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A lack of postoperative complications after pancreatectomy contributes to the long-term survival of patients with pancreatic cancer

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ABSTRACT

Background: /Objectives: The objectives of this study were to identify the factors affecting patients' survival and the characteristics of five-year survivors of pancreatic ductal adenocarcinoma (PDAC) after pancreatectomy as well as to clarify the correlation between the development of postoperative complications and a five-year survival.
Methods: A total of 104 patients underwent pancreatectomy for PDAC between April 2005 and March 2013 with curative intent. Patients who survived for more than five years after pancreatectomy were classified as long-term survivors. Sixteen demographic and clinical variables and 10 pathological variables were comprehensively assessed for their associations with the patients' survival time and long-term survival.
Results: The presence of preoperative comorbidity (OR: 1.65, 95% CI 1.02–2.67, $p = 0.042$), postoperative overall complications (OR: 1.78, 95% CI 1.03–3.10, $p = 0.041$), a lymph node positivity ratio of ≥0.2 (OR: 3.04, 95% CI 1.51–6.11, $p = 0.002$), and portal invasion (OR: 2.58, 95% CI 1.48–4.49, $p = 0.001$) were identified as independent factors affecting the patients' survival. The absence of postoperative overall complications was identified as an independent factor related to long-term survival in the multivariate analysis (OR: 0.08, 95% CI 0.01–0.82, $p = 0.034$).
Conclusions: The presence of preoperative comorbidity, postoperative overall complications, LNR ≥0.2, and portal invasion were prognostic factors affecting the patients' survival, and avoiding postoperative complications after pancreatectomy might contribute to the long-term survival of PDAC patients after pancreatectomy. The further improvement of surgical procedures and perioperative care in order to reduce the rate of postoperative complications should be attempted.

Introduction

While advancements in the early detection [1–6] and advent of new adjuvant chemotherapies [7–9] have lengthened the survival of patients with pancreatic ductal adenocarcinoma (PDAC), pancreatectomy remains the only curative treatment for this population [2,3]. Several recent retrospective studies have reported that the 5-year survival rate of PDAC patients who underwent pancreatectomy has been improved to approximately 20%–30% [1,4,10–13]. However, the proportion of five-year survivors after pancreatectomy has remained small, and improvements in the survival time have not led to the long-term survival or cure of patients with PDAC who undergo pancreatectomy [14–16].

A number of previous studies have revealed the pathological predictors affecting the PDAC patients' survival after pancreatectomy. However, long-term survivors have not all had these pathological predictors, and there are some limitations associated with the use of statistical prognostic factors to estimate the long-term survival of PDAC patients [2,4–6,17–19]. In addition to pathological predictors, recent studies have also shown that the development of postoperative complications can reduce patients' survival or increase the risk of disease recurrence in patients who undergo pancreatectomy for PDAC [20–28]. However, only a few studies

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have assessed the correlation between the development of postoperative complications after pancreatectomy and the five-year survival of PDAC [1,13]. The prognostic factors for the long-term survival can only be determined by analyzing actual long-term survivors [13,19].

In this retrospective study, we examined patients who underwent pancreatectomy for PDAC and had been observed for more than five years after their resection in order to identify the predictive factors influencing the patient survival and the characteristics of five-year survivors. The aim of this study was to identify the factors that significantly contribute to the long-term survival after pancreatectomy based on an analysis of actual long-term survivors (five years or longer).

Materials and methods

Patients

This study was reviewed and approved by the Institutional Review Board of Jichi Medical University. Before surgery, we communicated fully with the patients and their families and explained the advantages of surgery and possible complications. Written informed consent was obtained from all patients according to our institutional guidelines.

A total of 104 patients underwent pancreatectomy for PDAC with curative intent between April 2005 and March 2013. Preoperatively, if curative resection of PDAC was regarded as possible and distant metastases could be ruled out by standard imaging procedures, an indication of pancreatectomy was confirmed. When we found macroscopic peritoneal dissemination or hepatic metastasis, pancreatectomy was not performed. In addition, sampling of paraaortic lymph nodes (LNs) was routinely performed for patients undergoing pancreaticoduodenectomy (PD), and if LN metastasis was confirmed using frozen sections, PD was not performed [29]. Lymphadenectomy during pancreato-duodenectomy includes the suprapyloric LNs, infrapyloric LNs, LNs along the common hepatic artery, LNs in the hepaticoduodenal ligament, LNs on the surface of the pancreatic head, and LNs along the right lateral superior mesenteric artery [30]. Lymphadenectomy during left-sided pancreatectomy includes the LNs along the common hepatic artery, LNs around the celiac artery, LNs at the splenic hilum, LNs along the splenic artery, and LNs along the inferior margin of the pancreas [30].

