

RESEARCH ARTICLE

Normalization of CA19-9 Following Resection for Pancreatic Ductal Adenocarcinoma is not Tantamount to being Cured?

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Abstract

Background: Postoperative carbohydrate antigen 19-9 (CA19-9) is an independent predictor of survival for pancreatic ductal adenocarcinoma (PDAC), and more powerful than preoperative CA19-9. However, making decisions just dependent on postoperative CA19-9 may result in necessary treatments not being performed. **Materials and Methods:** A total of 178 patients with resected PDAC were eligible for this retrospective study, classified into two corresponding subgroups according to postoperative CA19-9. Prognostic significance of all clinicopathologic factors was evaluated by univariate and multivariate analyses. **Results:** Postoperative CA19-9, preoperative CA125 and lymph node status were independent predictors. Better predictive performances for overall survival (OS) and recurrence-free survival (RFS) were achieved by postoperative CA19-9 compared to preoperative CA125 and lymph node status. Particularly, preoperative CA125 was associated with poor OS ($p < 0.001$ for the normalized CA19-9 patients, $p = 0.012$ for the elevated) and RFS ($p = 0.005$ for the normalized, $p = 0.004$ for the elevated). Moreover, preoperative CA125 levels related with survival in double-negative patients. **Conclusions:** Normalization of CA19-9 is not tantamount to be cured. Preoperative CA125 is a critical predictor for PDAC patients, especially in double-negative patients.

Keywords: Postoperative CA19-9 - normalization - preoperative CA125 - pancreatic ductal cancer - prognosis

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Introduction

Although surgical management and adjuvant therapy develop rapidly, the prognosis of patients with resectable pancreatic ductal adenocarcinoma (PDAC) remains poor. Five-year survival rate was just 20% in the era of adjuvant chemo- or chemoradiotherapy (Siegel et al., 2013). So, it is particularly crucial to predict prognosis and guide postoperative treatment, which highlights the importance of adjuvant therapy.

Many serum markers are connection with PDAC, including serum carbohydrate antigen 19-9 (CA19-9), CA125, carcinoembryonic antigen (CEA) (Tempero et al., 2010; Liu et al., 2014; Zhang et al., 2014). Perioperative serum CA19-9 is the most widely used in the diagnosis, prognosis, and remains representative to monitor recurrence and metastasis after undergoing curative resection (Ferrone et al., 2006; Castellanos, 2014). Preoperative CA19-9 focuses on diagnosis, and postoperative CA19-9 corresponds to tumor recurrence after surgery. As always, baseline preoperative elevated serum CA19-9 levels indicate dismal prognosis in series of retrospective analyzes in PDAC (Lim et al., 2003; Schlieman et al., 2003; Ferrone et al., 2006). Recently, the role of postoperative CA19-9 levels was gradually recognized. Postoperative serum CA19-9, but

not preoperative CA19-9, significantly predicted the survival of PDAC patients (Ferrone et al., 2006; Kondo et al., 2010; Motoi et al., 2011; Hata et al., 2012; Tzeng et al., 2013). Failure of normalization of CA19-9 after resection for PDAC is tantamount to metastatic disease and adverse prognosis (Abdel-Misih et al., 2011). Dose normalization of CA19-9 following resection mean to be cured? The answer is not absolute. Some patients with slightly elevated postoperative CA19-9 have an excellent prognosis. Similarly, normalized postoperative CA19-9 is not tantamount to be cured. Therefore, it does not well evaluate the prognosis by postoperative CA19-9 alone, especially in normalized patients.

CA125, a high-molecular-weight mucin-like glycoprotein over-expressed in ovarian cancer and other cancers, is the most useful serologic marker for ovarian cancer detection and management (Schmidt, 2011; Tse et al., 2014). The prognostic value of CA125 had been described in previous studies (Liu et al., 2014). Importantly, it is not influenced by serum bilirubin (Haglund, 1986). In clinical work, perioperative CA19-9 and pathologic correlation parameters (presence of lymph node metastasis, TNM stages), as independent indicators, are widely used in adjustment of chemotherapy therapy (NCCN). This study focused on the prognostic impact of clinicopathologic factors, including serum CA125

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level, pathologic parameters in PDAC patients following macroscopically curative surgical resection based on postoperative serum CA19-9.

