion						
Negative	60	22	0.075			
Positive	52	36				
Perineural invasion						
Negative	20	5	0.114			
Positive	91	54				
Lymph node metastasis						
Negative	43	10	0.005*	1.87	0.71–4.98	0.208
Positive	72	51				
Histological differentiation						
Well/papillary	22	8	0.303			
Others	90	53				
Portal vein resection						
Yes	83	48	0.371			
No	32	13				

*Statistically significant.

TABLE 3. Factors Associated With Microscopically Positive Resection Margin (R1)

	No. Patients		Fisher Exact Test	Multivariate Analysis		
	R0 Resection	R1 Resection	*P*	OR	95% CI	*P*
Total patients	115	38				
Age						
≥60 yr	76	27	0.691			
<60 yr	39	11				
Sex						
M	77	22	0.332			
F	38	16				
Tumor size						
<2 cm	22	3	0.133			
≥2 cm	92	34				
Anterior pancreatic tissue invasion						
Negative	81	16	0.003*	2.25	0.93–5.43	0.072
Positive	34	22				
Retropancreatic tissue invasion						
Negative	53	6	0.001*	2.17	0.75–6.31	0.155
Positive	62	32				
Bile duct invasion						
Negative	32	11	1.000			
Positive	83	27				
Duodenal invasion						
Negative	54	14	0.347			
Positive	61	24				
Portal venous system invasion						
Negative	67	15	0.060			
Positive	48	23				
Arterial system invasion						
Negative	107	35	1.000			
Positive	8	3				
Extrapancreatic nerve plexus invasion						
Negative	97	14	<0.001*	7.17	3.01–17.12	<0.001*
Positive	18	24				
Lymph vessel invasion						
Negative	17	1	0.074			
Positive	95	35				
Venous invasion						
Negative	60	15	0.252			
Positive	52	21				
Perineural invasion						
Negative	20	4	0.320			
Positive	91	34				
Lymph node metastasis						
Negative	43	7	0.045*	1.82	0.65–5.13	0.258
Positive	72	31				
Histological differentiation						
Well/papillary	22	4	0.227			
Others	90	34				
Portal vein resection						
Yes	83	31	0.289			
No	32	7				

*Statistically significant.

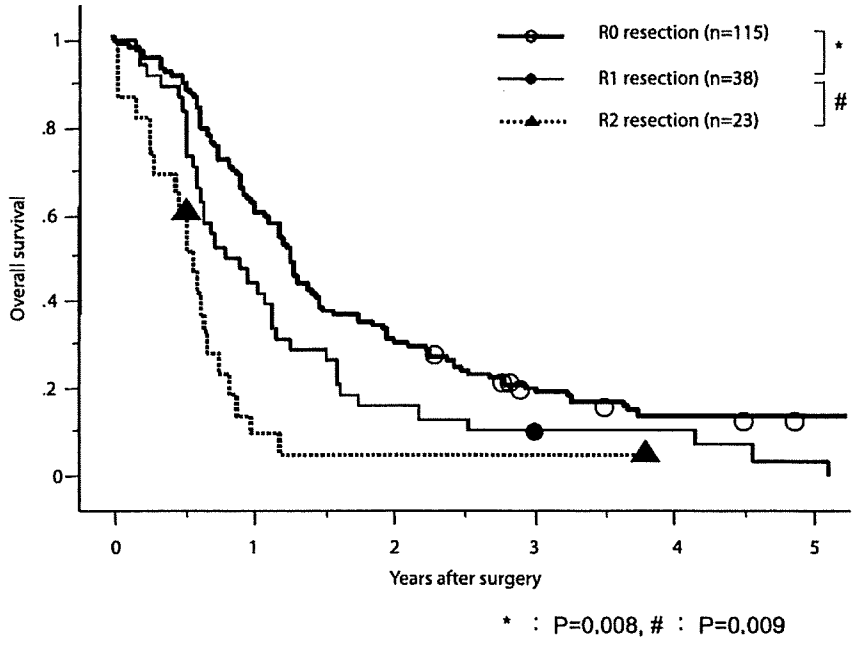

FIGURE 1. Comparison of OS curves for patients with pancreatic head cancer who underwent PD or PPPD according to the resection margin status. The median survival for 115 patients with R0 resection was 15.2 months, which was significantly longer ($P = 0.008$) than that for 38 patients with R1 resection (9.4 months). The median survival for 23 patients with R2 resection (6.2 months) was significantly shorter ($P = 0.009$) than that of R1 resection patients.

anterior pancreatic tissue invasion (OR, 2.50; 95% CI, 1.18–5.56) were independently associated with positive resection margins (Table 2). When patients with R2 resection were excluded from the analysis, only extrapancreatic nerve plexus invasion was independently associated with R1 resection (OR, 7.17; 95% CI, 3.01–17.21; Table 3).

Survival Analysis of Clinicopathologic Factors in Patients Who Underwent PD/PPPD for Pancreatic Head Cancer

The 1-year, 3-year, and 5-year OS rates of 176 patients were 51.5 %, 15.7 %, and 9.9 %, respectively, with a median OS time of 12.3 months. The median OS in patients with R0, R1, and R2 resections were 15.2 months, 9.4 months, and 6.2 months, respectively. The patients with R1 resection showed better OS compared with patients with R2 resection ($P = 0.009$) and worse OS than R0 resection patients ($P = 0.008$; Fig. 1). Univariate analysis of factors affecting OS showed that invasion of cancer cells into the anterior pancreatic tissue, retropancreatic tissue, bile duct, duodenum, portal venous system, arterial system, extrapancreatic nerve plexus, lymph vessels, blood vessels, and intrapancreatic nerves as well as lymph node metastasis, histological type (other than well-differentiated tubular adenocarcinoma and papillary adenocarcinoma), tumor size larger than 2 cm in diameter, and positive resection margins (either R1 or R2) were all associated with poor prognosis (Table 4). By multivariate analysis, lymph node metastasis (hazard ratio [HR], 1.77; 95% CI, 1.15–2.73), portal venous system invasion (HR, 1.53; 95% CI, 1.03–2.28), extrapancreatic nerve plexus invasion (HR, 1.54; 95% CI, 1.03–2.29), and R2 resection (HR, 3.52; 95% CI, 1.97–6.26) were identified as factors that independently affected OS (Table 5). When R1 resection was included as a covariate for analysis instead of R2 resection, R1 resection was not independently influential (HR, 0.97; 95% CI, 0.60–1.54). Lymph node metastasis (HR, 1.92; 95% CI, 1.21–3.05), portal venous system invasion (HR, 1.74; 95% CI, 1.13–2.70), and extrapancreatic nerve plexus invasion (HR, 1.61; 95% CI, 1.01–2.55) remained significant prognostic factors (Table 6).

