

Retrospective Study

## Preoperative evaluation of pancreatic ductal adenocarcinoma with synchronous liver metastasis: Diagnosis and assessment of unresectability

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### Abstract

#### AIM

To identify predictors for synchronous liver metastasis from resectable pancreatic ductal adenocarcinoma (PDAC) and assess unresectability of synchronous liver metastasis.

#### METHODS

Retrospective records of PDAC patients with synchronous liver metastasis who underwent simultaneous resections of primary PDAC and synchronous liver metastasis, or palliative surgical bypass, were collected from 2007 to 2015. A series of pre-operative clinical parameters, including tumor markers and inflammation-based indices, were analyzed by logistic regression to figure out predictive factors and assess unresectability of synchronous liver metastasis. Cox regression was used to identify prognostic factors in liver-metastasized PDAC patients after surgery, with intention to validate their conformance to the indications of simultaneous resections and palliative surgical bypass. Survival of patients from different groups were analyzed by the Kaplan-Meier method. Intra- and post-operative courses were compared, including complications. PDAC patients with no distant metastases who underwent curative resection served as the control group.

**RESULTS**

CA125 > 38 U/mL (OR = 12.397, 95%CI: 5.468-28.105,  $P < 0.001$ ) and diabetes mellitus (OR = 3.343, 95%CI: 1.539-7.262,  $P = 0.002$ ) independently predicted synchronous liver metastasis from resectable PDAC. CA125 > 62 U/mL (OR = 5.181, 95%CI: 1.612-16.665,  $P = 0.006$ ) and age > 62 years (OR = 3.921, 95%CI: 1.217-12.632,  $P = 0.022$ ) correlated with unresectability of synchronous liver metastasis, both of which also indicated a worse long-term outcome of liver-metastasized PDAC patients after surgery. After the simultaneous resections, patients with post-operatively elevated serum CA125 levels had shorter survival than those with post-operatively reduced serum CA125 levels (7.7 mo *vs* 16.3 mo,  $P = 0.013$ ). The survival of liver-metastasized PDAC patients who underwent the simultaneous resections was similar to that of non-metastasized PDAC patients who underwent curative pancreatectomy alone (7.0 mo *vs* 16.9 mo,  $P < 0.001$ ), with no higher rates of either pancreatic fistula ( $P = 0.072$ ) or other complications ( $P = 0.230$ ) and no greater impacts on length of hospital stay ( $P = 0.602$ ) or post-operative diabetic control ( $P = 0.479$ ).

**CONCLUSION**

The criterion set up by CA125 levels could facilitate careful diagnosis of synchronous liver metastases from PDAC, and prudent selection of appropriate patients for the simultaneous resections.

**Key words:** CA125; Pancreatic ductal adenocarcinoma; Liver metastasis; Unresectability; Prognosis

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**Core tip:** The presence of liver metastasis from pancreatic ductal adenocarcinoma (PDAC) usually deprives patients of opportunities for resection of PDAC. We utilized a series of clinical parameters for pre-operative evaluation of PDAC with synchronous liver metastasis, including diagnosis and assessment of unresectability. The criterion set up by serum CA125 levels could facilitate the careful judgement of the occurrence of synchronous liver metastases from PDAC, and the prudent selection of appropriate patients for simultaneous resections for primary PDAC and synchronous liver metastasis, for the sake of prolonged survival and substantial reduction in morbidity and mortality.

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**INTRODUCTION**

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive and progressive malignancy with increasing incidence and death rates<sup>[1,2]</sup>. Despite the steady improvement in survival for most cancers, progress has been limited for PDAC, for which the 5-year relative survival rate for all stages combined is 8%<sup>[2]</sup>. The rate of resection for primary PDAC is only 10%-20%, and approximately 50% of new PDAC cases are discovered to have distant metastases<sup>[3]</sup>. Some distant micro-metastases are undetectable at diagnosis through a thorough pre-operative imaging tests including positron emission tomography/computed tomography (PET/CT), and may only be confirmed by exploration during planned curative resection. Even those patients undergoing curative pancreatectomy are still at a 25%-50% risk of developing distant metastases<sup>[4-6]</sup>. The dismal prognosis of PDAC with distant metastasis has been acknowledged by its 5-year relative survival rate of 1%<sup>[7]</sup>.