Materials and Methods

Patient cohort and data collection

From March 2010 to May 2012, a total of 178 consecutive PDAC patients who underwent surgical resection were enrolled in this retrospective study at Department of Pancreas and Hepatobiliary Surgery, Fudan University, Shanghai Cancer Center. Patients with data on perioperative CA125, and postoperative CA19-9 levels were selected to investigate the role of these tumor markers in the prediction of prognosis. Preoperative serum levels of CA19-9 and CA125 were simultaneously measured within 14 days before surgery, and postoperative CA19-9 and CA125 were defined as the lowest levels within 3 to 4 months after resection. The normal upper limit of CA19-9 is 37 U/ml (Kondo et al., 2010; Motoi et al., 2011). Nonsecretors (CA 19-9 <5 U/ml) were excluded from this study. Other variables were also evaluated, included age, gender, tumor location, tumor size, type of resection, adjuvant chemotherapy, tumor differentiation, TNM stages, and presence of lymph node.

The study was approved by the Shanghai Cancer Center Research Ethics Committee. Informed consent was

Table 1. Clinicopathological Features

Features	Values/Counts (n=178)
Age (years, median (range))	61 (33-82)
Gender (male/female)	108/70
Tumor location (head/body, tail)	114/64
Tumor size (cm, mean±SD)	4.3±1.5
Lymph node metastasis (yes/no)	77/101
Tumor differentiation (I,II/III)	139/39
Neural invasion (yes/no)	14/31
Microvascular invasion (yes/no)	31/147
Preoperative CA 125 (U/mL, median (range))	133.0 (2.57≥251.50)
Postoperative CA 19-9 (U/mL, median (range))	22.1 (0.8≥2111.0)
T stage (I/II/III)	0/42/147
TNM stage (IB/IIA/IIB)	23/78/88

obtained from each patient according to the committee's regulations.

Follow-up

In the first year, serologic examination was done every month, and CT of the abdomen was done every 3.0 months. If recurrence was suspected, a CT, MRI or PET/CT was done immediately. Overall survival (OS) was defined as the time from the dates of surgery to death or last follow-up. Recurrence-free survival (RFS) was

Table 2 Relations between the Parameters and Pathological Features

	Postoperative CA19-9			Preoperative CA125		
	Low (n=117)	High (n=72)	p value	Low (n=96)	High (n=82)	p value
Age						
≤61 year	58	29	0.306	46	40	0.741
>61 year	59	43		50	42	
Gender						
Female	48	33	0.523	40	30	0.492
Male	69	39		56	52	
Tumor size						
≤ 3 cm	48	24	0.213	32	31	0.314
> 3 cm	69	48		64	51	
Lymph node metastasis						
No	74	38	0.015	55	46	0.874
Yes	43	34		41	36	
Neural invasion						
No	20	12	0.849	21	10	0.199
Yes	9	60		75	72	
Microvascular invasion						
No	101	56	0.069	79	68	0.735
Yes	16	16		17	14	
Tumor differentiation						
Poorly	92	58	0.810	72	68	0.283
Well/Moderately	25	14		24	14	
T stage						
T1	0	0	0.376	0	0	0.125
T2	30	11		27	15	
T3	87	61		69	67	
TNM stage						
IB	19	4	0.008	16	7	0.487
IIA	55	34		39	39	
IIB	43	34		41	36	

Table 3. Univariate and Multivariate Analyses of Factors Associated With Survival and Recurrence

Variables	Overall Survival				Time to Recurrence			
	Univariate	Mutivariate			Univariate	Mutivariate		
	P value	HR	95% CI	p value	p value	HR	95% CI	p value
Age (≤61 year / >61 year)	0.492	NA	NA	NA	0.560	NA	NA	NA
Gender (male/female)	0.372	NA	NA	NA	0.284	NA	NA	NA
Tumor location (head/body, tail)	0.307	NA	NA	NA	0.453	NA	NA	NA
Tumor size (≤3 cm / >3 cm)	0.246	NA	NA	NA	0.517	NA	NA	NA
Lymph node metastasis (yes/no)	0.001	1.670	1.117-2.495	0.012	0.001	1.826	1.271-2.623	0.001
Tumor differentiation (I/II/III)	0.709	NA	NA	NA	0.068	NA	NA	NA
Neural invasion (yes/no)	0.283	NA	NA	NA	0.157	NA	NA	NA
Microvascular invasion (yes/no)	0.951	NA	NA	NA	0.425	NA	NA	NA
TNM stage (IB/IIA/IIB)	0.008	1.391	1.001-1.933	0.049	0.003	1.490	1.111-1.999	0.008
T stage (I/II/III)	0.936	NA	NA	NA	0.947	NA	NA	NA
Postoperative CA19-9 (≤37 U/mL/>37 U/mL)	<0.001	1.941	1.288-2.927	0.002	<0.001	2.679	1.861-3.856	<0.001
Chemotherapy (yes/no)	0.010	0.421	0.222-0.799	0.008	0.035	0.0529	0.292-0.956	0.035
Preoperative CA125 (≤18.6 U/mL/>18.6 U/mL)	<0.001	2.391	1.600-3.572	<0.001	<0.001	2.096	1.454-3.020	<0.001