All patients were histologically confirmed to have the common type of PDAC, and those with other pancreatic neoplasms, such as intraductal papillary mucinous neoplasms, cystadenocarcinoma, and endocrine tumors, were excluded from this study. Patients' performance status was evaluated using the Eastern Cooperation Oncology Group performance scale, and all were judged to have a score of 0 or 1. Neoadjuvant chemotherapy was not applied during this period.

The preoperative and postoperative data were collected by a review of the patients' medical records. Patients were followed up in our hospital or by the patient's primary physician for at least five years or until their death. We defined the overall survival time as the length of time between the date of pancreatectomy and the date of death or last known contact via a hospital visit, or visit to the primary physician, or phone call. Those who survived for more than 5 years after pancreatectomy were classified as long-term survivors, while those with a shorter survival were classified as short-term survivors.

The 16 demographic and clinical variables included gender, age, preoperative comorbidity, preoperative serum total protein, preoperative serum albumin, preoperative serum C-reactive protein (CRP), presence of preoperative biliary drainage, preoperative serum carcinoembryonic antigen (CEA), preoperative serum carbohydrate antigen 19–9 (CA19-9), intraoperative estimated blood loss, intraoperative blood transfusion, postoperative overall complications, postoperative major complications, clinical relevant postoperative pancreatic fistula (CR-POPF), location of tumor (head/body + tail), and application of adjuvant chemotherapy. Preoperative comorbidities included hypertension, coronary artery disease, cerebral artery disease, diabetes mellitus, and chronic kidney disease. In 2008, we introduced adjuvant chemotherapy using gemcitabine [7,8], and since 2012, tegafur/gimeracil/oteracil potassium has also been used [9]. The administration and dosage of adjuvant chemotherapy were ultimately decided by the local medical oncologists according to the patients' condition or wish. We were unable to retrieve accurate information on potential interruptions and suspensions of adjuvant therapy. In this study, patients who received adjuvant chemotherapy were defined as those who received adjuvant chemotherapy, irrespective of the completion of the planned treatment or recurrent disease that developed during this treatment [22]. The cut-of values of preoperative serum total protein, serum albumin, serum CRP, and intraoperative estimated blood loss were set according to the median values of each variable. A receiver operating characteristics (ROC) curve was constructed to estimate the optimal cut-off values for preoperative serum CEA and CA19-9.

The 10 pathological variables included histologically assessed tumor size (<2 cm/≥2 cm), tumor depth (T1+T2/T3+T4), surgical margin status (positive/negative), tumor differentiation (G1+G2/G3+G4), number of resected lymph nodes (<15/≥15), lymph node positivity ratio (LNR) (<0.2/≥0.2), perineural invasion (positive/negative), lymphatic invasion (positive/negative, venous invasion (positive/negative), and portal invasion (positive/negative). Tumors were classified according to the TMN staging system of the UICC, 7th version. Surgical margins were divided into a negative margin (R0) and positive margins, including a microscopic positive margin (R1) and macroscopic positive margin (R2). The cut-off value of number of resected LNs was set at 15, because according to international consensus, the number of resected LNs ≥15 is required for standard lymphadenectomy in surgery for pancreatic adenocarcinoma [30]. The LNR was calculated as the number of metastatic lymph nodes divided by the total number of nodes examined. Recent studies have suggested that an LNR or ≥0.2 is a more refined indicator of the prognosis than LN metastasis [5,30]. Thus, in this study, the LNR was included as a variable but not the presence of LN metastasis, and we set the cut-off value of the LNR to 0.2 [5,30].

Definitions of postoperative complications

Postoperative complications were considered to include any deviation from the normal postoperative course, prolonging the length of the postoperative hospital stay and requiring supplementary care. The severity of complications was graded per the Clavien-Dindo classification, and major complications were defined as any complication of grade 3 or greater severity [31]. An intra-abdominal abscess was defined as intraabdominal fluid collection with a positive culture or organ/space surgical site infection in the abdominal cavity [32]. An intraabdominal infection (IAI) was defined as drainage fluid with positive cultures with or without abscess formation [33]. The presence of POPF [34], delayed gastric emptying (DGE) [35], and postpancreatectomy hemorrhaging (PPH) [36] were determined according to the International Study Group of Pancreatic Surgery criteria, and Grade B and C POPF were designated as CR-POPF. In patients with more than one complication, the highest grade was quoted [21,26]. Perioperative death was defined as any death occurring in the hospital or within 30 days after the operation.

