

Original Article

Preoperative corrected CA19-9 levels predict survival of patients with resected pancreatic cancer

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Abstract: Serum carbohydrate antigen 19-9 (CA19-9) is a useful diagnostic marker of resectable pancreatic ductal adenocarcinoma (PDAC). However, CA19-9 may be artificially elevated. Corrected CA19-9 (cCA19-9) might enable accurate prognosis. Preoperative CA19-9 levels were measured and corrected CA19-9 were calculated in 189 patients who underwent surgical resection for PDAC between 2009 and 2013. Wilcoxon two-sample test, univariate and multivariate methods were used to analyze their relationship with clinicopathological factors and overall survival. Preoperative cCA19-9 was associated with pathologic stage and postoperative survival. Overall survival rates were significantly different between groups with different preoperative cCA19-9 cutoff values (200, 500, and 1000 U/ml), especially in the subgroup UICC stage II/III, which was divided into two groups based on a preoperative cCA19-9 cutoff value of 200 U/ml ($P = 0.036$). In multivariate analysis, preoperative cCA19-9 cutoff value of 200 U/ml (hazard ratio, 1.587; $P = 0.014$) and perineural invasion (hazard ratio, 1.477; $P = 0.049$) were independent predictors of prognosis. In conclusion, the study suggested that preoperative cCA19-9 cutoff value of 200 U/ml is an accurate prognostic factor in clinical staging of resectable PDAC. Preoperative cCA19-9 is a valuable tool for the determination of appropriate treatment for PDAC.

Keywords: Overall survival, pancreatic ductal adenocarcinoma, perineural invasion, preoperative corrected CA19-9, prognostic factor

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death worldwide [1]. Approximately 250,000 people are diagnosed with PDAC worldwide each year, with an equal number of disease-related deaths. These data have not significantly changed over the past decade [2]. Surgical resection is still the major option for cure or long-term survival of PDAC patients, despite the development of multidisciplinary treatments. Resection rates have increased due to recent advances in surgery [3]. However, postoperative prognosis remains dismal due to the high rate of metastasis, recurrence, and peritoneal dissemination [4]. It is important to identify the diagnostic markers for accurate prognosis after pancreatectomy and to assess the therapeutic outcome, selection of reasonable follow-up treatment, and provide comprehensive prognostic data.

CA19-9, a carbohydrate tumor-associated antigen, was isolated from a human colorectal cancer cell line by Koprowski et al. [5, 6]. The monoclonal antibody 1116 NS 19-9 reacts with the sialylated Lewis^{ab} blood group substance. Approximately 5% of the population is Lewis^{a-b} without elevated serum CA19-9 levels [7]. Del Villano et al. [8] developed a radioimmuno-metric assay, which significantly increased the detection sensitivity for serum CA19-9. CA19-9 has been used as an important tool for the diagnosis, prognosis, and monitoring of pancreatic cancer patients [9]. In the past decade, studies suggested that serum CA19-9 is a useful marker for staging the disease, and prognosis after resection [10-18]. However, CA19-9 levels may be artificially elevated in benign pathologic conditions, such as pancreatitis and choledocholithiasis [19], which has limited the diagnostic utility of CA19-9 in patients presenting with biliary obstruction. Correction of CA19-9 levels relative to bilirubin levels may reduce

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Table 1. Clinical and pathological characteristics of pancreatic cancer patients

Characteristic	No. (%)
Age (yr)	
Mean	62.1
Median	63
Range	36-83
Male	121 (64)
Tumor location	
Head	118 (62.4)
Body/tail	71 (37.6)
Pathological differentiation	
Well	3 (1.6)
Moderate	94 (49.7)
Poor	92 (48.7)
UICC pT stage	
T1	6 (3.2)
T2	57 (30.2)
T3	102 (54.0)
T4	24 (12.7)
Stage	
IA	4 (2.1)
IB	46 (24.3)
IIA	49 (25.9)
IIB	48 (25.4)
III	22 (11.6)
IV	20 (10.6)
Lymph node metastasis	60 (31.7)
Residual tumor (R factor) R0	183 (96.8)
Perineural invasion (PI)	117 (61.9)
Preoperative size, cm	3.69
Preoperative CA 19-9, U/mL	
Mean	1012.17
Median	282.90
Range	0.80-20830
Preoperative corrected CA 19-9, U/mL	
Mean	565.00
Median	121.00
Range	0.06-20830.00
Type of resection	
Pancreaticoduodenectomy	118 (62.4)
Distal splenopancreatectomy	71 (37.6)

the interference of cholestasis, and improve the diagnostic value of CA19-9 [11, 20]. In addition, a majority of the past studies involved different PDAC cohorts, which included or excluded cases of jaundiced [10, 11], normal CA19-9 values [16, 18], and unresectable lesions [12-