defined as the interval between the dates of surgery and tumor recurrence or the last follow up.

Statistical analysis

Statistical Package for Social Science (SPSS) version 16.0 for Windows was used for statistical analysis. The quantitative variables age, follow-up time, serum levels of CA19-9 and CA125, were expressed as medians with interquartile ranges. Survival curves were calculated by using the Kaplan–Meier method and log rank tests for clinical and pathological factors. Factors found to be significant by univariate statistical analysis were entered into a multivariate analysis (Cox regression) to determine independent prognostic factors. Receiver operating characteristics (ROC) curves were used to evaluate the predictive performance for independent prognostic factors. In order to better evaluate the prognostic values, patients were divided according to postoperative CA19-9 and lymph node metastasis. The relation between CA125 and prognosis was also calculated. Two-sided P values were considered statistically significant at $p < 0.05$.

Results

Demographics and outcome

There were 178 patients had perioperative CA19-9 and CA125 values documented. There were 119 (66.4%) were men and 70 (33.6%) were women, the median age was 61 years (range 33 to 82 years). One hundred and eight patients (60.6%) underwent pancreaticoduodenectomy or total pancreatectom, and 64 (39.4%) underwent distal pancreatectomies. Of these patients, 77 (43.3%) had regional lymph node metastasis, and 164 patients received postoperatively adjuvant chemotherapy. In general, those patients underwent standard gemcitabine-based chemotherapy, and considered for second-line therapy that demonstrated recurrence or progression. Recurrence occurred in 124 patients (69.7%), overall survival rates at 1, 2, and 3 years were 91.6%, 60.1%, and 32.4%, and the median survival time was 19.7 (range 6.3 to 60.6) months. The demographic and clinical characteristics of the patients were list in Table 1.

A strong positive correlation was observed between postoperative CA19-9 and presence of lymph node metastasis ($r=0.182$, $p=0.015$), and TNM stage ($r=0.198$,

$p=0.008$). There were no statistically significant differences between postoperative CA19-9 or preoperative CA125 and other clinicopathological characteristics, such as tumor location, differentiation, microvascular invasion, neural invasion, or tumor size (Table 2).

Univariate and multivariate analysis for survival

To evaluate the predictive value of all above parameters, univariate and multivariate models were performed. The univariate analysis indicated that high postoperative CA19-9 and high preoperative high CA125 were statistically significant risk predictors of poor OS (both $p < 0.001$) and RFS (both $p < 0.001$), in addition to lymph node metastasis (both $p=0.001$), high TNM stages and postoperatively adjuvant chemotherapy (Fig 1). There was no significant relation between other clinicopathological indicators and either OS or RFS. Postoperative CA19-9 ($p=0.002$, HR=1.941, 95%CI, 1.288-2.927 for OS; $p < 0.001$, HR=2.679, 95%CI, 1.861-3.856 for RFS; respectively), preoperative CA125 ($p < 0.001$, HR=2.391, 95%CI, 1.600-3.572 for OS; $p < 0.001$, HR=2.096, 95%CI, 1.454-3.020 for RFS, respectively), lymph node metastasis ($p=0.012$, HR=1.670, 95%CI, 1.117-2.495 for OS; $p=0.001$, HR=1.826, 95%CI, 1.271-2.623 for RFS; respectively), TNM stages, and postoperative chemotherapy were independent predictors of poor survival in multivariate analysis (Table 3).

Better predictive performances for OS and RFS were achieved by postoperative CA19-9 (AUC=0.612 for OS, AUC=0.666 for RFS) compared to preoperative CA125 (AUC=0.610 for OS, AUC=0.591 for RFS), lymph node status (AUC=0.597 for OS, AUC 0.598 for RFS), TNM stages (AUC=0.606 for OS, AUC=0.608 for RFS), and chemotherapy (AUC=0.533 for OS, AUC=0.543 for RFS, respectively) by ROC analysis.