DISCUSSION

Many reports have referred to clinicopathologic factors influencing survival after resection for pancreatic cancer.[6–14,18] Whether a positive resection margin independently affects survival has always been a matter of controversy.[12–14] The conflict may be due to the differences in the study design (ie, whether the cases with R2 resection were included or not) or in the system used for the pathologic examination of the resected specimens.[19] In the recent literature, Raut et al[14] reviewed published studies and reported that R1 rates and R1 + R2 rates were 17% to 85% and 17% to 45%, respectively.

In the present study, we evaluated the resection margin status both macroscopically and microscopically and then assigned the patients into R0, R1, and R2 resection categories. As a result, 115 (65.3 %) of the 176 patients were evaluated as R0 resection, whereas 38 patients (21.6%) were evaluated as R1, and 23 patients (13.1%) as R2 resection. These rates did not deviate from the previously reported R1/R1 + R2 rates. This means that complete resection was not achieved in one third of patients who underwent PD/PPPD, despite extended pancreatectomies accompanied by portal vein resection and extrapancreatic nerve plexus dissection being performed. As a high-volume center, several of our cases were referred from other hospitals after being deemed unresectable because of locally advanced disease. A high percentage of noncurative resection would therefore seem inevitable. Indeed, the condition of the 107 (60.8%) of the 176 patients was diagnosed as pT4 under the classification of the JPS[17] on the ground that cancer cells invaded into the portal venous system, arterial system, extrapancreatic nerve plexus, or adjacent organs, and the proportion of patients receiving portal venous resection was unusually high. Among other studies

TABLE 4. Univariate Analysis of Factors Affecting OS After Surgery in Patients With Pancreatic Head Cancer

	No. Patients	OS Rates (%) 1 YR	3 YR	5 YR	P
Total patients	176	51.5	15.7	9.9	
Age					
≥60 yr	122	50.5	14.1	8.5	0.318
<60 yr	54	53.7	19.9	13.7	
Sex					
M	115	53.0	16.9	10.1	0.438
F	61	48.5	13.4	9.7	
Tumor size					
<2 cm	26	80.8	38.1	28.6	<0.001*
≥2 cm	148	46.3	12.0	7.1	
Anterior pancreatic tissue invasion					
Negative	103	62.3	20.0	12.9	<0.001*
Positive	73	36.3	9.8	5.9	
Retropancreatic tissue invasion					
Negative	60	68.3	22.2	17.8	<0.001*
Positive	116	42.7	12.2	5.6	
Bile duct invasion					
Negative	48	58.3	26.8	21.1	0.041*
Positive	128	48.9	11.6	6.0	
Duodenal invasion					
Negative	76	57.4	20.9	13.9	0.019*
Positive	100	47.0	12.0	7.0	
Portal venous system invasion					
Negative	91	64.8	23.7	14.9	<0.001*
Positive	85	37.0	7.2	4.8	
Arterial system invasion					
Negative	159	54.5	16.8	11.2	0.049*
Positive	17	23.5	5.9	0	
Extrapancreatic nerve plexus invasion					
Negative	121	58.9	20.6	13.5	<0.001*
Positive	56	35.7	5.4	0	
Lymph vessel invasion					
Negative	19	88.9	36.7	30.6	<0.001*
Positive	151	46.4	12.6	7.1	
Venous invasion					
Negative	82	64.3	20.4	15.4	<0.001*
Positive	88	38.6	10.2	5.1	
Perineural invasion					
Negative	25	75.3	44.9	39.2	<0.001*
Positive	145	47.6	10.2	5.2	
Lymph node metastasis					
Negative	53	71.2	30.5	22.6	<0.001*
Positive	123	43.1	9.6	5.1	
Histological differentiation					
Well/papillary	30	82.8	40.5	30.9	<0.001*
Others	143	46.2	11.1	6.1	
Radiation therapy					
IORT (+)	112	50.0	10.5	5.6	0.098
IORT (−)	64	54.1	25.3	17.5	
Chemotherapy					
Yes	77	58.4	16.7	10.8	0.223
No	91	45.7	14.5	8.3	
Chemotherapy with gemcitabine					
Yes	34	47.1	17.6	17.6	0.724
No	142	52.6	15.4	9.2	
Resection margin status					
R0	115	61.7	19.5	13.2	0.008*
R1	38	44.7	10.5	3.5	
R2	23	9.4	4.7	—	0.009*

*Statistically significant.

looking at the issue of resection margin, the cohort analyzed in the current study can be characterized as including a high proportion of locally advanced and challenging cancer treated with an aggressive policy toward complete resection.