Statistical analyses

Continuous variables were presented as median and range. Categorical variables were presented as absolute number and percentages. A univariate analysis identifying the variables affecting patients' survival was performed using the Kaplan-Meier method and the log-rank test. All variables were dichotomized for the analysis. $P < 0.05$ was considered statistically significant, and variables with a significance of $p < 0.05$ in the univariate analysis were entered into the multivariate analysis with the Cox proportional hazard model. Fisher's exact test was used to compare prognostic variables between long-term (≥5 years) and short-term (<5 years) survivors following surgical resection. Categorical variables were reported as the number and percentage. Variables with a significance of $p < 0.05$ in the univariate analysis were entered into the multivariate regression analysis to identify independent factors.

Results

Patients

There were no cases of postoperative mortality; thus, all 104 patients were studied. The study group consisted of 66 males (63.5%) and 38 females (36.5%) with a median age of 66 (range 37–79) years old. Eighty patients (76.9%) underwent PD/subtotal stomach-preserving PD, and distal pancreatectomy and total pancreatectomy were performed in 18 (17.3%) and 6 (5.8%) patients, respectively. As shown Table 1, 36 (34.6%) patients experienced postoperative complications. The details were as follows: intraabdominal abscess (n = 6), delayed gastric emptying (n = 6), intraabdominal infection (n = 4), CR-POPF (n = 3), PPH (n = 2), surgical site infection (n = 2), cholangitis (n = 1), ascites (n = 1), pneumonia (n = 1), peptic ulcer (n = 1), neurogenic bladder (n = 1), bowel obstruction (n = 1), splenic vein thrombosis (n = 1), and sepsis (n = 1). Among the 36 patients who experienced postoperative complications, major complications occurred in 10 patients; were all surgery-related complications. The details of major complications were follows: intraabdominal abscess (n = 5), PPH (n = 2), intraabdominal infection (n = 1), CR-POPF (n = 1), and ascites (n = 1). Two patients who developed PPH required radiological intervention under local anesthesia and ICU-management; thus, these were classified as grade 4a complications. The other 8 cases required radiological intervention under local anesthesia and were judged as grade 3a complications. They all recovered from complications and were discharged.

Survival analyses

Table 2 shows the results of a univariate analysis of factors that influenced the overall survival in 104 patients. An ROC curve demonstrated that a preoperative serum CEA level of 2.4 ng/ml was the optimal cut-off value for the analysis of overall survival, with 78.3% sensitivity and 57.1% specificity. The area under the curve (AUC) was 0.668 (Fig. 1a). An ROC curve demonstrated that a preoperative serum CA19-9 level of 162.0 U/ml was the optimal cut-off value for the analysis of overall survival, with 62.7% sensitivity and 66.7% specificity. The AUC was 0.668 (Fig. 1b). Preoperative comorbidity, preoperative serum CRP, preoperative serum CEA, intraoperative estimated blood loss, postoperative overall complications, tumor location, adjuvant chemotherapy, tumor size, number of resected LNs, and LNR, and portal invasion were identified as significant factors in the univariate analyses. Furthermore, as shown in Table 3, the following 4 factors were identified as independent factors in the multivariate analysis: the presence of preoperative comorbidity (OR:1.65, 95% CI 1.02–2.67, p = 0.042), postoperative overall complications (OR:1.78, 95% CI 1.03–3.10, p = 0.041), LNR ≥0.2 (OR: 3.04, 95% CI 1.51–6.11, p = 0.002), and portal invasion (OR: 2.58, 95% CI 1.48–4.49, p = 0.001). Table 4 shows the results of a univariate analysis comparing actual long-term (≥5 years, n = 21) and short-term (<5 years, n = 83) survivors following surgical resection. The univariate analysis showed that preoperative comorbidity, preoperative serum CRP, preoperative serum CEA, intraoperative estimated blood loss, postoperative overall complications, tumor size, venous invasion, and portal invasion were significant. Furthermore, as shown in Table 5, the absence of postoperative overall complications was identified as an independent factor associated with long-term survival in the multivariate analysis (OR: 0.08, 95% CI 0.01–0.82, p = 0.034).

Table 1
Characteristics of 104 cases who underwent pancreatectomy for pancreatic cancer.