14, 17, 20]. To the best of our knowledge, no study has specifically correlated preoperative cCA19-9 levels with potentially resectable PDAC in Chinese Hans. Therefore, the aim of the current study was to confirm the benefit of preoperative cCA19-9, and to identify a more precise cCA19-9 cutoff value for resectable PDAC cases in a large cohort of Chinese cases.

Materials and methods

Ethical approval

The study was approved by the Ethical and Research Committee of Shanghai Jiao Tong University. Informed consent was obtained.

Patient selection and preoperative assessment

A series of 189 consecutive patients who underwent resection for PDAC from January 2009 to October 2013 at the Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, were reviewed retrospectively. Preoperative workup included computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasonography (EUS) to evaluate primary and metastatic tumor sites. A diagnosis of pancreatic adenocarcinoma was confirmed histologically in all cases. Other patients with histological variants, such as mucinous cystic adenocarcinoma, intraductal papillary adenocarcinoma, acinar cell carcinoma, and endocrine carcinoma were excluded. Since patients with distant metastasis and peritoneal dissemination were unresectable, they were excluded from this analysis with the exception of patients who were young and healthy, with a solitary liver metastasis.

Pathological investigation and postoperative follow-up

The type of resection, pancreaticoduodenectomy or distal splenopancreatectomy, was performed by experienced skilled surgeons. The surgical specimens were analyzed histopathologically by an experienced pathologist. Based on the predominant pattern of histological differentiation, each tumor was classified as well, moderately, or poorly differentiated ductal ade-

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Table 2. Comparison of serum perioperative CA19-9 and corrected CA19-9 levels

	No. of patients	Preoperative cCA19-9		Preoperative CA19-9	
		Median (U/ml)	P value	Median (U/ml)	P value
Age (yr)					
< 63	88	722	0.268	1182	0.414
≥ 63	101	428		864	
Sex					
Male	121	617	0.602	1056	0.763
Female	68	473		934	
Tumor location					
Head	118	379	0.141	1059	0.756
Body/tail	71	875		934	
Type of resection					
Pancreaticoduodenectomy	118	379	0.141	1059	0.756
Distal splenopancreatectomy	71	875		934	
Pathological factors					
Residual tumor (R factor)					
R0	183	577	0.624	1036	0.481
R1	6	207		256	
Pathological differentiation					
Well/moderate	97	605	0.759	1228	0.252
Poor	92	524		784	
PI					
Yes	117	564	0.995	754	0.358
No	72	566		1152	
UICC pT stage					
T1/T2	63	206	0.008	648	0.185
T3/T4	126	745		1193	
Lymph node metastasis					
Yes	60	649	0.352	1181	0.086
No	129	385		648	
UICC stage					
I	50	210	0.009	689	0.318
II/IV	139	693		1128	

nocarcinoma. Histological evaluation include anterior serosal invasion, retropancreatic tissue invasion, splenic or portal vein invasion, splenic artery invasion, lymph node metastasis, and extrapancreatic nerve plexus invasion. If adenocarcinoma infiltrated the proximal or distal pancreatic transection line or was in the dissected peripancreatic soft-tissue margins, residual tumor (R factor) was considered as R1. All patients with R2 were excluded from this study. Tumor stage, lymph node metastasis, and final stage were classified based on the 7th edition of the International Union Against

Cancer (UICC) tumor-node-metastasis (TNM) classification [21]. Patients were followed at regular intervals after discharge, either by clinical examination or by contacting their general practitioner and/or oncologist to acquire information about disease progression or cancer-related death.

Measurement and adjustment of preoperative CA19-9

All serum CA19-9 values and bilirubin levels were measured at the Department of Clinical Laboratory, Ruijin Hospital, Shanghai. Serum bilirubin levels were routinely analyzed, and serum CA19-9 values were measured using a radioimmunoassay kit manufactured by Abbott Laboratories (Chicago, IL), just before surgery to avoid effects of obstructive jaundice. The stated upper limit of normal for CA19-9 was 37 U/ml. We controlled for bilirubin levels, as increased cholestasis falsely elevated CA19-9 levels, which were probably caused by the decreased capacity of cholestatic liver to degrade and excrete CA19-9. Analyses were performed using CA19-9 values in patients with normal and abnormal bilirubin

levels (≥ 2 mg/dL). In patients with total bilirubin levels of 2 mg/dL or more, the cCA19-9 value was divided by the bilirubin value (mg/dL) [11, 20, 22, 23].