We next analyzed the association of clinicopathologic characteristics with resection margin status and found that extrapancreatic nerve plexus, anterior pancreatic tissue, and retropancreatic tissue invasions were independently associated with positive resection margins (R1 and R2), whereas only extrapancreatic nerve plexus invasion was found to independently associate with R1 resection. Pancreatic head cancer often invades the extrapancreatic nerve plexus.[20,21] Indeed, 56 (31.8%) of the 176 patients in our series had microscopic invasion of cancer cells into the nerve plexus. Preoperative diagnosis of extrapancreatic nerve plexus invasion remains challenging, although the detection of soft tissue density behind the SMV or adjacent to the superior mesenteric artery (SMA) with multi–detector row CT may be a clue to its diagnosis.[22] Intraportal endovascular ultrasonography has been used to

TABLE 5. Multivariate Analysis of Factors Affecting OS After Surgery in Patients With Pancreatic Head Cancer (R2 Resection Was Included as a Covariate)

Covariate	HR	95% CI	P
Tumor size (≥2 cm)	1.21	0.66–2.21	0.531
Anterior pancreatic tissue invasion	0.98	0.66–1.46	0.912
Retropancreatic tissue invasion	1.06	0.71–1.58	0.785
Bile duct invasion	1.06	0.70–1.61	0.785
Duodenal invasion	1.29	0.84–1.98	0.247
Portal venous system invasion	1.53	1.03–2.28	0.035*
Arterial system invasion	0.76	0.40–1.47	0.420
Extrapancreatic nerve plexus invasion	1.54	1.03–2.29	0.034*
Lymph vessel invasion	0.97	0.48–1.96	0.930
Venous invasion	1.05	0.71–1.56	0.810
Perineural invasion	1.69	0.86–3.34	0.131
Lymph node metastasis	1.77	1.15–2.73	0.010*
Histological grade of differentiation†	1.60	0.95–2.69	0.076
Macroscopically positive margin; R2	3.52	1.97–6.26	<0.001*

*Statistically significant.

†Other than well-differentiated tubular adenocarcinoma and papillary adenocarcinoma.

TABLE 6. Multivariate Analysis of Factors Affecting OS After Surgery in Patients With Pancreatic Head Cancer (R1 Resection Was Included as a Covariate)

Covariate	Relative Hazard	95% CI	P
Tumor size (≥2 cm)	1.37	0.74–2.54	0.311
Anterior pancreatic tissue invasion	0.94	0.61–1.46	0.783
Retropancreatic tissue invasion	0.95	0.62–1.46	0.824
Bile duct invasion	0.98	0.63–1.53	0.928
Duodenal invasion	1.10	0.70–1.74	0.685
Portal venous system invasion	1.74	1.13–2.70	0.013*
Arterial system invasion	0.90	0.39–2.05	0.797
Extrapancreatic nerve plexus invasion	1.61	1.01–2.55	0.046*
Lymph vessel invasion	1.00	0.49–2.04	0.998
Venous invasion	0.98	0.64–1.50	0.923
Perineural invasion	1.82	0.91–3.64	0.089
Lymph node metastasis	1.92	1.21–3.05	0.006*
Histological grade of differentiation†	1.58	0.90–2.77	0.113
Microscopically positive margin, R1	0.97	0.60–1.54	0.882

*Statistically significant.

†Other than well-differentiated tubular adenocarcinoma and papillary adenocarcinoma.

diagnose not only portal vein invasion but also nerve plexus invasion during surgical exploration in our department.[23] On the basis of the findings with multi–detector row CT and/or intraportal endovascular ultrasonography, we have been performing complete or right semicircular dissection of the nerve plexus around the SMA along with the extrapancreatic nerve plexus to obtain a negative resection margin.[3] This policy can be justified from the viewpoint of the curability of the pancreatectomy, considering a strong association of nerve plexus invasion with positive resection margin presented in the present study. But it is still unclear whether this strategy can provide survival benefit to the patients undergoing PD/PPPD for pancreatic cancer.

To elucidate the significance of resection margin status as a prognostic factor, we conducted univariate and multivariate analyses of factors affecting OS. The OS in patients with R1 resection (median survival [MS], 9.4 months) was shorter than in patients with R0 resection (MS, 15.2 months) and was longer than in patients with R2 resection (MS, 6.2 months). The differences in survival between R0 and R1 and between R1 and R2 were statistically significant by the log-rank test ($P = 0.008$ and $P = 0.009$, respectively). This result indicates that although patients with a positive resection margin (R1 + R2, n = 61) rarely achieved longtime survival (5-year survival rate was 2.8%, MS, 7.6 months), a surgery with microscopically positive margin (R1 resection) might have some positive impact on survival when compared with a surgery with grossly affected margin (R2 resection). By multivariate analysis of variables that were confirmed to possibly affect the survival in the univariate analysis, R2 resection was identified as an independent factor affecting OS together with lymph node metastasis and portal venous system and extrapancreatic nerve plexus invasions. When R2 resection was replaced by R1 resection in the same analysis, however, R1 resection was found not to be an independent predictor of poor outcome, whereas lymph node metastasis and portal venous system and extrapancreatic nerve plexus invasions remained significant as indicators of poor prognosis. These results indicate that although grossly positive resection margin adversely affected the survival, microscopic residual disease in the resection margin did not influence the survival significantly after PD/PPPD for pancreatic cancer. The cases with R1 resection were more liable to have lymphatic involvement than R0 resection cases, and this might have been more important as a cause for poor prognosis. This remains a mere speculation because precise data on the pattern of recurrence were not available.

In summary, the present study shows that R0 resection achieved through an aggressive policy toward complete resection of pancreatic cancer had a significant impact on survival when compared with R2 resection. R1 resection was not a significant indicator of poor prognosis and was in sharp contrast with R2 resection that, together with lymph node metastasis, portal venous system invasion, and nerve plexus invasion, was found by multivariate analysis to adversely influence the survival. The patients treated with R1 resection actually lived longer than those who underwent R2 resection, although the survival time was rarely longer than 5 years. Thus, extended pancreatectomy for locally advanced pancreatic head cancer should be applied only in cases where R2 resection can be avoided.

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Pancreatic head resection with segmental duodenectomy for pancreatic neoplasms

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Abstract
Background/purpose We have experienced 67 cases of pancreatic head resection with segmental duodenectomy (PHRSD) for benign or low-grade malignant tumor of the pancreatic head region. Here we introduce our operative technique for these 67 cases.
Methods Pancreatic head resection is performed with segmental duodenectomy including minor and major papilla. By conserving the right gastric artery and the gastroduodenal artery, 5–7 cm of the first portion of the duodenum is preserved with good arterial circulation. In addition, by conserving the anterior inferior pancreatoduodenal artery, the third portion and anal side or the second portion of the duodenum are preserved with good arterial circulation. Cholecystectomy is performed. The procedure is completed by resection of the pancreatic head with 3–4 cm of segmental duodenectomy including minor and major papilla. Reconstruction of the alimentary tract is performed with pancreatogastrostomy, end-to-end duodenoduodenostomy and end-to-side choledochoduodenostomy.
Results In 67 cases with diseases of the pancreatic head region, chiefly intraductal papillary mucinous neoplasms, this procedure was successfully performed without operative or hospital death. Postoperative quality of life was quite satisfactory.
Conclusion Total resection of the pancreatic head can be performed safely and effectively by this procedure.