Demographic and clinical variables	
Gender	
Male	66 (63.5%)
Female	38 (36.5%)
Age (years)	66 (37–79)
Preoperative comorbidity, present	54 (51.9%)
Preoperative total protein (g/dL)	6.8 (4.5–8.7)
Preoperative albumin (g/dL)	3.8 (2.7–4.8)
Preoperative CRP (mg/dL)	0.27 (0.01–13.6)
Biliary drainage, present	55 (52.8%)
Preoperative CEA (ng/ml)	3.7 (0.5–36.8)
Preoperative CA19-9 (U/ml)	220.8 (2.0–28840)
Intraoperative estimated blood loss (ml)	845 (170–3850)
Blood transfusion, present	25 (24.0%)
Postoperative overall complications, present	35 (33.6%)
Postoperative major complications, present	10 (9.6%)
Clinically relevant postoperative pancreatic fistula, present	4 (3.8%)
Tumor location	
Head	82 (78.8%)
Tail + body	22 (11.2%)
Adjuvant chemotherapy, yes	78 (75.0%)
Pathological variables	
Tumor size	
<2 cm	8 (7.7%)
>2 cm	94 (90.4%)
Unknown	2 (1.9%)
T (UICC)	
T1+T2	74 (71.1%)
T3+T4	30 (28.9%)
Resectability	
R0	85 (81.7%)
R1+R2	17 (16.3%)
Unknown	2 (1.9%)
Tumor differentiation	
G1+G2	92 (89.4%)
G3+G4	12 (10.6%)
Resected lymph node number	26 (4–57)
Lymph node metastasis, present	75 (72.1%)
Lymph node metastasis ratio	
<0.2	94 (90.4%)
≥0.2	10 (9.6%)
Perineural invasion, present	89 (85.6%)
Lymphatic invasion, present	94 (90.4%)
Venous invasion, present	76 (73.1%)
Portal invasion, present	23 (22.1%)

Discussion

In this retrospective study, we comprehensively examined the correlation among 16 demographic and clinical variables, 10 pathological variables, and the survival of 104 patients who underwent pancreatectomy of PDAC. We found that the presence of preoperative comorbidity, postoperative overall complications, high LNR, and portal invasion were prognostic factors affecting the patients'

Table 2
Results of the univariate analysis for the overall survival.

Demographic and clinical variables	5-year survival (%)	Median survival time (months)	p-value
Gender			
male	25.0	26.2	0.161
female	42.6	39.9	
Age			
<66 years old	38.7	33.0	0.246
≥66 years old	25.0	33.3	
Preoperative comorbidity			
absent	37.8	39.9	0.024
present	.22.8	26.2	
Preoperative total protein			
<6.8 g/dL	38.3	37.8	0.400
≥6.8 g/dL	25.6	25.7	
Preoperative albumin			
<3.8 g/dL	30.9	28.4	0.251
≥3.8 g/dL	31.7	34.0	
Preoperative CRP			
<0.27 mg/dL	44.2	47.6	0.043
≥0.27 mg/dL	14.9	26.2	
Preoperative biliary drainage			
absent	41.8	47.7	0.071
present	23.2	21.4	
Preoperative CEA			
<2.4 ng/ml	51.6	68.3	0.004
≥2.4 ng/ml	16.7	25.7	
Preoperative CA19-9			
<162.0 U/ml	33.2	37.8	0.101
≥162.0 U/ml	19.6	21.4	
Intraoperative estimated blood loss			
<845 ml	38.7	42.2	0.022
≥845 ml	21.5	22.0	
Blood transfusion			
absent	31.1	33.3	0.211
present	30.3	38.3	
Postoperative overall complications			
absent	37.8	37.8	0.003
present	12.3	22.3	
Postoperative major complications			
absent	30.6	33.0	0.931
present	33.2	37.1	
Clinically relevant postoperative pancreatic fistula			
absent	30.4	33.0	0.777
present	49.8	32.1	
Tumor location			
head	25.6	26.2	0.012
tail + body	52.7	68.3	
Adjuvant chemotherapy			
no	46.8	48.5	0.028
yes	26.3	31.7	

Pathological variables	5-year survival (%)	Median survival time (months)	p-value
Tumor size			
<2 cm	74.9	104.8	0.017
≥2 cm	26.3	20.4	
Unknown			
T (UICC)			
T1+T2	32.8	34.0	0.068
T3+T4	24.3	26.0	
Resectability			
R0	31.7	36.7	0.124
R1+R2	16.9	22.0	
Unknown			
Tumor differentiation			
G1+G2	32.8	34.0	0.215
G3+G4	14.9	19.0	
Resected LN number			
<15	49.8	48.5	0.036
≥15	26.7	26.2	
Lymph node metastasis ratio			
<0.2	35.2	37.0	<0.001
≥0.2	0.0	10.3	
Perineural invasion			
absent	35.2	47.7	0.403
present	30.6	31.7	