PDAC shows a remarkable preference for the liver to metastasize due to its portal venous blood draining and lymphatic spread. Weh *et al*<sup>[8]</sup> summarized that the incidence of liver metastasis from PDAC ranged from 25% to 75%. About 12% of unsuspected liver metastases are not discovered until surgery, and liver metastasis reduces the survival of patients with PDAC to 5 mo<sup>[9,10]</sup>. Currently, chemotherapy remains the mainstay of treatment for liver metastasis from PDAC, with two combination chemotherapy regimens-FOLFIRINOX (bolus plus infusional fluorouracil, leucovorin, irinotecan, and oxaliplatin regimen) and gemcitabine plus nanoparticle albumin-bound paclitaxel-emerging as new standards<sup>[11-13]</sup>.

The doctrine that the presence of liver metastasis from resectable PDAC contradicts a curative resection and indicates a palliative surgical bypass, deprives patients of an incremental benefit from simultaneous curative resections for primary and metastatic PDAC, even at a R1 status. An unconventional surgical option to curatively resect primary PDAC and synchronous liver metastasis may be merely justified by prolonged survival, a longer recurrence-free interval and, at least, no more surgical-related morbidity and mortality. Pancreaticoduodenectomy (PD) combined with additional organ resection has been indicated for locally advanced PDAC with the same safety as PD alone<sup>[14]</sup>. Even if palliative PD can be performed instead, patients can benefit from significantly longer survival and low morbidity rate<sup>[15,16]</sup>. Thus, simultaneous curative resections for primary PDAC and synchronous liver metastasis can also be advocated on highly individual basis. However, the threshold comprised of conventional clinical indexes has not been first established to pre-operatively distinguish

the occurrence of liver metastasis among patients with resectable PDAC. And, the criterion also needs to be set for selection for patients whom the simultaneous resections favor in a proper sense.

As the predictive accuracy of serum CA125 levels has been reported in a two-center clinical study where we were involved<sup>[17,18]</sup>, here we highlighted the relationships between serum CA125 levels and both synchronous liver metastasis from PDAC and unresectability of liver-metastasized PDAC, and focused on the long-term outcome of liver-metastasized PDAC patients after individualized surgeries indicated by serum CA125 levels.

## MATERIALS AND METHODS

### Patients

Sixty-nine patients with resectable primary PDAC and synchronous liver metastasis who underwent surgery at the Huashan Hospital between March 2007 and December 2015 were identified in a prospective database. Of these, 30 patients underwent simultaneous curative resections for primary PDAC and synchronous liver metastases, and 39 patients underwent palliative surgical bypass prior to gemcitabine-based chemotherapy due to unresectable liver metastases. All data collected was consented by these patients and approved by the Ethical Committee and Institutional Review Board. Only patients with histologically confirmed PDAC and liver metastasis who underwent surgery were included in the current study. Patients with unresectable primary PDAC, neuroendocrine tumor, cystadenocarcinoma, ampullary cancer, distal bile duct, and duodenal carcinoma as well as extrahepatic metastatic disease such as serosal implants or peritoneal metastases were not considered in the study. To investigate the predictors for synchronous liver metastasis, 138 patients with no evidence of distant metastases who underwent curative resection for primary PDAC alone were selected at the same period mentioned above for matching with the control group in a 1:2 fashion. These patients were matched as closely as possible to the baseline characteristics of the liver metastasis cohort.

### Pre-operative evaluation

Routine pre-operative diagnostics consisted of a baseline history, physical examination and clinical laboratory tests and imaging tests. The tumor markers CA19-9, CA125 and CEA were used as serum diagnostic tools. Ultrasonography, computed tomography scanning and PET were performed in all instances. Pre-operative biliary drainage, endoscopic retrograde biliary drainage or percutaneous transhepatic cholangial drainage was indicated for jaundice.

### Surgical procedures

Depending on the location of primary PDAC, curative resection was performed as pancreatoduodenectomy, or total pancreatectomy, or distal splenopancreatectomy, accompanied by lymphadenectomy. Selected patients underwent portal/superior mesenteric vein resection and artificial blood vessel replacement. The number and distribution of metastatic diseases, which were assessed by intra-operative ultrasonographic measurement once more to detect liver micro-metastases under suspicious conditions, determined the extent of liver resection. During the laparotomy, the abdomen was completely staged. Given that no acknowledged guidelines of surgery for liver metastasis from PDAC offered the use of reference to surgeons, the decision for resection was made by the intention to reach a R0 status in both the pancreas and the liver and a good performance status (American Society of Anesthesiologists ASA classification  $\leq$  III). The palliative Roux-en Y bypass was constituted by retrocolic end-to-side hepaticojejunal anastomosis and antecolic gastroenterostomy.