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Keywords Pancreatic head resection with segmental duodenectomy · Organ-preserving pancreatectomy · Pancreatogastrostomy · Intraductal papillary mucinous neoplasms of pancreatic head

Introduction

Organ-preserving pancreatic resections are reasonable surgical options for benign or low-grade malignant tumors of the pancreas. Pylorus-preserving pancreatoduodenectomy (PpPD) [1] has now been recognized as the ideal surgical method for treating benign, low-grade malignancy and malignant tumors of the pancreatic head region. Duodenum-preserving pancreatic head resection (DpPHR) [2] is also one of the options for organ-preserving pancreatic head resection. In the DpPHR, there are two types of operation: combined resection of the common bile duct and common bile duct preservation [2–4]. In DpPHR the arterial blood circulation of duodenum or common bile duct is a great problem. Ischemia of the duodenum, or common bile duct, causes necrosis of the duodenum or common bile duct and leads to perforation [3, 4]. The other major problem with DpPHR and partial resection of the pancreatic head is failure to complete extirpation of intraductal papillary mucinous neoplasms (IPMN), because IPMN tends to spread into the main or branch pancreatic ducts. To prevent these complications, we have been performing complete pancreatic head resection with segmental duodenectomy (PHRSD) [5–7], including the minor and major papilla, for mainly benign or low-grade malignant tumors of the pancreatic head region in 67 cases. Reconstruction of the alimentary tract after PHRSD has been performed with pancreatogastrostomy, end-to-end duodenoduodenostomy

and end-to-side choledochoduodenostomy. We report here the operative procedure of PHRSD and postoperative results.

Patients and methods

From 1988 to 2008, 67 patients who underwent PHRSD had 47 IPMNs, 7 non-functional endocrine tumors of the pancreatic head region, 6 papilla of Vater cancers, 2 serous cytadenomas, 1 pancreas head cancer, 1 common bile duct cancer, 1 insulinoma, 1 annular pancreas and 1 anomalous engagement of the pancreatobiliary ductal system. Laparotomy is done by upper midline skin incision. The gastrocolic and duodenocolic ligaments are divided with preservation of the right gastroepiploic artery (RGEA) and vein to explore the front of the pancreas. The right gastroepiploic vein is ligated and divided at the root. The anterior–superior pancreatoduodenal artery (ASPDA), the posterior–superior pancreatoduodenal artery (PSPDA) and a few other branches running from the gastroduodenal artery (GDA) towards the pancreas are ligated and divided. By conserving the RGEA and GDA, 5–7 cm of the first portion of the duodenum is preserved with good arterial circulation. The pancreas is divided on the line of the portal vein. The extrapancreatic nerve plexus between the uncinate process and the superior mesenteric artery is preserved, so the inferior pancreatoduodenal artery (IPDA) is preserved. The anterior–inferior pancreatoduodenal artery (AIPDA) is preserved, and the posterior–inferior pancreatoduodenal artery (PIPDA) is ligated and divided. The AIPDA is ligated and divided near the major papilla (Figs. 1, 2). Cholecystectomy is performed. The common bile duct is divided at the upper border of the pancreas. A 2–3 cm ischemic area of the duodenum, including the major and minor papilla, is observed (Fig. 3). The oral side of the duodenum is divided 5–7 cm from the pyloric ring. The anal side of the duodenum is divided at the point of AIPDA ligation. Thus, PHRSD with preservation of GDA is completed. The length of the resected duodenum ranges from 3 to 5 cm (Fig. 2). Reconstruction of the alimentary tract is performed with pancreatogastrostomy (temporary pancreatic stent in the main pancreatic duct of the remnant pancreas and drained externally), end-to-end duodenoduodenostomy, and end-to-side choledochoduodenostomy (temporary transhepatic biliary stenting) (Fig. 4).

Results

No operative or hospital death was observed in the 67 cases. Minor leakage from the anastomosis portion of alimentary tract such as pancreatogastrostomy in 19.4%,

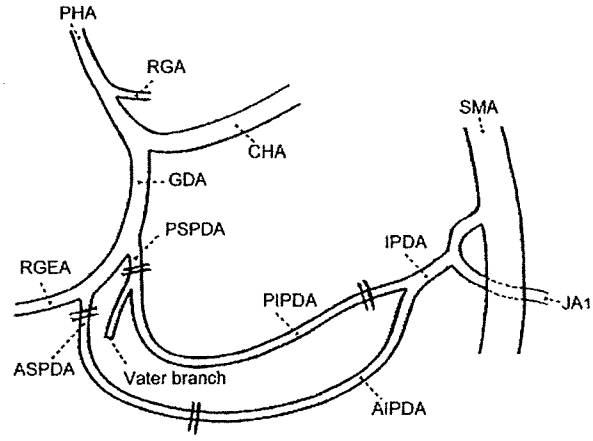

Fig. 1 Divided lines of the pancreatoduodenal arteries in pancreatic head resection with segmental duodenectomy. *PHA* proper hepatic artery, *RGA* right gastric artery, *CHA* common hepatic artery, *GDA* gastroduodenal artery, *RGEA* right gastroepiploic artery, *PSPDA* posterior–superior pancreatoduodenal artery, *ASPDA* anterior–superior pancreatoduodenal artery, *IPDA* inferior pancreatoduodenal artery, *PIPDA* posterior–inferior pancreatoduodenal artery, *AIPDA* anterior–inferior pancreatoduodenal artery, *JA1* first jejunal artery, *SMA* superior mesenteric artery

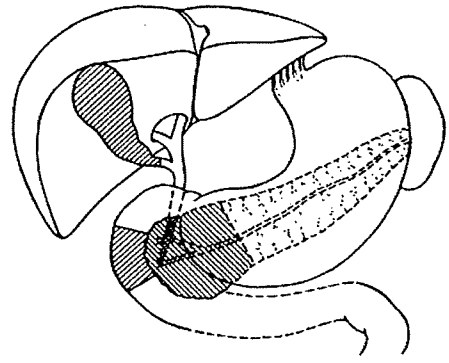

Fig. 2 Resected portion in pancreatic head resection with segmental duodenectomy

choledochoduonenostomy in 4.5% and duodenoduodenostomy in 1.5% were observed, but healed with conservative treatment. Intraabdominal bleeding was observed in two cases, but successfully treated by transarterial embolization. All patients discharged from the hospital showed extremely good postoperative quality of life (QOL).