Statistical analysis

The patients were divided into two groups on the basis of clinical and pathological factors. The between-group difference in median preoperative CA19-9 and cCA19-9 levels was evaluated using the Wilcoxon two-sample test. Overall survival was analyzed by the Kaplan-

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Table 3. Univariate analysis of overall survival based on clinicopathological factors

	No. of patients	Overall Survival	
		Median (Range) (months)	P value
Age (yr)			
< 63	88	25 (3-70)	0.03
≥ 63	101	19 (1-57)	
Sex			
Male	121	21 (1-70)	0.809
Female	68	22 (3-65)	
Tumor location			
Head	118	21 (1-70)	0.926
Body/tail	71	22 (1-65)	
Pathological factors			
Residual tumor (R factor)			
R0	183	22 (1-70)	0.574
R1	6	20 (7-34)	
Pathological differentiation			
Well/moderate	97	21 (1-69)	0.676
Poor	92	22 (2-70)	
PI			
Yes	117	19 (1-70)	0.011
No	72	25 (3-69)	
UICC pT stage			
T1/T2	63	25 (2-70)	0.000
T3/T4	126	19 (1-59)	
Lymph node metastasis			
Yes	60	19 (1-46)	0.032
No	129	23 (3-70)	
UICC stage			
I	50	45 (2-70)	0.000
II/IV	139	20 (1-57)	
Adjacent organ invasion			
Yes	112	19 (1-57)	0.004
No	77	25 (2-70)	
Large vascular invasion			
Yes	24	27 (1-70)	0.896
No	165	21 (5-43)	

Meier method, and significance was determined by the log-rank (Mantel-Cox) test. The Kaplan-Meier method and log-rank tests were used to determine differences in overall survival between the two groups based on clinical and pathological factors, and according to five preoperative CA19-9 cutoff values of 37, 100, 200, 500, and 1000 U/ml as reported previously [10]. Factors found significant by univariate

analysis were entered into a multivariate proportional hazards regression model (Cox regression) to determine independent factors predictive of overall survival. All statistical analyses were performed with SPSS version 18. $P < 0.05$ was considered statistically significant.

Results

Demographic data and pathological assessment

Of the 189 patients, 121 (64%) were male and 68 (36%) were female, with a median age of 63 (range, 36-83) y. The pancreatic tumor was confined to the head and body/tail of the pancreas in 118 (62.4%) and 71 patients (37.6%), respectively. Pancreaticoduodenectomy and distal splenopancreatectomy were performed in 118 (62.4%) and 71 patients (37.6%), respectively. R0 and R1 resections were performed in 183 (96.8%) and 6 (3.2%) patients, respectively. Tumors were identified as well-differentiated adenocarcinoma in 3 patients (1.6%), moderately differentiated adenocarcinoma in 94 patients (49.7%), and poorly differentiated adenocarcinoma in 92 patients (48.7%). According to TMN classification, 6 (3.2%), 57 (30.2%), 102 (54.0%) and 24 patients (12.784%) had T1, T2, T3 and T4 tumors, respectively, and 60 patients (31.7%) had lymph node metastasis. Finally, 4 (2.1%), 46 (24.3%), 49 (25.9%), 48 (25.4%), 22 (11.6%) and 20 (10.6%) patients were diagnosed with stage IA, IB, IIA, IIB, III and IV, respectively (Table 1).

Relationship of preoperative CA19-9 and cCA19-9 levels with clinicopathological factors

Preoperative CA19-9 and cCA19-9 levels were compared for clinical and pathological factors (Table 2). Preoperative cCA19-9 levels were significantly higher in patients with UICC pT3/T4 (median = 745 U/ml) than in patients with UICC pT1/T2 (median = 206 U/ml) ($P = 0.008$), or in patients with UICC stage II/IV (median = 693 U/ml) compared with patients with UICC stage I (median = 210 U/ml) ($P = 0.009$). In contrast, uncorrected CA19-9 levels had no significant relationship with any clinicopathological factors.