### Data collection

The following data were assessed prospectively for each patient: demographics, pre-operative symptoms and previous history, histology of primary PDAC and synchronous liver metastasis, pre-operative treatments, blood parameters, operative details, post-operative course. Among them, plasma fibrinogen and platelets have been shown to play a possible role of both predictive and prognostic factors of distant metastasis<sup>[19,20]</sup>. Blood neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR) and prognostic nutritional index (PNI, albumin [g/L] + 5×total lymphocyte count [ $\times 10^9$ /L]) have acted as inflammation-based indices to predict the clinical outcome of primary or metastasized cancers after surgery or chemotherapy<sup>[21-25]</sup> as well as the association with metastasized cancer burden<sup>[26-27]</sup>. Body-mass-index (BMI), NLR, LMR, PLR and PNI were obtained by calculation during the initial evaluation. All pathologic specimens were reviewed through intra-operative frozen section analysis or routine paraffin section analysis by two independent pathologists to unanimously confirm the diagnosis of primary PDAC and synchronous liver metastasis. Post-operative course included post-operative morbidity such as pancreatic fistula, and mortality defined as any death during hospitalization and within 30 d of surgery. Follow-up information was obtained through review of the medical records and direct contact with the patients. When the date of death was inaccessible, patients were censored at the last contact or record from hospitalization or oncological outpatient clinics.

### Statistical analysis

Summary statistics were reported using mean or

**Table 1** Clinicopathologic characteristics of 207 pancreatic ductal adenocarcinoma patients undergoing surgery

Parameter	No. of patients			
	Simultaneous resections (Group A) <i>n</i> = 30	Palliative surgical bypass (Group B) <i>n</i> = 39	Total (Group A + Group B) <i>n</i> = 69	Pancreatectomy alone (Group C) <i>n</i> = 138
Mean age ± SD, yr	62.2 ± 10.0	63.0 ± 10.4	62.6 ± 10.1	58.8 ± 10.6
Sex (Female)	10	12	22	45
ASA				
I	11	10	21	37
II	19	27	46	97
III	0	2	2	4
IV	0	0	0	0
Primary tumor location				
Head/neck	15	38	53	106
Body/tail	15	1	16	32
Median primary tumor size [IQR], cm	4.0 (2.5-5.0)	-	-	3.0 (2.0-3.5)
Pathology (PDAC)	30	39	69	138
TNM stage				
I	0	0	0	22
II A	0	0	0	22
II B	0	0	0	94
III	0	0	0	0
IV	30	39	69	0
Primary tumor differentiation				
Well/moderate	13	-	-	71
Poor	17	-	-	67
Ki67 [IQR], %	20 (8-30)	-	-	30 (15-50)
Venous invasion	3	19	22	37
Lymph node invasion	14	-	-	82
Hepatic metastasis	30	39	69	0
Surgery for primary tumor				
Total pancreatectomy	1	0	1	5
Pancreaticoduodenectomy	11	0	11	95
Distal pancreatectomy	18	0	18	38
Palliative bypass	0	39	39	0

median values where appropriate. Student's *t*-test or analysis of variance was used for mean comparison of continuous variables distributed normally, whereas Mann-Whitney *U* test or Kruskal-Wallis *H* test was used to compare skewed continuous variables. Fisher's exact test or Pearson's  $\chi^2$  test was used to compare frequencies of categorical variables among groups. The cutoff value of fibrinogen, NLR, LMR, PLR, PNI and platelet was determined by widely accepted thresholds<sup>[19,20,23,28]</sup>, allowing comparison with the available literature. Serum CA19-9 level of 400 U/mL used for indicating distant metastasis of PDAC<sup>[29,30]</sup> was adopted as a cutoff for logistic regression analysis and Cox regression analysis. According to receiver operating characteristic (ROC) curve, an optimal cutoff serum CA125 level of 38 U/mL was identified for analysis of predictors for synchronous liver metastasis, and 62 U/mL for assessment of unresectability for synchronous liver metastasis and overall survival for PDAC patients with synchronous liver metastasis. Predictors for synchronous liver metastasis from PDAC and unresectability for synchronous liver metastasis were estimated by logistic regression analyses. Prognostic factors for overall survival were estimated by Cox proportional hazards models. The Kaplan-Meier method was used to analyze the overall survival from the date