Discussion

Organ-preserving pancreatic resection for benign tumor of the pancreatic head or chronic pancreatitis such as PpPD [1] or DpPHR [2] has been recognized as the ideal surgical method. There are two types of DpPHR operation: combined resection of the common bile duct [3] and

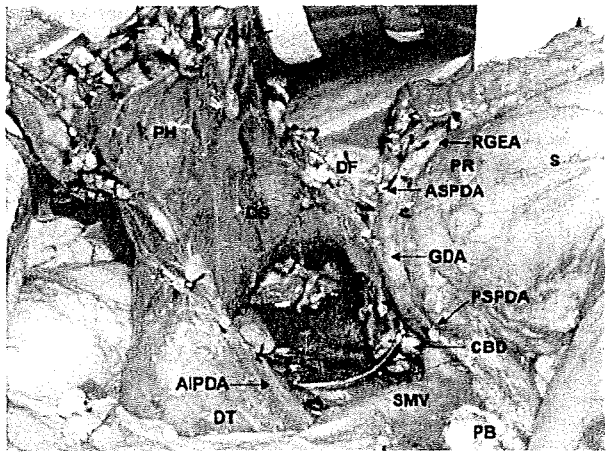

Fig. 3 Segmental duodenectomy completes the total pancreatic head resection. *PH* pancreatic head, *PB* pancreatic body, *DF* duodenal first portion, *DS* duodenal second portion, *DT* duodenal third portions, *S* stomach, *PR* pyloric ring, *CBD* common bile duct, *GDA* gastroduodenal artery, *PSPDA* posterior–superior pancreatoduodenal artery, *ASPDA* anterior–superior pancreatoduodenal artery, *RGEA* right gastroepiploic artery, *SMV* superior mesenteric vein

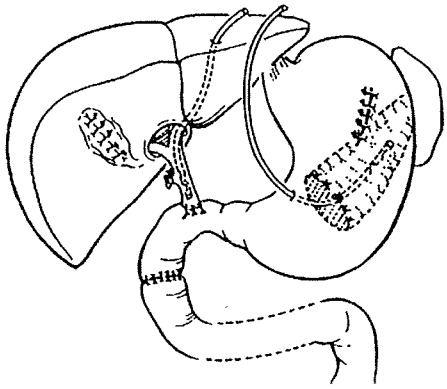

Fig. 4 Schematic of alimentary tract reconstruction after pancreatic head resection with segmental duodenectomy

preservation of the common bile duct [2, 4]. To preserve the duodenum and common bile duct, the preservation of the pancreatic head arcade of the arteries is very important. The anatomy of the arcade of the arteries of the pancreatic head has been studied [8, 9]. The branch of the PSPDA that runs along the right side of the common bile duct and toward the major papilla (Vater branch) is important to preserve the common bile duct and major papilla [8, 9], but this branch is difficult to visualize during operation. The preservation of the pancreatic parenchyma between the common bile duct and duodenum (groove area) is necessary to preserve this branch in DpPHR with the preservation of the common bile duct and sphincter function of major papilla [9]. The preservation of the anterior arcade of the arteries in the pancreatic head is technically difficult near the minor and major papilla. If these arteries cannot be preserved, postoperative ischemic necrosis or perforation of the common bile duct or duodenum may result [10, 11]. Successful complete resection of the pancreatic head with preservation of the common bile duct and duodenum has been reported [10, 11]. However, complete resection of the pancreatic head including the pancreatic parenchyma between the common bile duct and duodenum will cause ischemia of the common bile duct and major papilla. However, complete preservation of the arcade of the arteries of the pancreatic head with common bile duct preservation is technically difficult and impossible. DpPHR with incomplete resection of the pancreatic head cannot ensure complete extirpation of IPMN, because IPMN tends to spread into the main or branch ducts. High morbidity and mortality rates were observed in DpPHR [12]. We have already reported the advantage of PHRSD compared with PpPD in delayed gastric emptying, endocrine function, body weight decrease and postoperative enzyme substitution [7]. We recommend PHRSD for the above reasons.

Conclusions

PHRSD is a safe and reasonable technique appropriate for selected patients with benign or low-grade malignant tumor of the pancreatic head region, especially with benign or noninvasive IPMN.

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original article

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A history of smoking is inversely correlated with the incidence of gemcitabine-induced neutropenia

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Background: Smoking may affect the efficacy of chemotherapy and the incidence of adverse events. We investigated the correlation between smoking history and gemcitabine-induced neutropenia.

Patients and methods: Data on smoking history and incidence of grade 3–4 neutropenia were retrospectively gathered for 103 chemo-naive patients treated with gemcitabine monotherapy (59 patients with pancreatic, 41 with hepatobiliary and three with other cancers).

Results: There was a significantly higher incidence of grade 3–4 neutropenia among patients without a history of smoking (55.7%) than among those with a history of smoking (including current and ex-smokers; 23.6%) [odds ratio (OR) 0.244, 95% confidence interval (CI) 0.105–0.569; $P < 0.001$]. After adjustment for age, gender, platelet and baseline neutrophil counts, history of surgery for primary cancer, creatinine concentration, hemoglobin concentration, aspartate aminotransferase concentration, alanine aminotransferase concentration and total bilirubin concentration, logistic regression analysis identified a history of smoking as an independent inverse predictor of gemcitabine-induced neutropenia (OR 0.188, 95% CI 0.057–0.618; $P = 0.006$).