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Table 2 (*continued*)

Pathological variables	5-year survival (%)	Median survival time (months)	p-value
Lymphatic invasion			
absent	35.6	47.7	0.559
present	29.8	33.0	
Venous invasion			
absent	48.1	38.3	0.094
present	24.1	32.1	
Portal invasion			
absent	38.0	37.8	0.004
present	0.0	25.7	

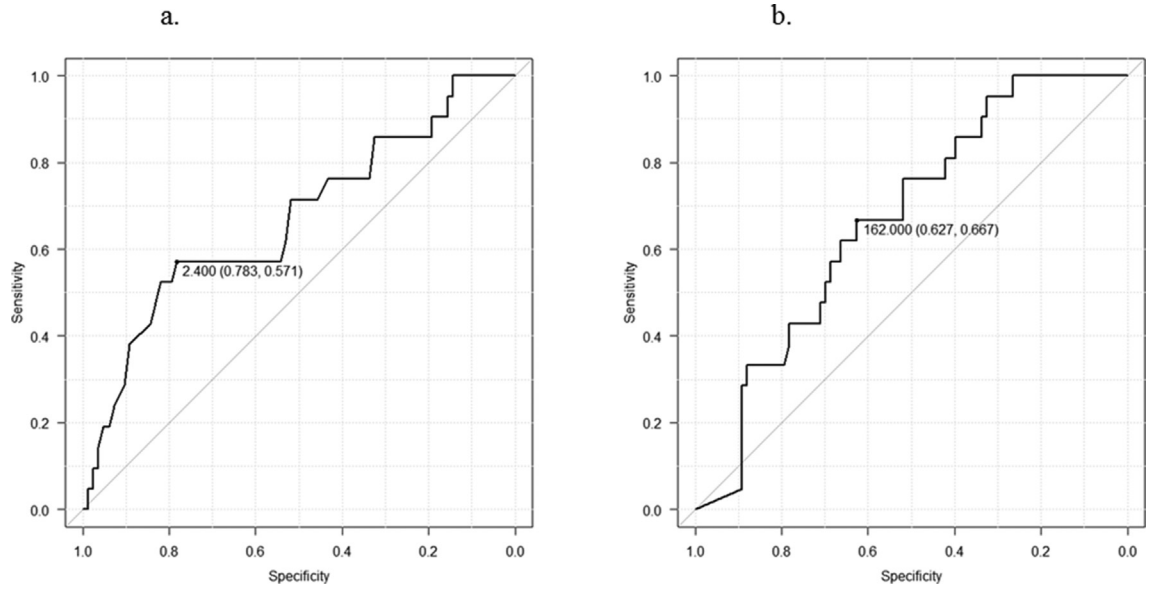

Fig. 1. The receiver operative characteristic curve (ROC) analysis to determine the cutoff value of CEA (Fig. 1a) and CA19-9 (Fig. 1b). ROC curve (thick line), 95% CI bounds (narrow line).
An ROC curve demonstrated that a preoperative serum CEA level of 2.4
ng/ml was the optimal cut-off value for the analysis of overall survival, with 78.3% sensitivity and 57.1% specificity. The area under the curve (AUC) was 0.668 (Fig. 1a). An ROC curve demonstrated that a preoperative serum CA19-9 level of 162.0 U/ml was the optimal cut-off value for the analysis of overall survival, with 62.7% sensitivity and 66.7% specificity. The AUC was 0.668 (Fig. 1b).

Table 3
Results of a multivariate analysis for the overall survival.

Variables	Odds ratio	95% confidence interval	p-value
Preoperative comorbidity, present	1.65	1.02–2.67	0.042
Preoperative CRP, ≥0.27 mg/dL	1.32	0.78–2.21	0.300
Preoperative CEA, ≥2.4 ng/ml	1.35	0.66–2.74	0.410
Intraoperative estimated blood loss, ≥845 ml	1.15	0.68–1.96	0.600
Postoperative overall complications, present	1.78	1.03–3.10	0.041
Tumor location, head	0.59	0.27–1.26	0.170
Adjuvant chemotherapy, yes	1.31	0.66–2.58	0.450
Tumor size, ≥2 cm	2.18	0.58–8.13	0.250
Resected LN number, ≥15	0.90	0.39–2.07	0.800
Lymph node metastasis ratio ≥0.2	3.04	1.51–6.11	0.002
Portal invasion, present	2.58	1.48–4.49	0.001

survival after pancreatectomy for PDAC. We also learned that absence of postoperative complications was related to the five-year survival of patients of PDAC. Of note, the prognostic factors affecting the patients' survival differed from the characteristics of long-term survivors. Indeed, previous studies have also shown a similar discrepancy between the prognostic factors of the overall survival obtained from statistical analyses and those obtained from an analysis of actual long-term survivors [6,17–19]. Thus, an analysis investigating the factors related to the long-term survival should be performed in actual five-year survivors.

