

Impact of Postoperative Complications on Survival and Recurrence in Pancreatic Cancer

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Abstract. *Background:* We investigated the impact of postoperative complications on survival and recurrence after curative surgery for pancreatic cancer. *Patients and Methods:* This study included 164 patients who underwent curative surgery for pancreatic cancer between 2005 and 2014. The patients were classified into those with postoperative complications (C group) and those without postoperative complications (NC group). The risk factors for overall survival (OS) and recurrence-free survival (RFS) were identified. *Results:* Postoperative complications were found in 61 out of the 164 patients (37.2%). The RFS rate at five years after surgery was 10.6% in the C group and 21.0% in the NC group. The RFS tended to be worse in the C group than in the NC group ($p=0.1756$). The OS rate at five years after surgery was 7.4% in the C group and 22.8% in the NC group, which was significantly different ($p=0.0189$). The multivariate analysis demonstrated that the occurrence of postoperative complications was a significant independent risk factor for OS and a marginally significant risk factor for RFS. *Conclusion:* The development of postoperative complications was a risk factor for a decreased overall survival in the patients who underwent curative surgery for pancreatic cancer. The surgical procedure, perioperative care and the surgical strategy should be carefully planned to avoid complications.

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Pancreatic cancer is a major cause of cancer death world-wide, with a five-year survival rate of less than 5% (1, 2). Complete resection is essential for the cure of pancreatic cancer. Although the resection rate has increased gradually, the prognosis remains poor (3). Therefore, it is important to identify reliable predictive factors for patients at high risk.

Recent studies have demonstrated that the development of postoperative complications reduce patients' survival or increase the risk of disease recurrence in various types of malignancies (4-9). For example, Hayashi *et al.* examined 502 patients with gastric cancer and classified them into those with infectious complications and those without infectious complications (10). They found that infectious complications were a risk factor for gastric cancer recurrence. Moreover, some authors have suggested that the immunological response against postoperative complications enhanced the viability of undetectable residual tumor cells after surgery, thereby increasing disease recurrence (5, 7, 8).

The morbidity rate after pancreatic surgery with lymph node dissection has been reported to range from 30 to 65% (11-15). Although the influence of the surgeon is sometimes limited due to the histopathological findings, it is apparent that surgery itself might play an important role in the outcome of pancreatic cancer. Despite the numerous studies performed in patients with various types of malignancies, limited studies have demonstrated a correlation between postoperative complications and poor survival in patients with pancreatic cancer (16, 17). However, there were some drawbacks to the previous studies. These two previous studies included patients whose surgery was not curative, and the types of surgery were limited. These differences could have overestimated the relationships between postoperative complications and the patient's survival and risk of recurrence.

The aim of the present study was to determine whether the overall survival (OS) and recurrence-free survival (RFS) would be shortened by the development of any postoperative

Table I. Comparison clinicopathological factors between the patients with surgical complications group (C group) and the patients without surgical complications group (NC group).

Factor	C group (n=61)		NC group (n=103)		p-Value
	Number	(%)	Number	(%)	
Gender					0.865
Male	34	(56)	56	(54)	
Female	27	(44)	47	(46)	
Median age (range), years	70 (47-83)		68 (40-86)		0.033
Tumor location					0.014
Body or tail	9	(15)	33	(32)	
Head	52	(85)	70	(68)	
Median tumor diameter (range), mm	35 (15-83)		35 (5-90)		0.305
Histology					0.624
Well, mod	51	(84)	89	(86)	
Poor	10	(16)	14	(14)	
UICC T status					0.046
T1 or T2	1	(2)	10	(10)	
T3	60	(98)	93	(90)	
LN metastasis					0.610
Negative	17	(28)	25	(24)	
Positive	44	(72)	78	(76)	
Lymphatic invasion					0.182
Absent	35	(57)	48	(47)	
Present	26	(43)	55	(53)	
Vascular invasion					0.015
Absent	13	(16)	41	(40)	
Present	48	(84)	62	(60)	
Adjuvant chemotherapy					0.802
Yes	50	(82)	86	(83)	
No	11	(18)	17	(17)	

Well, mod: Well/moderately differentiated, Poor: poorly differentiated, LN: lymph node; UICC: Union for International Cancer Control.

complications of grade 2 or higher, as defined by the Clavien-Dindo classification (18), in patients who underwent curative resection for pancreatic cancer.