Conclusion: Patients without a history of smoking may be at higher risk of developing gemcitabine-induced neutropenia. The mechanism underlying this phenomenon is unclear at this point.

Key words: adverse effects, chemotherapy, gemcitabine, neutropenia, smoking

introduction

Gemcitabine is a deoxycytidine analogue that is widely used for many solid tumors as a single agent or in combination with other anticancer drugs [1–4]. The recommended dosage regimen for gemcitabine monotherapy consists of a 4-week cycle with 1000 mg/m^2 doses administered over 30 min on days 1, 8 and 15 [1, 5]. This dosage regimen is supported by the results of a Japanese phase I study involving pancreatic cancer patients [6]. However, in daily practice, we often encounter patients who cannot tolerate the recommended 1000 mg/m^2 dose of gemcitabine because of hematological adverse events, especially neutropenia. For some patients, it has been necessary to reduce the dose of gemcitabine to less than half the recommended dose because of gemcitabine-induced neutropenia.

Several enzymes are known to be involved in gemcitabine metabolism [7]. A recent study demonstrated that single-nucleotide polymorphisms (SNPs) in the cytidine deaminase (CDA) gene, which encodes a key enzyme in gemcitabine inactivation, influence the pharmacokinetics and toxicity of gemcitabine [8]. Considering the low allele frequencies of these SNPs, however, it seems that one or more unknown factors affect the pharmacokinetics and toxicity of gemcitabine. Smoking has been identified as a factor that potentially affects the pharmacokinetics of several anticancer drugs. Recent studies have demonstrated that smoking significantly lowers exposure to irinotecan and reduces the risk of irinotecan-induced neutropenia, at least in part by modulating irinotecan metabolism [9], and decreases the blood level of erlotinib by affecting erlotinib clearance rates [10, 11]. These findings prompted us to perform the current study to investigate the potential correlation between a history of smoking and gemcitabine-induced neutropenia.

patients and methods

patients

From November 2003 to November 2007, 103 chemo-naive patients underwent gemcitabine monotherapy at Kyoto University Hospital. For these patients, we retrospectively obtained data on smoking history and

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grade 3–4 gemcitabine-induced neutropenia from the hospital's electronic medical records system (CyberOncology®, CyberLaboratory Inc., Tokyo, Japan) [12]. Hematological adverse events were graded according to the Common Terminology Criteria for Adverse Events version 3.0 [13]. All patients provided written informed consent for the use of clinical data in the medical records system for the purposes of research. This study was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (E-377).

treatment

Gemcitabine monotherapy was initiated at doses of 460–1000 mg/m^2 administered over 30 min on days 1, 8 and 15 over a 4-week cycle. The initial gemcitabine dose was adjusted at the discretion of individual physicians according to baseline bone marrow function, liver function, age and the risk of infection. For each cycle, if necessary, the dose and schedule of gemcitabine administration were adjusted in response to adverse events (hematological and otherwise) observed during the previous cycle. The most common cause of dose adjustment was hematological toxicity, especially neutropenia. Granulocyte colony-stimulating factor (G-CSF) was used for 11 patients.

smoking history

Information about the patients' smoking history was retrieved from electronic medical records based on information recorded during patient interviews. Patients were classified into smoking and non-smoking groups based on this information. The non-smoking group comprised those who stated that they had never been smokers, and the smoking group comprised both current and ex-smokers. Since most smokers had quit after their diagnosis of cancer, there were only 11 current smokers; therefore, we pooled current and ex-smokers in this study.

statistical methods

Data are presented as the median and range, unless stated otherwise. For statistical analysis, the χ^2 test for dichotomous variables or the Mann–Whitney *U* test for continuous variables was carried out. Logistic regression analysis was carried out to assess the correlation between gemcitabine-induced neutropenia and the following covariates: smoking history, age, gender, baseline neutrophil count, creatinine concentration, history of surgery for primary cancer, hemoglobin concentration, platelet count, aspartate aminotransferase (AST) concentration, alanine aminotransferase (ALT) concentration and total bilirubin concentration. $P < 0.05$ was regarded as significant. All statistical analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC).

results

patient characteristics

Data for 103 consecutive chemo-naive patients who underwent gemcitabine monotherapy from November 2003 to November 2007 at Kyoto University Hospital were analyzed. Patient baseline characteristics are summarized in Table 1. Fifty-nine patients had pancreatic cancer, 41 had hepatobiliary cancer, one had mesothelioma, one had liposarcoma and one had leiomyosarcoma. Fifty-one patients were classified into the smoking group and 52 patients into the non-smoking group. G-CSF was administered to three patients in the smoking group and eight in the non-smoking group. Baseline white blood cell (WBC) count, hemoglobin concentration and creatinine concentration were significantly higher in the smoking group, and the proportion of females was significantly higher in the non-smoking group. There was no significant difference between the numbers of patients in the smoking and non-smoking groups.

smoking history and gemcitabine-induced neutropenia

The overall incidence of grade 3–4 neutropenia was 24% in the smoking group and 56% in the non-smoking group [odds ratio (OR) 0.244, 95% confidence interval (CI) 0.105–0.569; $P < 0.001$; Table 2]. Logistic regression analysis was carried out using gender, age, baseline neutrophil count, creatinine concentration, history of surgery for primary cancer, hemoglobin concentration, platelet count, AST concentration, ALT concentration and total bilirubin concentration. A statistician confirmed the validity of the assumption of linearity by categorizing the continuous variables in the logistic regression analysis. After logistic regression analysis, a history of smoking was retained as an independent inverse predictor of gemcitabine-induced neutropenia (OR 0.188, 95% CI 0.057–0.618; $P = 0.006$; Table 3). The incidence of grade 3–4 neutropenia during the first cycle of gemcitabine treatment was higher in the non-smoking group than in the smoking group although the difference was not found to be significant in logistic regression analysis (OR 0.201, 95% CI 0.040–1.026; $P = 0.054$; Table 3).

discussion

Gemcitabine has a wide spectrum of antitumor activity with minimal non-hematological adverse events [1–4]. Although the recommended dosage regimen for gemcitabine monotherapy comprises three doses of 1000 mg/m^2 per cycle [1, 5, 6, 14], in the present study the maximum tolerated dose of gemcitabine (i.e. the dose that could be repeatedly administered without toxicity) ranged from 130 mg/m^2 to the recommended dose of 1000 mg/m^2 (Table 1). Thus, some patients required the gemcitabine dose to be reduced several times until a tolerable dose was reached. Actually, relative dose intensity of gemcitabine was significantly lower in the non-smoking group (Table 1), probably reflecting the fact that gemcitabine dose reduction was more common among non-smokers because of neutropenia.