Univariate analysis of overall survival

The median follow-up time after surgery was 17 (range, 1-70) months for 189 patients. Their

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Table 4. Univariate analysis of overall survival based on cCA19-9 levels

Perioperative cCA19-9 cutoff value (U/ml)	No. of patients	Overall Survival	
		Median (range) (months)	P value
< 37	8	22 (12-65)	0.27
≥ 37	181	21 (1-70)	
< 100	85	25 (3-69)	0.115
≥ 100	104	21 (1-70)	
< 200	119	23 (3-70)	0.006
≥ 200	70	19 (1-60)	
< 500	144	23 (3-70)	0.001
≥ 500	44	16 (1-60)	
< 1000	169	22 (3-70)	0.015
≥ 1000	20	14 (6-35)	

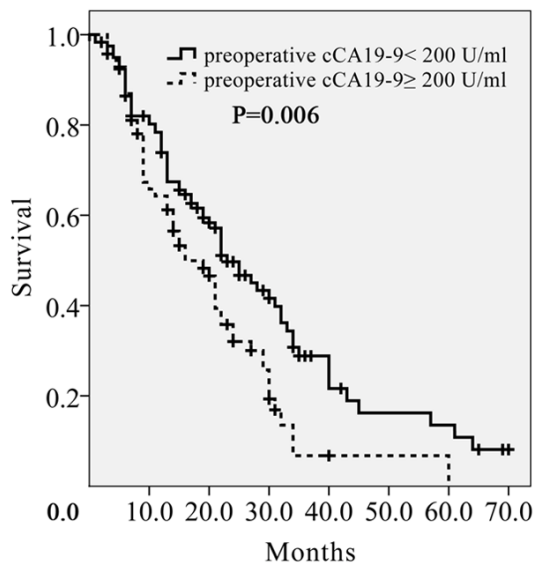


Figure 1. Comparison of postoperative overall survival based on a preoperative CA19-9 cutoff value of 200 U/ml.

overall survival rate was 68.3% at 1 year, 28.6% at 2 years, and 3.2% at 5 years.

The log-rank test results of eleven clinicopathological factors are shown in **Table 3**. Five factors (sex, tumor location, residual tumor, degree of pathological differentiation and large vascular invasion) did not influence overall survival. However, age ($P = 0.03$), PI ($P = 0.011$), UICC final stage ($P = 0.000$), lymph node metastases ($P = 0.032$), adjacent organ invasion ($P = 0.004$) and UICC pT stage ($P = 0.000$) were significantly associated with overall survival.

Since uncorrected CA19-9 levels had no significant relationship with any clinicopathological factors, overall survival was evaluated by univariate analysis based on different cutoff values of preoperative cCA19-9. As shown in **Table 4**, the preoperative cCA19-9 level had a significant effect on prediction of overall survival. When the cCA199 increased from 200 to 1000 U/ml, the median overall survival decreased from 19 to 14 mos. Since 200 U/ml was the lowest cutoff value, which had significant relationship with overall survival among the five preoperative cCA19-9 cutoff points, this value seemed to be the most useful threshold for predicting long-term survival, and was used for univariate analysis of overall survival in this study. As shown in **Figure 1**, the Kaplan-Meier survival curves for groups based on the 200 U/ml cutoff value were significantly different ($P = 0.006$).

In addition, there was a significantly different overall median survival between UICC stage I (45 mo) and II/IV (20 mo). We wondered whether the preoperative cCA19-9 cutoff value of 200 U/ml was prognostic in subgroups of UICC stages. Kaplan-Meier survival curves were created for UICC subgroup stages I, II/III and IV. As shown in **Figure 2**, the threshold demonstrated significant differences in the UICC stage II/III subgroup, but not subgroup stages I and IV.

Multivariate analysis of overall survival

Finally, a multivariate proportional hazards regression model was used to analyze seven factors identified by previous univariate analysis (**Table 5**). Although the UICC final stage was significant in univariate analysis, it was not included in the multivariate analysis because the UICC final stage itself depended upon pT stage and lymph node metastasis, which were confounding factors. This analysis identified a preoperative CA19-9 cutoff value > 200 (HR, 1.587; 95% CI, 1.099-2.292; $P = 0.014$) and PI (HR, 1.477; 95% CI, 1.002-2.178; $P = 0.049$) as independent predictors of poor overall survival.