Patients and Methods

Patients. The patients were selected from the medical records of consecutive patients who underwent pancreatic surgery at Kanagawa Cancer Center from 2005 to 2014, according to the following criteria: (i) a pathologically common type of pancreatic cancer according to the seventh edition of the Union for International Cancer Control (UICC) TNM (19); (ii) those who had undergone extended radical resection (D2) for pancreatic cancer as initial treatment and who achieved curative resection (R0); (iii) patients without synchronous or metachronous malignancies. The resected specimens were examined histopathologically and were staged according to the seventh edition

Table II. Details of postoperative complications.

Complication	Grade				Total %
	2	3a/3b	4a/4b	5	
Pancreatic fistula	9	3/3	0/1	0	9.8
Abdominal abscess	8	4/2	0/1	1	7.3
Anastomotic leakage	1	2/0	0/0	0	1.8
Pneumonia	3	0/0	0/0	0	1.8
Postoperative bleeding	2	1/1	0/0	0	2.4
Wound abscess	8	0/0	0/0	0	4.9
Delayed gastric empty	21	0/0	0/0	0	12.8
Anastomotic stenosis	2	0/0	0/0	0	1.2
Portal vein thrombosis	2	0/0	0/0	0	1.2
Atrial fibrillation	1	0/0	0/0	0	0.6
Delirium	7	0/0	0/0	0	4.3
Cholangitis	4	0/0	0/0	0	2.4
Chylous ascites	1	2/0	0/0	0	1.8
Ascites	6	0/0	0/0	0	6.1
Upper gastrointestinal bleeding	2	0/0	0/0	0	1.2
Urinary tract infection	1	0/0	0/0	0	0.6
Pleural effusion	1	0/0	0/0	0	0.6
Pulmonary edema	0	0/0	1/0	0	0.6
Septic shock	0	0/0	1/1	0	1.2

of the UICC TNM. Patients with other pancreatic and periampullary neoplasms, such as intraductal papillary mucinous neoplasms, cystadenocarcinoma and endocrine tumors, were excluded.

Surgical procedure. All pancreatic surgeries were performed in accordance with standardized procedures described elsewhere (14, 20-22). Briefly, in cases of distal pancreatectomy, lymph node dissection was performed in the region of the celiac trunk and the superior mesenteric artery and vein, as well as behind the pancreas, along the left side of the renal vein and the left adrenal gland. In each case, intraperitoneal drains were placed close to the pancreatic anastomosis and stump. In cases of pancreaticoduodenectomy, we performed pylorus-preserving pancreaticoduodenectomy as the standard procedure. Lymph node dissection along the hepatoduodenal ligament, common hepatic artery, vena cava, superior mesenteric vein and the right side of the superior mesenteric artery was a standard part of the procedure. Multiple intraperitoneal drains were placed: the first was posterior to the hepaticojejunostomy and the second was on the anterior surface of the pancreaticojejunostomy or the closed pancreas remnant.

Definition of postoperative complications. Postoperative complications of grade 2-5 according to the Clavien-Dindo classification that occurred during hospitalization /or within 30 days after surgery were retrospectively determined from the patient's records (18). Grade 1 complications were not evaluated to exclude the possibility of a description bias in the patient's records. The patients were classified

Table III. Univariate and multivariate Cox proportional hazards analysis of clinicopathological factors for recurrence-free survival.

Factor	No. of patients	Univariate analysis			Multivariate analysis		
		OR	95% CI	p-Value	OR	95% CI	p-Value
Age (years)							
<70	102	1.000			1.000		
≥70	62	1.227	0.856-1.906	0.231	1.305	0.850-2.003	0.224
Gender							
Female	74	1.000			1.000		
Male	90	1.411	0.966-2.061	0.075	1.314	0.890-1.938	0.170
Tumor diameter (mm)							
<35	87	1.000			1.000		
≥35	77	1.789	1.221-2.619	0.003	1.412	0.939-2.124	0.097
Tumor location							
Body or tail	42	1.000			1.000		
Head	122	1.450	0.931-2.259	0.101	1.267	0.801-2.005	0.313
UICC T status							
T1-T2	11	1.000			1.000		
T3	153	3.378	1.240-9.199	0.017	1.986	0.684-5.766	0.207
Lymph node metastasis							
Negative	42	1.000			1.000		
Positive	122	1.519	0.975-2.365	0.064	1.013	0.566-1.614	0.864
Surgical complication							
No	103	1.000			1.000		
Yes	61	1.312	0.884-1.946	0.177	1.457	0.937-2.264	0.094
Lymphatic invasion							
Absent	83	1.000			1.000		
Present	81	2.187	1.488-3.213	<0.001	1.935	1.223-3.063	0.005
Vascular invasion							
Absent	54	1.000			1.000		
Present	110	1.271	0.850-1.900	0.243	1.116	0.715-1.742	0.629
Adjuvant chemotherapy							
Yes	136	1.000			1.000		
No	28	1.302	0.791-2.142	0.299	1.315	0.762-2.268	0.325