Our analysis identified a significant inverse correlation between a history of smoking and the incidence of gemcitabine-induced neutropenia among chemo-naive patients treated with gemcitabine monotherapy (OR 0.244, 95% CI 0.105–0.569; $P < 0.001$; Table 2). There were only 11 current smokers in this study, two of whom developed grade 3–4 neutropenia, so to ensure robust statistical analysis we pooled the data from the ex-smokers and current smokers. Obviously, whether a patient is a current or an ex-smoker is likely to be pertinent, so future studies are warranted to evaluate the relative incidence of neutropenia among current smokers, ex-smokers and non-smokers. The proportion of women was significantly larger in the non-smoking group, which might have affected the current results; however, no clinically significant difference was found in gemcitabine clearance between men and women (E. Lilly, unpublished data). Smoking is known to increase the

Table 1. Patient characteristics

Characteristic	All patients (n =103)	Smoking group (n =51)	Non-smoking group (n =52)	P value
Gender				<0.01
Male	59 (57%)	43 (84%)	16 (31%)	
Female	44 (43%)	8 (16%)	36 (69%)	
Age (years)				0.63
Median	65	64	65	
Range	33–84	33–83	40–84	
Tumor type				0.75
Pancreatic	59 (57%)	30 (59%)	29 (56%)	
Hepatobiliary	41 (40%)	19 (37%)	22 (42%)	
Others	3 (3%)	2 (4%)	1 (2%)	
History of surgery for primary cancer	59 (57%)	27 (53%)	32 (62%)	0.38
Performance status (0/1/2)	(94/9/0)	(46/5/0)	(48/4/0)	
Total no. of gemcitabine administrations				0.69
Median	13	13	12	
Range	2–52	3–52	2–32	
Relative dose intensity of gemcitabine (mg/m^2)				0.03
Median	0.68	0.68	0.59	
Range	0.19–1.00	0.29–1.00	0.19–1.00	
Maximum tolerated dose of gemcitabine (mg/m^2)				0.13
Median	700	800	607	
Range	133–1000	200–1000	133–1000	
Baseline hematological data				
WBC count (× 10^9/l)				<0.01
Median	5.4	5.6	5.0	
Range	2.4–20.2	3–20.2	2.4–10.8	
Neutrophil count (× 10^9/l)				0.12
Median	3.3	3.4	2.9	
Range	1.7–17.2	3.2–17.2	1.1–8.8	
Hemoglobin concentration				<0.01
Median	12	12.3	11.5	
Range	7.2–17.9	8.8–17.9	7.2–15.5	
Platelet count (× 10^9/l)				0.48
Median	221	221	215	
Range	90–540	95–385	90–540	
Baseline blood chemistry				
AST concentration (IU/l)				0.90
Median	27	25	26	
Range	14–114	14–102	14–114	
ALT concentration (IU/l)				0.19
Median	30	31	26	
Range	9–167	9–167	10–125	
Total bilirubin concentration (mg/dl)				0.93
Median	0.7	0.7	0.7	
Range	0.3–4.0	0.4–4.0	0.3–2.6	
Creatinine concentration (mg/dl)				<0.01
Median	0.6	0.7	0.6	
Range	0.3–1.7	0.3–1.7	0.4–0.9	

The smoking group comprised patients who were current and ex-smokers. The non-smoking group comprised patients who had never been smokers. WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

proliferation rate of myeloid progenitor cells [15–17], which might partly explain the significantly higher baseline WBC count and hemoglobin level in the smoking group in the present study (Table 1). The lower hemoglobin level in the non-smoking group could also be attributed to the larger proportion of women in this group. It is unlikely that G-CSF support affected our current results because G-CSF was used only after development of grade 3/4 neutropenia and was more common in the non-smoking group (three patients in the smoking group and eight patients in non-smoking group). Furthermore, G-CSF was never used to maintain gemcitabine dose intensity. We initially intended to examine the correlation between smoking history and gemcitabine-induced grade 3–4 anemia and thrombocytopenia; however, the incidences of grade 3–4 anemia and thrombocytopenia were too low (3.8% for both) to allow statistical analysis.

Logistic regression analysis with adjustment for age, gender, baseline neutrophil count, creatinine concentration, history of surgery for primary cancer, hemoglobin concentration, platelet count, AST concentration, ALT concentration and total bilirubin concentration identified smoking history as an independent predictive factor of gemcitabine-induced neutropenia (OR 0.188, 95% CI 0.057–0.618; $P = 0.006$; Table 3). Although the incidence of grade 3–4 neutropenia during the first cycle of treatment was higher in the non-smoking group than in the smoking group, the difference was not significant (OR 0.201, 95% CI 0.040–1.026; $P = 0.054$; Table 3). We speculate that this was due to the small sample size of the current study.