Recent studies have suggested that an LNR of ≥0.2 is a more refined indicator of the prognosis in comparison to the presence of LN metastasis [5,30], and our results also revealed that an LNR ≥0.2 was a significant predictor of the survival of PDAC patients. The LNR is the number of metastatic LNs divided by the total number of LNs examined, so its value is influenced by the total number of resected LNs. The median number of resected LNs in this series was 26, which fulfilled the criteria for standard lymphadenectomy in

Table 4
Results of a univariate analysis comparing the patients with a long- and short-term survival.

Demographic and clinical variables	Long-term survivor (n = 21)	Short-term survivor (n = 83)	p-value
Gender			
male	11 (52.4%)	55 (66.3%)	0.311
female	10 (47.6%)	28 (33.7%)	
Age			
<66 years old	13 (61.9%)	33 (39.8%)	0.087
≥66 years old	8 (38.1%)	50 (60.2%)	
Preoperative comorbidity			
absent	15 (71.4%)	35 (42.2%)	0.026
present	6 (28.6%)	48 (57.8%)	
Preoperative total protein			
<6.8 g/dL	11 (52.4%)	36 (43.4%)	0.474
≥6.8 g/dL	10 (47.6%)	47 (56.6%)	
Preoperative albumin			
<3.8 g/dL	8 (38.1%)	43 (51.8%)	0.331
≥3.8 g/dL	13 (61.9%)	40 (48.2%)	
Preoperative CRP			
<0.27 mg/dL	17 (81.0%)	35 (42.2%)	0.003
≥0.27 mg/dL	4 (19.0%)	48 (57.8%)	
Preoperative biliary drainage			
absent	12 (57.1%)	37 (44.6%)	0.336
present	9 (42.9%)	46 (55.4%)	
Preoperative CEA			
<2.4 ng/ml	11 (52.4%)	17 20.5 (%)	0.005
≥2.4 ng/ml	10 (47.6%)	66 (79.5%)	
Preoperative CA19-9			
<162.0 U/ml	13 (61.9%)	31 (37.3%)	0.050
≥162.0 U/ml	8 (38.1%)	52 (62.7%)	
Intraoperative estimated blood loss			
<845 ml	15 (71.4%)	37 (44.6%)	0.049
≥845 ml	6 (28.6%)	46 (55.4%)	
Blood transfusion			
absent	18 (85.7%)	61 (73.5%)	0.391
present	3 (14.3%)	22 (36.5%)	
Postoperative overall complications			
absent	19 (90.5%)	50 (60.2%)	0.009
present	2 (9.5%)	33 (39.8%)	
Postoperative major complications			
absent	19 (90.5%)	75 (90.4%)	1
present	2 (9.5%)	8 (9.6%)	
Clinically relevant postoperative pancreatic fistula			
absent	20 (95.2%)	80 (96.4%)	1
present	1 (4.8%)	3 (3.6%)	
Tumor location			
head	14 (66.7%)	68 (81.9%)	0.142
tail + body	7 (33.3%)	15 (18.1%)	
Adjuvant chemotherapy			
No	7 (33.3%)	19 (22.9%)	
Yes	14 (66.7%)	64 (77.1%)	0.398
Pathological variables	**Long-term survivor (n = 21)**	**Short-term survivor (n = 83)**	**p-value**
Tumor size			
<2 cm	6 (28.6%)	2 (2.4%)	<0.001
≥2 cm	15 (71.4%)	79 (95.2%)	
Unknown		2 (2.4%)	
T (UICC)			
T1+T2	18 (85.7%)	56 (67.5%)	0.114
T3+T4	3 (14.3%)	27 (32.5%)	
Resectability			
R0	19 (90.5%)	66 (79.5%)	0.182
R1+R2	1 (4.8%)	16 (19.3%)	
Unknown	1 (4.8%)	1 (1.2%)	
Tumor differentiation			
G1+G2	20 (95.2%)	72 (86.7%)	0.455
G3+G4	1 (4.8%)	11 (13.3%)	
Resected LN number			
<15	14 (66.7%)	38 (45.8%)	0.052
≥15	7 (33.3%)	45 (54.2%)	
Lymph node metastasis ratio			
<0.2	21 (100.0%)	73 (88.0%)	0.068
≥0.2	0 (0.0%)	10 (12.0%)	
Perineural invasion			
absent	4 (19.0%)	11 (13.3%)	0.497