CI: Confidence interval; OR: Odds ratio; UICC: Union for International Cancer Control.

into those with postoperative complications (C group) and those without postoperative complications (NC group).

Follow-up. Patients were followed-up at outpatient clinics. Hematological tests and physical examinations were performed at least every three months for five years. In the patients who received adjuvant chemotherapy, hematological tests and physical examinations were performed at least every two weeks during adjuvant chemotherapy, and at least every three months for five years after the patients had finished the adjuvant chemotherapy. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) tumor marker levels were checked at least every three months for five years. Patients underwent a computed tomographic examination every three months during the first three years after surgery, and then every six months until five years after surgery.

Evaluations and statistical analyses. The significance of correlations between postoperative complications and clinicopathological parameters was determined using Fisher's exact test or the χ^2 test. The OS was defined as the period between surgery and death. The RFS was defined as the period between surgery and the occurrence

of an event, recurrence or death, whichever came first. The data for patients who had not experienced an event were censored as of the date of the final observation. The OS and RFS were evaluated by univariate and multivariate analyses. The OS and RES curves were calculated using the Kaplan–Meier method, and were compared by the log-rank test. A Cox proportional hazards model was used to perform the univariate and multivariate survival analyses. A value of $p < 0.05$ was defined as being statistically significant. The survival data were obtained from hospital records or from the city registry system. The SPSS software package (v11.0 J Win; SPSS, Chicago, IL, USA) was used for all statistical analyses. This study was approved by the Institutional Review Board (IRB) of the Kanagawa Cancer Center (IRB number 26-11 and 26-14).

Results

Patients. We evaluated 164 patients in this study. Figure 1 shows the consort diagram of this study. The patients' ages ranged from 40 to 86 years (median=68 years); 90 patients were male, and 74 were female. The type of surgery was distal

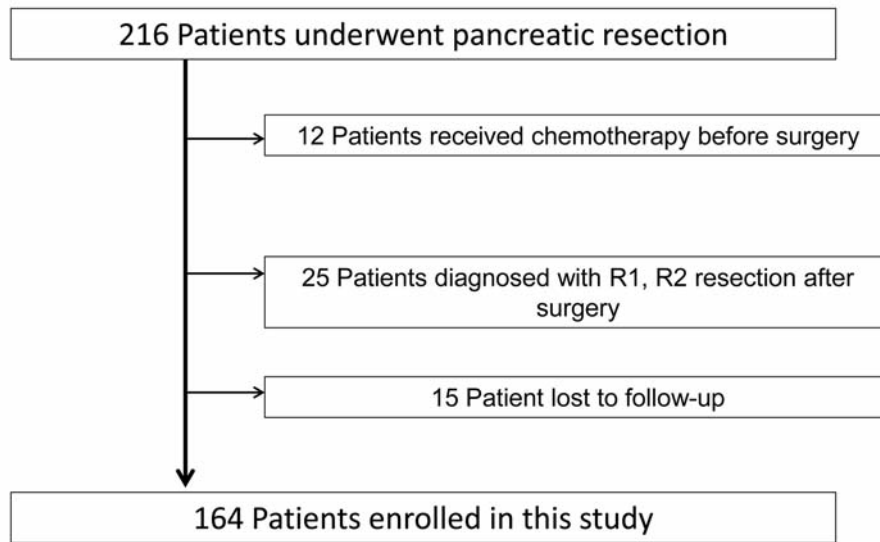


Figure 1. The consort diagram of the 164 patients.

pancreatectomy in 42 patients, pancreaticoduodenectomy in 111 patients and total pancreatic resection in 11 patients. The median follow-up period was 41.4 months (range=3.9-110.5 months). Table I summarizes the patients' demographic and clinical characteristics. The age, tumor location, UICC T status and vascular invasion were significantly different between the two groups. In the C group, the age tended to be higher, pancreatic head tumors were dominant, there was a more advanced T status and vascular invasion was more common than in the NC group.