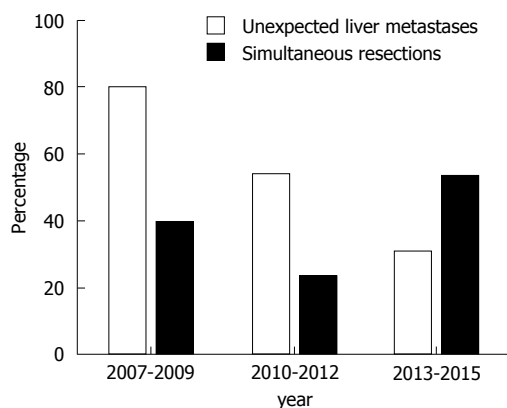
of surgery. Differences in survival were examined using the log-rank test. A two-sided *P* value of < 0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed by utilizing SPSS statistics 20 (IBM corporation, Armonk, NY, United States).

## RESULTS

### Patient characteristics

Table 1 shows the clinicopathologic characteristics of 69 PDAC patients (group A and B) with liver metastasis, who were the focus of the study, and 138 PDAC patients (group C) with no distant metastases, who were enrolled as a matched group. In the case group, the majority of 69 patients were male (*n* = 47, 68.1%) with an overall mean age of 62.6 years. According to ASA grading system, 21 (30.4%) patients were evaluated as grade I, 46 (66.7%) as grade II, and 2 (2.9%) as grade III. The primary PDAC site was largely head or neck (*n* = 53, 76.8%). Primary PDAC displayed venous invasion in 22 (31.9%) patients and lymph node invasion in 14 (46.7%) patients.

Among these 69 patients, 30 patients (group A) underwent simultaneous curative resections for primary PDAC as well as synchronous liver metastasis,



**Figure 1** Trends in the occurrence of unexpected liver metastases identified during surgeries and implementation of the simultaneous resections among all cases across the study period.

and 39 patients (group B) underwent palliative surgical bypass. The curative resections for primary PDAC included PD ( $n = 11, 36.7\%$ ), distal pancreatectomy ( $n = 18, 60.0\%$ ) and total pancreatectomy ( $n = 1, 3.3\%$ ), with portal/superior mesenteric vein resection and artificial blood vessel replacement ( $n = 3, 2.2\%$ ). The mean age at the time of surgery was 62.2 years in group A, and 63.0 years in group B. Half of group A and 38 of group B suffered from adenocarcinoma of the head/neck of the pancreas. Fifteen of group A and 20 of group B were found to have unexpected liver metastases by direct-view or intra-operative ultrasonographic measurement during surgeries. The proportion of the successful simultaneous resections was triennially rising across the study period (Figure 1).

Most patients of the matched cohort (group C) were male ( $n = 93, 68.1\%$ ) with an overall mean age of 58.8 years. Thirty-seven (26.8%) patients were evaluated as ASA grade I, 97 (70.3%) as grade II, and 4 (2.9%) as grade III. As adenocarcinoma of the head/neck of the pancreas ( $n = 106$ ) accounted for 76.8% of all resectable pancreatic adenocarcinoma, the majority of surgical options were PD ( $n = 95, 68.9\%$ ), and the rest were distal pancreatectomy ( $n = 38, 27.5\%$ ) and total pancreatectomy ( $n = 5, 3.6\%$ ). Thirty-seven (26.8%) patients underwent portal/superior mesenteric vein resection and artificial blood vessel replacement ( $n = 3, 2.2\%$ ) due to venous invasion. After lymphadenectomy, 82 of group C were found to have lymph node invasion.