Interestingly, Laufman et al. [18] reported that smokers have a higher absolute neutrophil count than non-smokers when treated with gemcitabine monotherapy, while smokers have a lower absolute neutrophil count when treated with docetaxel monotherapy. These findings are consistent with our current results. Several mechanisms have been posited to explain the interaction between smoking habit and other antitumor drugs. Smoking potentially affects irinotecan metabolism, lowering exposure to the drug and reducing drug-induced neutropenia, at least in part by modulating CYP3A and UGT1A1 enzymes [9]. Smoking is also thought to enhance the clearance of erlotinib and lower the level of the drug in the blood by inducing CYP1A1/CYP1A2 enzyme expression [10, 11]. More than 90% of gemcitabine administered is converted into the inactive metabolite 2′-deoxy-2′,2′-difluorouridine by CDA [7]. Given that smoking is thought to modulate the irinotecan- and erlotinib-metabolizing enzymes as mentioned above, it is tempting to speculate that smoking could also affect gemcitabine metabolism by modulating CDA activity. There are other possible mechanisms. Several effects of smoking are known to persist for a long time after cessation of smoking. For example, the inflammatory response to smoking in patients with chronic obstructive pulmonary disease can continue after the patient stops smoking. Similarly, it can take at least 5 years for smoking-induced leukocytosis to resolve [17, 19, 20]. These reports prompted us to speculate that some unknown persistent change in ex-smokers also affected the current results. Further study is warranted to test this hypothesis.

In the non-smoking group, the incidence of gemcitabine-induced grade 3–4 neutropenia was 56%, which is much higher than previously reported figures, which have ranged from 20% to 30% [1, 6, 14]. In contrast, the corresponding incidence was 24% in the smoking group, which is comparable to previously reported values. Because of the high incidence of neutropenia (especially among non-smokers) and the broad range of

Table 2. Incidence of gemcitabine-induced grade 3–4 neutropenia according to smoking history

Time period	Smoking group ($n = 51$), n (%)	Non-smoking group ($n = 52$), n (%)	Odds ratio (95% CI)	P value
First cycle	4 (8)	19 (37)	0.148 (0.046–0.475)	0.001
Overall	12 (24)	29 (56)	0.244 (0.105–0.569)	<0.001

The smoking group comprised patients who were current and ex-smokers. The non-smoking group comprised patients who had never been smokers. CI, confidence interval.

Table 3. Odds ratios for the incidence of gemcitabine-induced grade 3–4 neutropenia during the first cycle and overall treatment

Factor	First cycle		Overall	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
History of smoking	0.201 (0.040–1.026)	0.054	0.188 (0.057–0.618)	0.006
Gender	0.388 (0.074–2.027)	0.262	0.664 (0.168–2.614)	0.558
Age	0.992 (0.923–1.066)	0.825	0.939 (0.946–1.062)	0.939
Neutrophil count	0.320 (0.158–0.646)	0.001	0.500 (0.315–0.793)	0.003
Creatinine concentration	9.250 (0.281–304.505)	0.212	12.159 (0.585–252.754)	0.107
History of surgery for primary cancer	0.651 (0.165–2.580)	0.542	1.198 (0.402–3.568)	0.746
Hemoglobin concentration	0.869 (0.551–1.370)	0.545	1.231 (0.878–1.724)	0.228
Platelet count	0.998 (0.989–1.007)	0.720	1.002 (0.996–1.009)	0.476
AST concentration	1.049 (0.998–1.103)	0.061	1.057 (1.007–1.109)	0.024
ALT concentration	0.963 (0.916–1.011)	0.130	0.970 (0.939–1.002)	0.070
T-bilirubin concentration	0.561 (0.139–2.270)	0.418	0.525 (0.172–1.605)	0.259

CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

maximum tolerated doses, physicians sometimes start with a dose <1000 mg/m^2 to avoid neutropenia and repeated reduction in doses thereafter. But this approach comes with the risk of not achieving the maximum benefit from gemcitabine and should be avoided where possible; therefore, identifying patients at high risk of developing gemcitabine-induced neutropenia will help physicians to select an optimal gemcitabine dose.

Whether smoking also affects the antitumor effect of gemcitabine could not be investigated in the current study because of the heterogeneity of the study population with respect to tumor type and treatment aim (31 patients were treated with gemcitabine as adjuvant chemotherapy). Even if smoking does not affect the antitumor effect of gemcitabine, smoking remains highly detrimental to cancer patients in many ways and is clearly not an appropriate approach to avoid gemcitabine-induced neutropenia [21].

In summary, our present data indicate that patients without a history of smoking are at higher risk of developing grade 3–4 gemcitabine-induced neutropenia in daily clinical practice. Future studies including a larger number of patients are warranted to verify our results and to clarify the underlying mechanism.

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Prognostic value of metastin expression in human pancreatic cancer

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Abstract

Background: *KiSS-1* was identified as a metastasis-suppressing gene in melanoma cells. The *KiSS-1* gene product (metastin) was isolated from human placenta as the ligand of GPR54, a G-protein-coupled receptor. The role of metastin and GPR54 in tumor progression is not fully understood.

Methods: We investigated the clinical significance of metastin and GPR54 expression in pancreatic cancer. We evaluated immunohistochemical expression of metastin and GPR54 in pancreatic ductal adenocarcinoma tissues obtained from 53 consecutive patients who underwent resection between July 2003 and May 2007 at Kyoto University Hospital. In 23 consecutive patients, the plasma metastin level was measured before surgery by enzyme immunoassay.

Results: Strong immunohistochemical expression of metastin was detected in 13 tumors (24.5%), while strong expression of GPR54 was detected in 30 tumors (56.6%). Tumors that were negative for both metastin and GPR54 expression were significantly larger than tumors that were positive for either metastin or GPR54 ($p = 0.047$). Recurrence was less frequent in patients who had metastin-positive tumors compared with those who had metastin-negative tumors (38.5% versus 70.0%, $p = 0.04$). Strong expression of metastin and GPR54 was significantly correlated with longer survival ($p = 0.02$). Metastin expression by pancreatic cancer was an independent prognostic factor for longer survival (hazard ratio, 2.1; 95% confidence interval, 1.1–4.7; $p = 0.03$), and the patients with a high plasma metastin level ($n = 6$) did not die after surgical resection.

Conclusion: Strong expression of metastin and GPR54 by pancreatic cancer is associated with longer survival. Metastin expression is an independent prognostic factor for the survival of pancreatic cancer patients. The plasma metastin level could become a noninvasive prognostic factor for the assessment of pancreatic cancer.