Surgical morbidity and mortality. Postoperative complications were found in 61 out of the 164 patients (37.2%). Surgical mortality was observed in one patient due to an abdominal abscess (0.6%). The details of the complications are shown in Table II. Delayed gastric emptying was the most frequently diagnosed complication, followed by pancreatic fistula and abdominal abscess. Grade 2 complications occurred in 65.5% of the patients, grade 3 in 26.2%, grade 4 in 6.7% and grade 5 in 0.6%.

Survival analysis. The RFS rates at three and five years after surgery were 10.6% and 10.6%, respectively, in the C group and were 26.9% and 21.0%, respectively in the NC group. The RFS therefore tended to be worse in the C group than in the NC group ($p=0.177$). The RFS curves are shown in Figure 2. In the univariate analysis, tumor diameter, T status and lymphatic invasion were found to be significantly associated with RFS. The multivariate analysis demonstrated that lymphatic invasion was a significant independent risk factor for RFS (Table III). Moreover, postoperative complications and tumor diameter were found to be marginally significantly associated with the RFS.

The OS rates at three and five years after surgery were 7.4% and 7.4%, respectively, in the C group, and were 34.1% and 22.8%, respectively, in the NC group, which were significantly higher ($p=0.0189$). The OS curves are shown in Figure 3. In the univariate analysis, the T status, tumor diameter, presence of lymph node metastases, postoperative complications, lymphatic invasion and use of adjuvant chemotherapy were all found to be significantly associated with OS. The multivariate analysis demonstrated that postoperative complications and lymphatic invasion were independent risk factors significantly associated with a decreased OS (Table IV).

Subgroup analysis. The subgroup analyses were performed according to the type of complications and the type of surgical procedure.

When comparing the relationship between the prognosis of patients and 'infectious complication' (abdominal abscess, pancreatic fistula, *etc.*), the OS rates of the patients with infectious complication and those without were 8.2% and 30.2% at 3 years, 8.2% and 19.2% at 5 years, respectively ($p=0.1819$). The 3- and 5-year survival tended to be worse in the patients with infectious complications than the patients without infectious complications. Moreover, when comparing the relationship between the prognosis of patients and non-infectious complications (delayed gastric empty, portal vein thrombosis, *etc.*), the OS rates of the patients with non-infectious complication and without were 6.5% and 29.5% at 3 years, and 6.5% and 22.6% at 5 years, respectively ($p=0.0878$). The 3-year and 5-year survival also tended to be worse in patients with non-infectious complications than in those without non-infectious complications.