**Predictors for synchronous liver metastasis from PDAC**

To determine which pre-operative factors are independent predictors for synchronous liver metastasis from PDAC, a univariate analysis was performed for preliminary screening of clinical parameters followed by a stepwise logistic regression analysis of the occurrence of synchronous liver metastasis from PDAC. In univariate analysis, there was a trend toward a higher incidence of no synchronous liver metastases in patients with CA19-9  $> 400$  U/mL ( $P < 0.001$ ), CA125  $> 38$

**Table 2** Predictors of synchronous liver metastasis from resectable pancreatic ductal adenocarcinoma

Parameter	Total (Group A + Group B) $n = 69$	Pancreatectomy alone (Group C) $n = 138$	P value (univariate)
Age, yr			
≤ 62	32	80	
> 62	37	58	0.116
Sex			
Male	47	93	
Female	22	45	0.916
BMI			
< 18 kg/m <sup>2</sup>	6	11	0.196
18-25 kg/m <sup>2</sup>	54	101	
> 25 kg/m <sup>2</sup>	9	26	0.965
Smoke			
No	50	97	
Yes	19	41	0.745
ASA			
I	21	37	
II-III	48	101	0.584
CA19-9			
≤ 400 U/mL	40	116	
> 400 U/mL	29	22	< 0.001
CA125			
≤ 38 U/mL	20	121	
> 38 U/mL	49	26	< 0.001
CEA			
≤ 5 U/mL	42	112	
> 5 U/mL	27	26	0.002
Fibrinogen			
≤ 4.0 g/L	50	101	
> 4.0 g/L	19	37	0.912
NLR			
≤ 5	59	131	
> 5	10	7	0.026
PLR			
≤ 150	36	78	
> 150	33	60	0.553
PNI			
> 45	42	101	
≤ 45	27	37	0.072
Platelet			
≤ 250 × 10 <sup>9</sup> /L	53	108	
> 250 × 10 <sup>9</sup> /L	16	30	0.813
Jaundice			
No	34	78	
Yes	35	60	0.431
Albumin			
> 35 g/L	42	82	
≤ 35 g/L	27	56	0.841
Diabetes mellitus			
No	39	101	
Yes	30	37	0.017
Pancreatitis			
No	42	93	
Yes	27	45	0.354

U/mL ( $P < 0.001$ ), CEA  $> 5$  U/mL ( $P = 0.002$ ), NLR  $> 5$  ( $P = 0.026$ ), and diabetes mellitus ( $P = 0.017$ ) (Table 2). In multivariate analysis, both CA125  $> 38$  U/mL (OR = 12.397, 95%CI: 5.468-28.105,  $P < 0.001$ ) and diabetes mellitus (OR = 3.343, 95%CI: 1.539-7.262;  $P = 0.002$ ) were determined to independently predict synchronous liver metastasis from PDAC (Table 3). The area under the ROC curve (AUC) of serum CA125 level was 0.821 (95%CI: 0.752-0.891), with sensitivity of

**Table 3 Multivariate analysis of predictors of synchronous liver metastasis**

Parameter	Odds ratio	95%CI	P value
CA19-9			
≤ 400 U/mL			
> 400 U/mL	2.398	0.909-6.327	0.077
CA125			
≤ 38 U/mL			
> 38 U/mL	12.397	5.468-28.105	< 0.001
CEA			
≤ 5 U/mL			
> 5 U/mL	0.672	0.249-1.817	0.434
NLR			
≤ 5			
> 5	0.934	0.283-3.083	0.911
Diabetes mellitus			
No			
Yes	3.343	1.539-7.262	0.002

**Table 4 Risk factors for unresectability of synchronous liver metastasis from pancreatic ductal adenocarcinoma**

Parameter	Simultaneous resections (Group A) n = 30	Palliative surgical bypass (Group B) n = 39	P value (univariate)
Age, yr			
≤ 62	20	12	
> 62	10	27	0.004
Sex			
Male	20	27	
Female	10	12	0.821
BMI			
< 18 kg/m <sup>2</sup>	2	4	0.664
18-25 kg/m <sup>2</sup>	23	31	
> 25 kg/m <sup>2</sup>	5	4	0.472
Smoke			
No	23	27	
Yes	7	12	0.494
ASA			
I	11	10	
II-III	19	29	0.326
CA19-9			
≤ 400 U/mL	22	18	
> 400 U/mL	8	21	0.026
CA125			
≤ 38 U/mL	11	9	
> 38 U/mL	19	30	0.221
CA125			
≤ 62 U/mL	21	11	
> 62 U/mL	9	28	0.001
CEA			
≤ 5 U/mL	22	20	
> 5 U/mL	8	19	0.066
Fibrinogen			
≤ 4.0 g/L	21	29	
> 4.0 g/L	9	10	0.688
NLR			
≤ 5	26	33	
> 5	4	6	0.811
PLR			
≤ 150	17	19	
> 150	13	20	0.513
PNI			
> 45	22	20	
≤ 45	8	19	0.066