Survival analysis in subgroups divided by postoperative CA19-9 or/and lymph node metastasis

In the subgroups divided by postoperative CA19-9, preoperative CA125 was a significant prognostic factor for both OS ($p < 0.001$ for the normalized, $p=0.012$ for the elevated, respectively) and RFS ($p=0.005$ for the normalized, $p=0.004$ for the elevated, respectively), whereas lymph node status ($p=0.041$ for OS, $p=0.080$ for RFS, respectively) was significant in the normalized only.

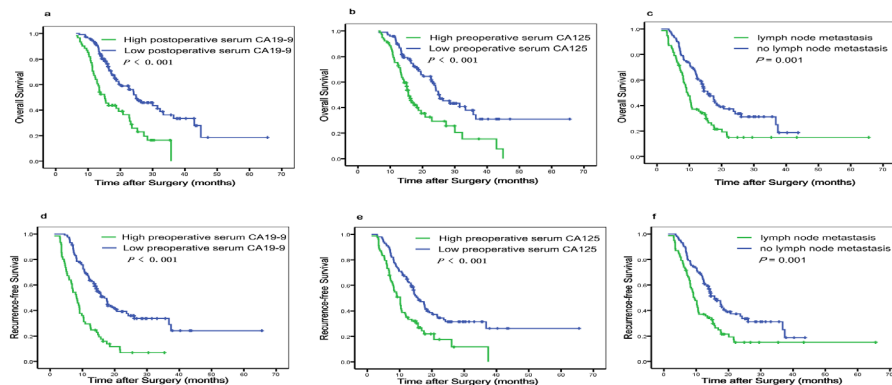


Figure 1. Kaplan-Meier Analysis for Survival. (A, D): Kaplan-Meier survival curves for OS and RFS based on postoperative CA19-9 (both $p < 0.001$); (B, E): Kaplan-Meier survival curves for OS and RFS based on preoperative CA125 (both $p < 0.001$); (C, F): Kaplan-Meier survival curves for OS and RFS based on lymph node metastasis (both $p=0.001$)

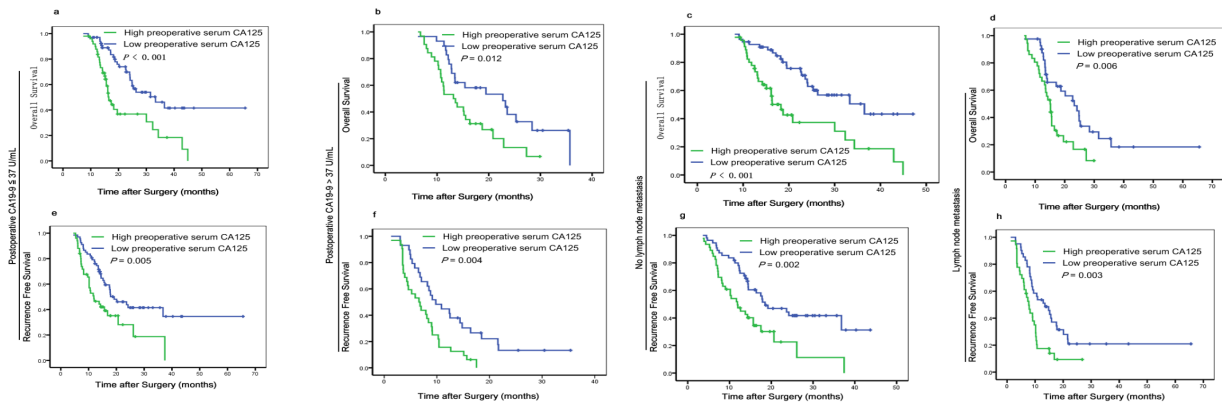


Figure 2. Kaplan-meier Analysis of Survival in the Subgroups Divided by Postoperative CA19-9 or Lymph Node Metastasis. Preoperative CA125 was a significant prognostic factor for both OS ($p < 0.001$ for the normalized, $p = 0.012$ for the elevated, respectively) (A, B), and RFS ($p = 0.005$ for the normalized, $p = 0.004$ for the elevated, respectively) (E, F). The same conclusion was drawn in subgroup divided by lymph node metastasis (C, D, G, H)