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Table 4 (*continued*)

Pathological variables	Long-term survivor (n = 21)	Short-term survivor (n = 83)	p-value
present	17 (81.0%)	72 (86.7%)	
Lymphatic invasion			
absent	2 (9.5%)	7 (8.4%)	1
present	18 (85.7%)	76 (91.6%)	
unknown	1 (4.8%)		
Venous invasion			
absent	10 (47.6%)	18 (21.7%)	0.026
present	11 (52.4%)	65 (78.3%)	
Portal invasion			
absent	21 (100.0%)	60 (72.3%)	0.003
present	0 (0.0%)	23 (27.7%)	

Table 5
Results of a multivariate analysis comparing the patients with a long- and short-term survival.

Variables	Odds ratio	95% confidence interval	p-value
Preoperative comorbidity, absent	0.332	0.08–1.31	0.116
Preoperative CRP, <0.27 mg/dL	0.40	0.10–1.69	0.214
Preoperative CEA, ≥2.4 ng/ml	0.356	0.09–1.49	0.158
Intraoperative Estimated Blood Loss, <845 ml	0.54	0.13–2.21	0.392
Postoperative overall complications, absent	0.08	0.01–0.82	0.034
Tumor size, <2 cm	0.08	0.01–1.21	0.069
Venous invasion, absent	0.24	0.05–1.09	0.065
Portal invasion, absent	0.00	0.00-Inf	0.992

surgery for pancreatic adenocarcinoma [30]. The LNR in this series therefore seems to reflect the LN status accurately. Multiple studies have reported that PDAC with portal invasion is associated with a high probability of early recurrence of local and systemic disease, resulting in poor outcomes [37–39]. According to the National Comprehensive Cancer Network (NCCN) guidelines [40], any tumor that presented with radiographic evidence of portal invasion was defined as borderline resectable pancreatic cancer (BRPC), and the NCCN guidelines and recent studies recommend neoadjuvant therapy for the treatment of BRPC, but not up-front surgery [37–40]. In this series, we also found that portal invasion was a significant predictor of the survival of PDAC patients who underwent pancreatectomy. The presence of high LNR and portal invasion are biological features related to PDAC or are indicative of tumor progression. In addition, the presence of preoperative comorbidities was also a significant predictor of the survival of PDAC patients who underwent pancreatectomy. The presence of preoperative comorbidity is closely related to poor physiology, and reduces survival [3,26]. The presence of preoperative comorbidities and old age or postoperative complications may be closely related [41,42]; thus, it may not be possible to administer more aggressive therapies to patients with preoperative comorbidities. Geriatric assessments before pancreatectomy will become more important with the increasing number of elderly PDAC patients undergoing pancreatectomy [3,26]. Thus, these factors may affect survival after pancreatectomy for PDAC.

Postoperative complications have a negative effect on long-term survival in patients with various type of gastrointestinal cancer [23,43]. The impact of postoperative complications after pancreatectomy on the survival of PDAC patients has been unclear. Several studies have shown an association between the development of postoperative complications or postoperative major complications and an impaired PDAC patient survival [20–27], but the two largest studies conducted to date found no correlation between these factors [1,28]. One possible reason for these conflicting results is the difference in the incidence of postoperative major complications (Table 6). In previous reports analyzing the correlation between the postoperative complications and patient survival, the incidence of overall complications was uniformly around 50%, but the incidence of major complications ranged from 6.9% to 25.8% [1,20–28]. Several reports in which the incidence of postoperative major complications seemed to be high, ranging from 16.6% to 25.8% [20–22,24–28], showed that postoperative major complications resulted in a reduction in the administration of adjuvant

Table 6
Correlations between incidence of postoperative complications and patients' survival in previous reports.