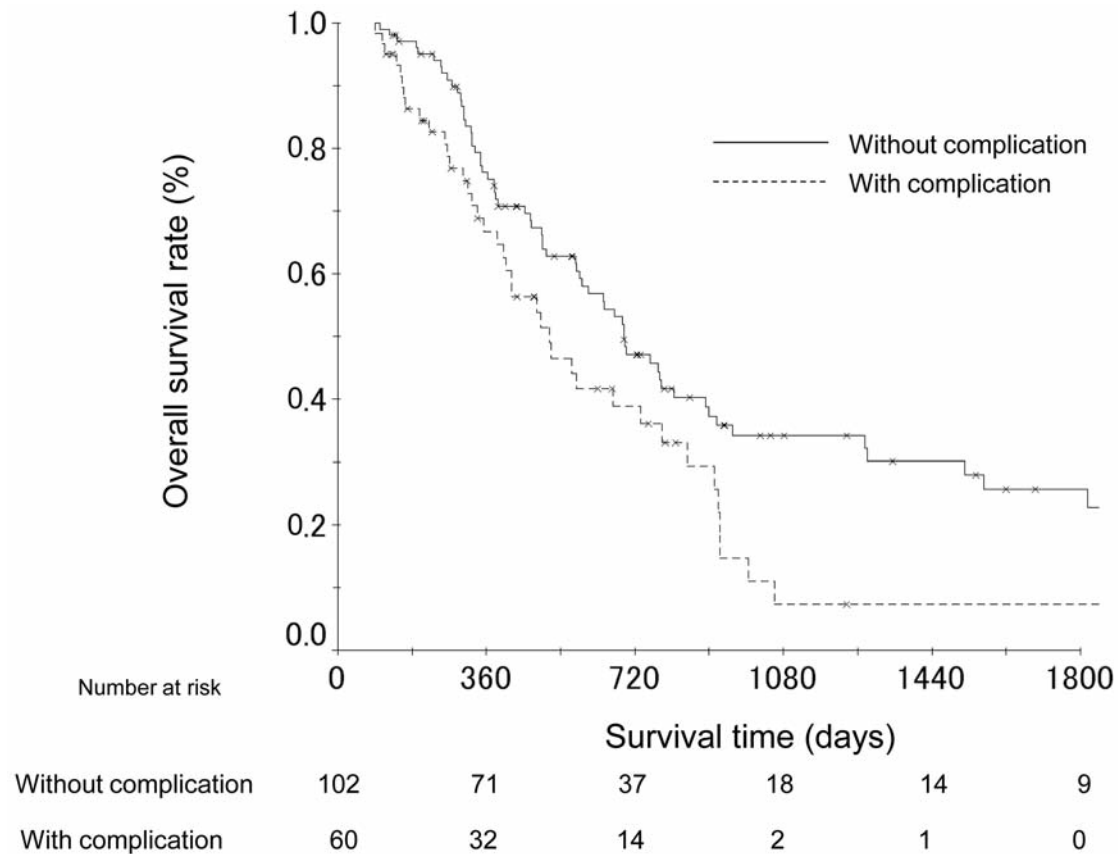


Figure 2. The recurrence-free survival curves of those with surgical complications and those without surgical complications.

When comparing the relationship between the prognosis of patients and the surgical complications in the patients who underwent pancreaticoduodenectomy or total pancreatectomy, the OS rates of the patients with and without surgical complications were 8.7% and 27.3% at 3 years, and 4.4% and 23.4% at 5 years, respectively ($p=0.0587$). When comparing the relationship between the prognosis of patients and the surgical complications in the patients who underwent distal pancreatectomy, the OS rates of the patients with surgical complications and those without were 0.0% and 48.2% at 3 years, 0.0% and 33.1% at 5 years, respectively ($p=0.0593$). The prognosis tended to be worse in patients with surgical complications than in those who without, regardless of the operative procedures.

Discussion

The present study examined whether postoperative complications were associated with a poorer OS and RFS after curative surgery for pancreatic cancer. Our findings clearly indicated that postoperative complications were an

independent risk factor for OS. Similar trends were observed regardless of the type of complication and type of surgical procedures. Moreover, postoperative complications were found to be marginally significantly associated with RFS.

There are several possible reasons why postoperative complications affect the long-term outcome of patients with pancreatic cancer. One possible reason for this association is that the patients who developed postoperative complications may have had some factors that led to decreased host immunity against the tumor. For example, Goldfarb *et al.* reported that treatment aimed at perioperative enhancement of cell-mediated immunity with simultaneous inhibition of excessive catecholamine and prostaglandin responses could be successful in limiting postoperative immune suppression and metastatic progression (23). In addition, Dunn *et al.* suggested that the adaptive immune system could function by identifying and eliminating nascent tumor cells in experimental models (24). Another possible reason for this association is that postoperative complications might be associated with the omission of or a delay in adjuvant chemotherapy. Since 1997, the outcomes of patients with pancreatic cancer have been

Table IV. Univariate and multivariate Cox proportional hazards analysis of clinicopathological factors for overall survival.