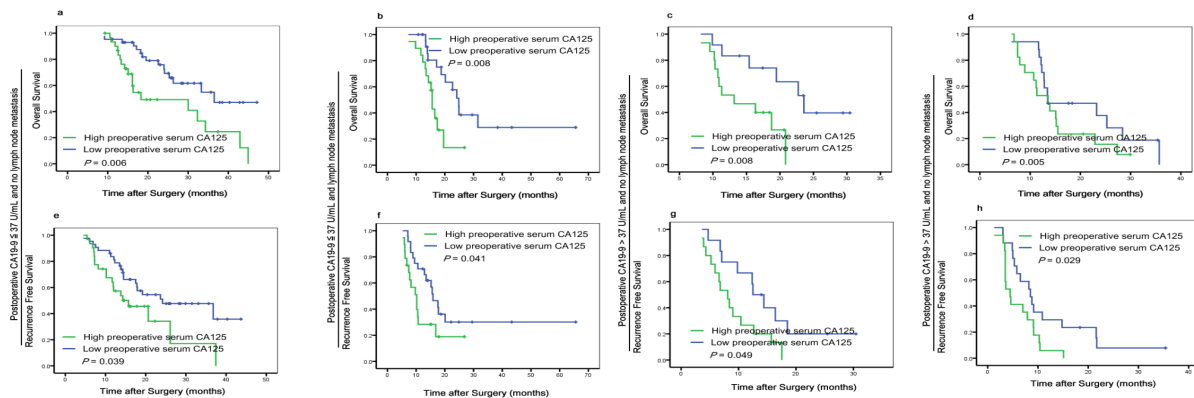


Figure 3. Kaplan-Meier Analysis of Survival in Subgroups by Postoperative CA19-9 and Lymph Node Metastasis

Similarly, preoperative CA125 was related with patient survival (no lymph node metastasis patients: $p < 0.001$ for OS, $p = 0.002$ for RFS; lymph node metastasis patients: $p = 0.006$ for OS, $p = 0.003$ for RFS, respectively) (Figure 2).

To further eliminate the effect from lymph nodes, subgroup analysis according to postoperative CA19-9 and lymph nodes status showed that preoperative CA125 was also a risk factor for OS ($p = 0.008$ for negative lymph nodes patients with elevated CA19-9, $p = 0.008$ for lymph nodes metastasis patients with normalized CA19-9, respectively) and RFS ($p = 0.041$ for negative lymph nodes patients with elevated CA19-9, $p = 0.049$ for lymph nodes metastasis patients with normalized CA19-9, respectively) (Figure 3). What is worth mentioning is that CA125 is related with survival ($p = 0.006$ for OS, $p = 0.039$ for RFS, respectively) in the double-negative patients, regardless of lymph node status and postoperative CA19-9.

Discussion

Because of microscopic metastatic disease occult at time of surgery, PDAC portends dismal prognosis even in patients with surgical resection. Therefore, an accurate prediction of the prognosis makes a timely treatment for patients and improves their prognosis. Serum preoperative CA19-9 levels reflect tumor burden and related with patient survival (Ferrone et al., 2006; Xu et al., 2014). Clinicians generally utilize perioperative CA19-9 to monitor tumor recurrence and guide treatment

strategies. However, CA19-9 is not a perfect predictive marker: hyperbilirubinaemia induces an increase in serum CA19-9 levels (Katz et al., 2010), and the nearly 30 % of patients did not show an increase in CA19-9 levels (Schlieman et al., 2003). In previous retrospective studies, hyperbilirubinaemia and nonsecretors were excluded from their analysis (Ferrone et al., 2006; Motoi et al., 2011). Recently, clinicians begin to focus on the prognostic value of postoperative CA19-9, which had been demonstrated as an independent predictor of survival, and a better prognostic marker than preoperative CA19-9 (Ferrone et al., 2006; Barugola et al., 2009; Kondo et al., 2010; Abdel-Misih et al., 2011; Hata et al., 2012; Humphris et al., 2012; Hartwig et al., 2013). Because of no postoperative jaundice and short half-life period of serum CA19-9 after surgery (Rapellino et al., 1994), this indicator escapes from the interference of hyperbilirubinaemia and preoperative CA19-9. Previous reports revealed that persistent CA19-9 elevation after resection was analogous to metastatic disease and the elevated had significantly poorer survival in comparison with the normalized ones. In fact, some normalized CA19-9 PDAC patients also had a poor prognosis, and even worse than those elevated patients. This phenomenon is also worth considering. Here, we showed preoperative serum CA125 had a distinct potential utility in PDAC patients, when assessed at distinct clinical decision follow surgical resection.