Discussion

CT is the most acceptable method of imaging patients with PDAC as it enables accurate evaluation of the localization of cancer [24]. CT, in combination with other imaging modalities, such as, ERCP, EUS, positron emission tomog-

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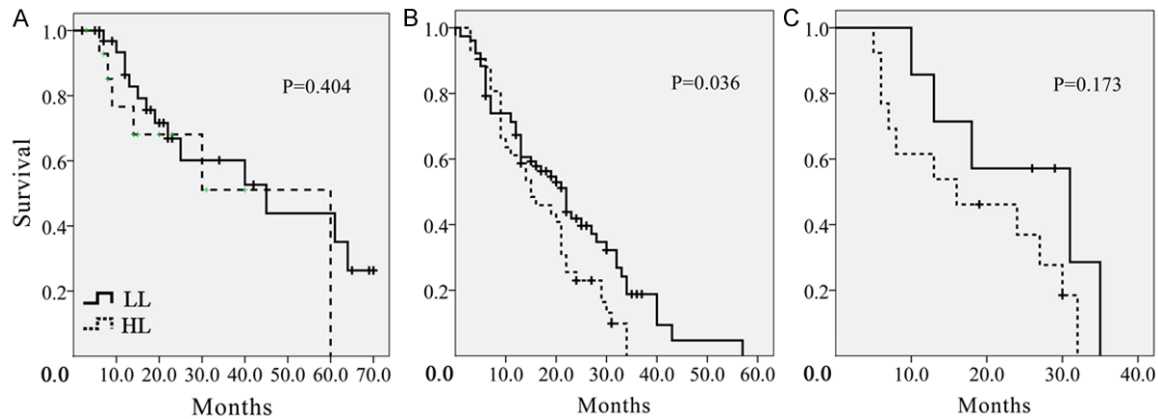


Figure 2. Kaplan-Meier survival curves in the UICC subgroups of stage I, stage II/III and stage IV, based on the preoperative cCA19-9 cutoff value of 200 U/ml. A: Subgroup of UICC stage I (P = 0.404); B: UICC subgroup of stage II/III (P = 0.036); C: Subgroup of stage IV; HL (high level): preoperative cCA19-9 \geq 200 U/ml; LL (low level): preoperative cCA19-9 < 200 U/ml.

Table 5. Multivariate overall survival analysis of significant factors identified by univariate overall survival analysis

Factors	Beta value	Hazard ratio	95% CI	P value
Age (yr): \geq 63 vs. < 63	0.156	1.434	0.999-2.059	0.051
PI: Yes vs. No	0.169	1.477	1.002-2.178	0.049
UICC pT stage: T3/T4 vs. T1/T2	0.242	1.748	0.902-3.390	0.098
Lymph node metastasis: Yes vs. No	0.102	1.265	0.860-1.861	0.232
Adjacent organ invasion: Yes vs. No	0.010	1.024	0.577-1.818	0.935
Preoperative cCA19-9: \geq 200 vs. < 200	0.201	1.587	1.099-2.292	0.014

raphy-computed tomography (PET-CT), also facilitates assessment of the relationship of the tumor with the superior mesenteric artery, celiac axis, superior mesenteric vein, and portal vein [25]. Despite advances in imaging technology, occult peritoneal or liver metastatic disease and occult vascular involvement are often missed [24]. An ideal serum marker with independent prognostic significance facilitates the diagnosis and monitoring for recurrence in patients indicated for more intensive therapy [10]. For better outcomes, we analyzed whether preoperative cCA19-9 predicted the pathologic stage or postoperative survival. We also considered preoperative cCA19-9 values in a multivariate survival analysis to ensure that preoperative cCA19-9 values predicted survival better than other traditional predictors of survival. In this study, preoperative cCA19-9 eliminated interference from high bilirubinemia and demonstrated higher significance than preoperative CA19-9 in the pathologic staging of cohorts simultaneously.

CA19-9 correlated with the disease burden and predicted postoperative prognosis [17]. Schlieman *et al.* showed that the mean adjusted CA19-9 level was significantly lower in localized pancreatic than in locally advanced cancer, which indicated that among the patients with resectable pancreatic cancer based on preoperative

imaging studies, those with abnormally high serum levels of CA19-9 may have unresectable disease [20]. Halm *et al.* reported that the median preoperative CA19-9 levels were lower in NO patients compared with patients with positive nodes and in T1/T2 patients versus T3 patients, which demonstrated that preoperative CA19-9 levels correlate with the stage of disease in patients with PDAC [10]. In the current study, we demonstrated significantly different overall survival between UICC stage I and II/IV, which confirmed the high malignancy of PDAC underscoring the need for early diagnosis and treatment of PDAC. The current results showing significant differences in median preoperative cCA19-9 levels between UICC stage I and II/IV confirm the association with postresection pathologic stage, and are consistent with a previous report [14]. As Humphris *et al.* showed that perioperative serum CA19-9 measurements were informative in pancreatic cancer and have potential clinical utility in predicting outcome [22]. Even though these results