Platelet			
≤ 250 × 10 <sup>9</sup> /L	26	27	
> 250 × 10 <sup>9</sup> /L	4	12	0.097
Albumin			
> 35 g/L	23	19	
≤ 35 g/L	7	20	0.021
Diabetes mellitus			
No	17	22	
Yes	13	17	0.983
Pancreatitis			
No	22	20	
Yes	8	19	0.066

**Table 5 Multivariate analysis of risk factors for unresectability of synchronous liver metastasis from pancreatic ductal adenocarcinoma**

Parameter	Odds ratio	95%CI	P value
Age, yr			
≤ 62			
> 62	3.921	1.217-12.632	0.022
CA19-9, U/mL			
≤ 400 L			
> 400	1.760	0.517-5.992	0.366
CA125, U/mL			
≤ 62			
> 62	5.181	1.612-16.665	0.006
Albumin			
> 35 g/L			
≤ 35 g/L	1.796	0.516-6.253	0.357

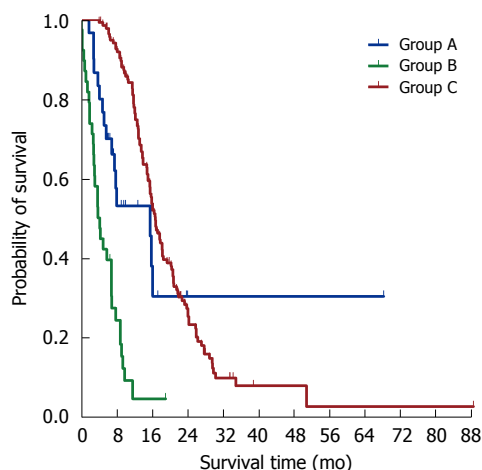
71.01% and specificity of 87.61% at the threshold of 38 U/mL.

**Risk factors for unresectability of synchronous liver metastasis**

Table 4 compares the clinical parameters between the curative group (group A) and the palliative group (group B), all of whom had primary PDAC and synchronous liver metastasis. In univariate analysis, the probability of unresectability was significantly increased when patients presented with age > 62 (*P* = 0.004), CA19-9 > 400 U/mL (*P* = 0.026), CA125 > 62 U/mL (*P* = 0.001) and albumin ≤ 35 g/L (*P* = 0.021). In multivariate analysis, one clinical index and one tumor marker, age > 62 (OR = 3.921, 95%CI: 1.217-12.632, *P* = 0.022) and CA125 > 62 U/mL (OR = 5.181, 95%CI: 1.612-16.665, *P* = 0.006), were found to correlate with increased unresectability when a 62-U/mL threshold of CA125 was used (Table 5). The AUC of serum CA125 level was 0.701 (95%CI: 0.576-0.826), with sensitivity of 71.79% and specificity of 70.00% at the threshold of 62 U/mL.

**Prognostic factors for PDAC patients with synchronous liver metastasis**

Following their respective surgeries, PDAC patients with synchronous liver metastasis had a decreased median survival compared to those with PDAC and no distant metastasis (7.0 mo vs 16.9 mo, *P* <



No. at risk	
Group A	30 13 6 2 1 1 1 1 1 0
Group B	39 8 1 0
Group C	138 126 67 22 8 3 3 1 1 1 1 1

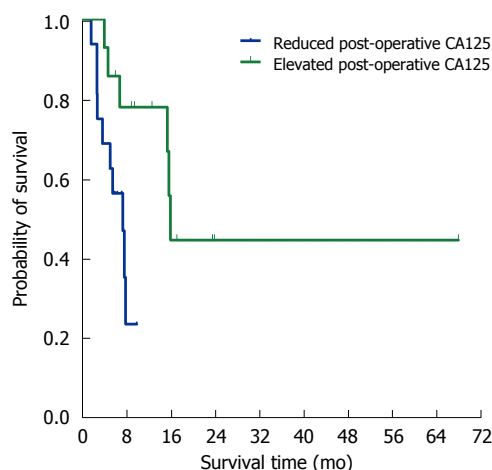
**Figure 2** Kaplan-Meier survival curves of PDAC patients with synchronous liver metastasis who underwent simultaneous resections for primary PDAC and synchronous liver metastasis (group A) and palliative surgical bypass (group B) and PDAC patients with no distant metastases who underwent curative resection for primary PDAC alone (group C).