Serum CA125 had been proved as a potential predictor for PDAC survival (Haglund, 1986; Cwik et al., 2006; Liu

et al., 2014), and related with carcinomatosis in pancreatic cancer and other cancers (may partly originate from the peritoneum in patients with metastatic disease) (Haridas et al., 2011; Chen et al., 2012; Emoto et al., 2012; Wagner et al., 2013). We have been demonstrated that “triple positive PDAC patients” (CEA+/CA125+/CA19-9 \geq 1,000 U/mL) had a poor prognosis following resection (Liu et al., 2014). More importantly, serum CA125 levels were not interfered by serum bilirubin levels (Haglund, 1986). In this retrospective analysis, postoperative CA19-9, preoperative CA125, and presence of lymph node metastasis were independent prognosticators for both OS and RFS after adjusting for age, sex, tumor size, location, differentiation, neural invasion, and microvascular invasion. And the prognostic value of postoperative CA19-9 was prior to perioperative CA125, preoperative CA19-9 and presence of lymph node metastasis by ROC curve, which coincides with the present studies (Abdel-Misih et al., 2011).

In order to better predict prognosis and guide treatments, patients were divided into two subgroups by postoperative CA19-9 levels: the normalized and the elevated. Those patients with high preoperative CA125 had shorter median OS times (the normalized: median survival time 23.1 vs 40.5 months, $p < 0.001$; the elevated: OS 15.2 vs 22.1 months, $p = 0.012$) and RFS times (the normalized: 17.1 vs 33.2 months, $p = 0.005$; the elevated: 7.5 vs 13.7 months, $p = 0.004$) than patients with low CA125. And similar results were found in patients with positive lymph nodes, but not for postoperative CA125.

To get an in-depth research, patients were stratified into four groups according for postoperative CA19-9 and lymph nodal status, and the prognostic value of preoperative CA125 was also assessed. Arguably, preoperative CA125 levels related with survival in double-negative patients (median survival time 25.9 vs 34.8 months, $p = 0.006$ for OS; 18.6 vs 27.4 months, $p = 0.039$ for RFS, respectively), lymph node metastasis patients with normalized CA19-9 (median survival time 16.4 vs 33.9 months, $P = 0.008$ for OS; 12.4 vs 28.8 months, $p = 0.041$ for RFS, respectively) and no lymph node metastasis patients with elevated CA19-9 (median survival time 14.8 vs 22.9 months, $p = 0.017$ for OS; 9.1 vs 15.4 months, $p = 0.049$ for RFS, respectively). These results might cause by micro metastases disease at the time of surgery and postoperative timely adjuvant chemotherapy. In patients with lymph node metastasis, postoperative adjuvant chemotherapy maybe induce a decrease in serum CA19-9 levels. It may be also caused by distance undetected metastases disease, in addition to lymph node metastasis. For no lymph node metastasis patients with elevated postoperative CA19-9 levels, incomplete lymph node dissection, skip metastasis and preoperative micro metastases disease may lead to a poor prognosis. However, preoperative CA125 levels were not related with survival in the double-positive subgroup, which had the worst prognosis patients. Similarly, the postoperative CA125 was also evaluated its prognostic value by the same measure, no significant relationship with survival was confirmed.

Our study is inherently limited for general applications by its retrospective design. A large number of patients were

excluded due to inadequate follow-up of postoperative CA19-9 levels. Additionally, serum CA125 and CA19-9 are not unique indicators of pancreatic cancer. For example, CA125 rises in response to cardiovascular (Kouris et al., 2005) and chronic liver disease (Miralles et al., 2003), endometriosis, and ovarian cancer (Longuespee et al., 2012). And colorectal cancer, gallbladder cancer, bile duct cancer, liver cancer and stomach cancer induce increase in CA19-9 levels. Finally, different surgeons have different lymph node dissections, which also lead to errors.

In conclusion, postoperative CA19-9 is an excellently prognostic indicator than preoperative CA19-9 and the presence of lymph node. However, normalization of postoperative CA19-9 for PDAC is not tantamount to be cured. Making decisions just dependent on postoperative CA19-9 may lose the necessary treatments or received excessive chemotherapy. This study suggests that it is necessary to bind postoperative CA19-9 with preoperative CA125 to design treatment strategies, especially for the normalized CA19-9 patients. Preoperative CA125 is related with survival in normalized and elevated CA19-9 patients.

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