Authors	n	Surgical procedure	Overall complications	Effect on survival	Major complications	Effect on survival
Present study	104	All procedures	34.6%	Yes	9.6%	No
Shin SH et al.[1]	2029	All procedures	35.9%	No	6.9%	No
Aoyama T et al.[24]	164	All procedures	37.2%	Yes	12.8%	N.A.
Lewis R et al.[26]	424	All procedures	58.0%	No	14.9%	N.A.
Kamphues C et al.[27]	428	All procedures	33.6%	No	16.6%	Yes
Sandini M et al.[20]	616	All procedures	57.5%	No	18.5%	Yes
Watanabe Y et al.[22]	122	All procedures	63.9%	No	31.0%	Yes
Wu W et al.[25]	1144	PD	49.1%	Yes	18.0%	N.A.
Pugalenthi A et al.[28]	596	PD	51.0%	No	25.3%	No
Le A et al.[21]	93	PD	60.2%	No	25.8%	Yes

PD; Pancreaticoduodenectomy.
N.A.; Not available.

chemotherapy, thereby leading to a poor survival of PDAC patients [21,22,25,44]. Conversely, a recent large study by Shin et al. found no correlation between postoperative major complications and the patients' survival in 2029 patients who underwent pancreatectomy, and the incidence of major complications was 6.9% [1]. The incidence of major complications in the present study was 9.6%, which was comparable to the results of Shin et al. Therefore, the low incidences of postoperative major complications in the present study and that of Shin et al. might have contributed to postoperative major complications not being selected as a significant predictor of the patients' survival after pancreatectomy. However, avoiding postoperative major complications after pancreatectomy is still important, as some reports have shown that the adverse effects of postoperative major complications on patients' survival were independent of the receipt of adjuvant chemotherapy and might affect the survival directly [20].

Previous reports evaluating the pathological characteristics related to the long-term survival after pancreatectomy for PDAC in actual five-year survivors showed that the patient age [2,5], pathologic T stage [2], tumor size [4,5], tumor differentiation [2,5,6,17], surgical margin [4,5,18,19], LN metastasis [4, 5., 18, 19], LNR [5], perineural invasion [6,17,19], and lymphovascular invasion [6,19] were significant factors. However, those previous studies did not include postoperative complications as variables, so we examined the correlation between five-year survivors after pancreatectomy for PDAC and the development of postoperative complications. We found that the absence of postoperative complications was significantly associated with the actual long-term survival of PDAC. Conversely, PDAC-related pathologic factors were not identified in this comprehensive analysis. Some authors have suggested that postoperative complications may be directly responsible for a long-standing immune-suppressive effect, with consequent increased susceptibility to cancer recurrence and death [45,46]. In this study, we were unable to make any definitive speculation, as the presence or grade of long-term immune suppression in patients who suffered from postoperative complications after pancreatectomy was not assessed. However, our results showed that avoiding postoperative complications after pancreatectomy might contribute to substantial improvements in the long-term survival of PDAC patients. The therapeutic impact of previously reported pathological characteristics related to the long-term survival is often limited, as such factors cannot be easily influenced by surgeons, if at all. Therefore, the further improvement of surgical procedures and perioperative care remain the main challenging issue to be addressed by surgeons. The incidence of postoperative complication can be reduced by high-volume surgeons and high-volume centers [27,47,48]. Pancreatectomy for PDAC should be performed in specialized centers in order to reduce the risk of postoperative complications and maximize the chance of a long-term survival of PDAC patients.

Several limitations associated with the present study warrant mention. First, this was a retrospective cohort study conducted at a single institution, and the number of enrolled patients was relatively small. Second, because of the long duration of patient enrollment, the policy and regimens concerning adjuvant chemotherapy changed, and we were unable to retrieve accurate information concerning potential interruptions and suspensions of adjuvant therapy. Third, we were unable to evaluate the presence of long-term immune suppression in patients after pancreatectomy. For these reasons, we could not clearly explain the significant correlation between the development of postoperative complication and the long-term survival of patients after pancreatectomy nor draw any definitive conclusions.

However, since we aimed to clarify the factors associated with the actual five-year survival of patients after pancreatectomy for PDAC, our findings may have important implications. In particular, avoiding postoperative complications after pancreatectomy might contribute to the long-term survival of PDAC patients after pancreatectomy. Further large-scale validation studies will be needed to confirm our findings.

Conclusions

In conclusion, the presence of preoperative comorbidity, postoperative overall complications, LNR $\geq$0.2, and portal invasion were prognostic factors affecting patient survival, and the avoidance of postoperative complications after pancreatectomy might contribute to the long-term survival of PDAC patients after pancreatectomy. Pancreatectomy is the only curative treatment for patients with PDAC, and the further improvement of surgical procedures and perioperative care in order to reduce the rate of postoperative complications should be attempted.

Data availability statement

All data generated or analyzed during this study are included within the article.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.06.012.

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