Factor	No. of patients	Univariate analysis			Multivariate analysis		
		OR	95% CI	p-Value	OR	95% CI	p-Value
Age (years)							
<70	102	1.000			1.000		
≥70	62	1.151	0.762-1.737	0.505	1.230	0.789-1.916	0.361
Gender							
Female	74	1.000			1.000		
Male	90	1.376	0.932-2.032	0.109	1.296	0.869-1.933	0.204
Tumor diameter (mm)							
<35	87	1.000			1.000		
≥35	77	1.577	1.069-2.327	0.022	1.230	0.791-1.830	0.388
Tumor location							
Body or tail	42	1.000			1.000		
Head	122	1.417	0.905-2.219	0.128	1.096	0.687-1.748	0.701
UICC T status							
T1-T2	11	1.000			1.000		
T3	153	3.976	1.259-12.563	0.019	2.051	0.599-7.019	0.252
Lymph node metastasis							
Negative	42	1.000			1.000		
Positive	122	1.706	1.071-2.718	0.025	1.249	0.720-2.169	0.429
Surgical complication							
No	103	1.000			1.000		
Yes	61	1.616	1.078-2.422	0.020	1.857	1.155-2.986	0.011
Lymphatic invasion							
Absent	83	1.000			1.000		
Present	81	2.115	1.423-3.143	<0.001	1.783	1.108-2.870	0.017
Vascular invasion							
Absent	54	1.000			1.000		
Present	110	1.391	0.925-2.091	0.112	1.040	0.664-1.628	0.864
Adjuvant chemotherapy							
Yes	136	1.000			1.000		
No	28	1.663	1.033-2.676	0.036	1.607	0.945-2.733	0.080

CI: Confidence interval; OR: Odds ratio; UICC: Union for International Cancer Control.

gradually improved by the introduction of effective adjuvant chemotherapies, such as gemcitabine and S-1, which is the oral 5-fluorouracil prodrug tegafur combined with oteracil and gimeracil (25-27). In fact, 83% (136/164) of patients received adjuvant chemotherapy in this study. Merkow *et al.* evaluated 2,047 patients who underwent resection for stage I-III pancreatic adenocarcinoma and classified them into groups of patients who did not experience any postoperative surgical complications, and those who had a serious postoperative surgical complication (28). They found that 57.7% of the overall patient population received adjuvant chemotherapy, with a rate of 61.8% in the patients not experiencing any complications and 43.6% among those who had a serious complication. Serious complications increased the likelihood of not receiving adjuvant therapy by over twofold (odds ratio=2.20, 95% confidence interval=1.73-2.80). The authors of that study concluded that postoperative surgical complications were associated with a marked reduction in the use of adjuvant therapy, and among the patients who were

ultimately treated with chemotherapy, the complications increased the time interval between surgical resection and the initiation of chemotherapy. It was previously reported that incomplete treatment with adjuvant chemotherapy resulted in markedly inferior disease-free survival in patients with breast cancer (29).

Previous studies that investigated the effects of post-operative complications on OS and RFS following surgery generally used their own criteria to grade the severity of the complications, making it difficult to evaluate the results of the study. On the other hand, we used the Clavien-Dindo classification to assess the postoperative complications in the present study (18). Clavien *et al.* proposed general principles to classify complications of surgery based on a therapy-oriented, 4-level severity grading in 1992. Subsequently, the severity grading was refined and applied to compare the results of laparoscopic *versus* open cholecystectomy and liver transplantation. Recently, they re-evaluated and modified the grading to increase its accuracy and its