emphasized that the CA19-9 value is not a definitive predictor of pathologic stage in an individual patient, higher CA19-9 values suggested more extensive tumor burden. In those patients with low CA19-9 values and resectable lesions on preoperative imaging, the need for laparoscopy to detect unsuspected metastases may be diminished. However, a high CA19-9 value may justify laparoscopy even if the lesion appears therapeutically resectable on preoperative imaging [26].

Preoperative CA19-9 levels were found to be inversely proportional to tumor resectability and survival rates [14], which was confirmed in the current study. Given that different CA19-9 cutoff values were used in various previous studies [11, 20, 27-29], we searched for a more valuable cCA19-9 cutoff value in this study. In this univariate analysis, preoperative cCA19-9 cutoff values of 200, 500 and 1000 U/ml were tested for significant differences in overall survival. UICC stage I and UICC stage IV showed relatively good and poor prognosis, respectively. The 200 U/ml cutoff threshold demonstrated to be significant for the subgroup UICC stage II/III, represented a useful preoperative cCA19-9 threshold for predicting postoperative prognosis in non-early stage and metastatic cases, constituting a majority of resectable PDAC cases. In addition to preoperative cCA19-9 levels, we identified several predictive prognostic factors, which included age, PI, lymph node metastasis, adjacent organ invasion, UICC pT stage and UICC final stage. According to Halm *et al.*, poor prognostic factors included lymph-node metastases, a high tumor grade, a large tumor, high levels of CA19-9, persistently elevated postoperative levels of CA19-9, and positive margins of resection [10]. Except for CA19-9 levels, other factors were all based on pathological investigations of resected specimens after surgery. In the current study, we found similar results and showed that PI and age were the other risk factors. Recent studies have shown that among all gastrointestinal malignancies, the PI severity score was the highest in pancreatic cancer and was significantly associated with diminished survival [30]. Another study reported that PI plays an important role in the progression of PDAC and in predicting the prognosis in this group of patients [31]. Tas *et al.* concluded that patient age (≥ 60 y versus < 60 y) was a major prognostic factor affecting the survival of pati-

ents with metastatic pancreatic cancer [32]. These results indicated that it is crucial to evaluate preoperative patient profile, which includes age before selecting resectable candidates.

Multivariate analysis showed that PI and preoperative cCA19-9 cutoff value of 200 U/ml independently predict the prognosis of PDAC. These results indicated that preoperative cCA19-9 was related to tumor status based on postoperative pathological investigations, mostly before the surgery. Wang *et al.* reported that preoperative serum CA19-9 level was a predictive marker for PI in patients with pancreatic cancer [33]. However, in the current study, we did not find a significant difference in median preoperative CA19-9 between the groups based on PI. More studies are needed to identify preoperative surrogates for PI in the future.

Limitations of the current study include its retrospective design, which may have resulted in biased conclusions. However, the preoperative CA19-9 levels are still considered reliable. The postoperative loss to follow-up is another limitation. We found that the loss ratio of follow-up was less than 20%. The parameters, which included characteristics and pathological assessments, serum perioperative CA19-9 level, and jaundice status, were similar regardless of the duration of the follow-up. Although the number of cases for which survival data were unavailable was relatively large, the follow-up duration was adequate to identify potential prognostic factors. Another limitation was that it was a single center study. However, the cohort that was studied was traced to a large catchment area of Eastern China suggesting that data obtained after prognosis of PDCA are probably representative of the Chinese Han population.

Conclusion

In summary, we have identified preoperative cCA19-9 with a cutoff value of 200 U/ml as an independent predictive factor and an accurate marker of tumor stage. We found that this preoperative cCA19-9 cutoff value was a prognostic marker for stage II/III, but not for I and IV, which suggests that the 200 U/ml cutoff value is a valuable threshold for predicting postoperative prognosis for the majority of resectable PDAC cases. We suggest that these predictive factors should be utilized to effectively screen

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patients for further diagnostic evaluation (MRI, EUS, PET/CT) and for alternative or palliative treatment. Adjuvant therapy and palliative care are effective alternatives for patients with adverse risk parameters, to prolong overall survival.

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Disclosure of conflict of interest

None.

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