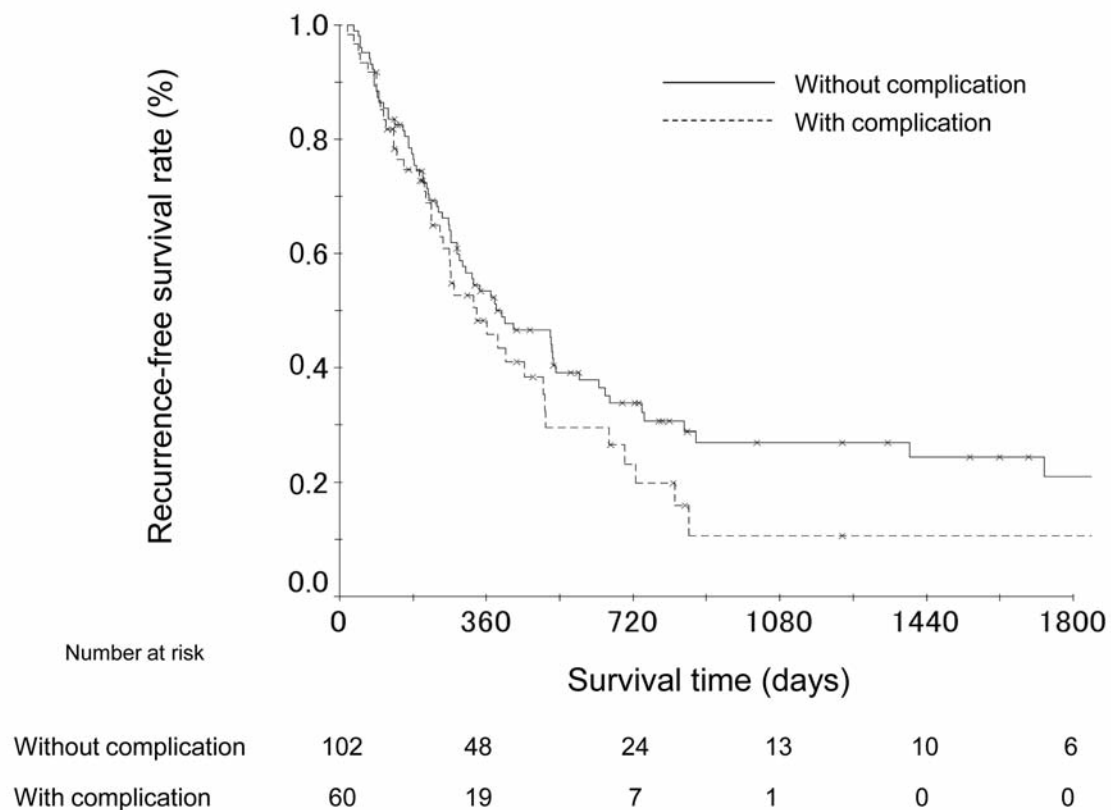


Figure 3. The overall survival curves of those with surgical complicationsthose without surgical complications.

acceptability in the surgical community. Modifications mainly focused on the manner of reporting life-threatening and permanently disabling complications. Therefore, the Clavien-Dindo classification appears reliable and may represent a compelling tool for quality assessment in surgical complications. Moreover, this classification was also used by Kamphues *et al.*, in a study from Germany, who found severe postoperative complications (grade III-IV) have a strong negative impact on the long-term survival of patients with pancreatic head cancer (16).

Limited studies have focused on postoperative complications and long-term outcomes of pancreatic cancer. As mention above, Kamphues *et al.* reported a correlation between postoperative complications and a poorer survival (16). Another study from Switzerland, by Peterman *et al.*, evaluated 101 patients who underwent resection of pancreatic head cancer, and reported a correlation between post-operative complications and poor survival in patients with R1 resection (17). There were several differences between the previous studies and the present study.

Firstly, the curability was different. The present study included only patients whose surgery was curative, while the

previous two studies included patients whose surgery was not curative. Secondly, the surgical procedures were different. The present study included distal pancreatectomy, pancreaticoduodenectomy and total pancreatectomy, while the previous studies included only pancreaticoduodenectomy. Generally, pancreatic cancer surgery requires a variety of surgical procedures for curative treatment. Moreover, it is unclear whether their results can be adopted by East-Asian countries due to the differences between ethnic groups. For these reasons, we re-evaluated the relationships between postoperative complications and the OS and RFS in patients with pancreatic cancer.

Special attention is required when interpreting the current results because there are several potential limitations associated with this study. Firstly, this study was a retrospective single-center study with a relatively small sample size. Postoperative complications were recorded from the patient's records. Most treatments were selected by the individual physicians, not based on a specific protocol. Our findings might therefore have been obtained by chance. Moreover, this study might have possible selection bias. Secondly, the definition and classification of

morbidity were different from those used in the previous studies. These differences might also have affected the results. However, the incidence of surgical morbidity was similar to that in the previous reports. For example, the incidence of pancreatic fistula formation in our study was about 9.8%, similar to the reported rates in many other large studies (11-13). Thirdly, the degree of immune suppression was not assessed in this study. The previous studies demonstrated that the prognosis of the patients with pancreatic adenocarcinoma is influenced by their general status, nutritional status, and immune status (30, 31). However, we were unable to evaluate these factors. Therefore, future studies should focus on this issue. Considering these limitations, the current results should be validated in other series with a larger number of patients.

In conclusion, the development of postoperative complications was a risk factor for poorer OS and disease recurrence in patients who underwent curative surgery for pancreatic cancer. To improve the survival of patients with pancreatic cancer, it is necessary to avoid postoperative complications. The surgical procedure, perioperative care and the surgical strategy should be carefully planned to help reduce complications.

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Conflicts of Interest

None declared

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