0.001) (Figure 2). However, the median survival of patients who underwent simultaneous curative resections for primary PDAC and liver metastasis was not significantly different from that of those who underwent curative resection for primary PDAC alone (15.7 mo vs 16.9 mo,  $P = 0.085$ ). Unfortunately, patients who underwent palliative bypass merely had a 4.4-mo survival because of unresectable liver metastases.

Prognostic factors for overall survival of PDAC patients with synchronous liver metastasis were illustrated using Cox regression analysis (Table 6). Univariate analysis revealed that patients with age > 62 ( $P = 0.006$ ), CA19-9 > 400 U/mL ( $P = 0.042$ ) and CA125 > 62 U/mL ( $P = 0.003$ ) tended to have a diminished survival. Multivariate analysis demonstrated that age > 62 (HR = 2.191, 95%CI: 1.182-4.060,  $P = 0.013$ ) and CA125 > 62 U/mL (HR = 2.601, 95%CI: 1.403-4.832,  $P = 0.002$ ) were still retained as significant and independent prognostic factors for long-term survival. Moreover, after the simultaneous resections, patients with post-operatively elevated serum CA125 levels had shorter survival than those with post-operatively reduced serum CA125 levels (7.7 mo vs 16.3 mo,  $P = 0.013$ ) (Figure 3).

**Comparison of intra- and post-operative courses**

During the intra-operative period, mean operative time, median blood loss and frequency of intra-operative RBC transfusion were similar between patients in group A and group C ( $P = 0.494$ ,  $P = 0.780$ ,  $P = 0.691$ ) (Table 7). During the post-operative course, pancreatic fistula was the most frequent complication in both group A ( $n$



No. at risk	
> 62 U/mL	16 3 0
≤ 62 U/mL	14 10 6 2 1 1 1 1 1 0

**Figure 3** Kaplan-Meier survival curves according to post-operative CA125 levels of PDAC patients with synchronous liver metastasis who underwent simultaneous resections for primary PDAC and synchronous liver metastasis (group A).

= 9, 40.9%) and group C ( $n = 22$ , 33.3%). Only one patient in group A had two complications, pancreatic fistula and cerebral infarction. Three patients in group C had two complications, pancreatic fistula and delayed gastric emptying, delayed gastric emptying and gastrointestinal hemorrhage, pancreatic fistula and pneumonia respectively. The rates of pancreatic fistula and other complications in group A were not significantly greater than in group C ( $P = 0.072$ ,  $P = 0.230$ ). As for alteration of post-operative glycemic status by surgery, 53.8% ( $n = 7$ ) of patients in group A with diabetes mellitus were cured of diabetes post-operatively, whereas 46.2% ( $n = 6$ ) had either no change in diabetic status or experienced worsening of glucose control. Among patients without pre-operative diabetes mellitus in group A, 35.3% ( $n = 6$ ) remained nondiabetic post-operatively and 64.7% ( $n = 11$ ) developed new-onset. These two surgical options of group A and C did not have significantly different impacts on post-operative diabetic control ( $P = 0.602$ ). Two in group A and 4 in group C were readmitted because of biliary reflux or delayed gastric emptying. There was no in-hospital mortality in either group. The median length of hospital stay in group A was not longer than in group C due to additional resection for synchronous liver metastases ( $P = 0.479$ ).

**DISCUSSION**

Although incidental liver metastases from PDAC identified during surgeries are not an unusual finding to surgeons, intra-operative surprises probably make patients lose opportunities to receive a more rational treatment modality which surgeons have weighed the

**Table 6** Cox regression analysis of prognostic factors in pancreatic ductal adenocarcinoma patients with synchronous liver metastasis undergoing surgery

Parameter	n	Median OS (95%CI) (mo)	Univariate analysis	Multivariate analysis		
			P value	Hazard ratio	95%CI	P value
Age, yr						
≤ 62	32	9.988 (5.215-14.760)				
> 62	37	4.534 (3.294-5.774)	0.006	2.191	1.182-4.060	0.013
Sex						
Male	47	5.388 (2.454-8.322)				
Female	22	7.129 (5.820-8.439)	0.428			
BMI, kg/m <sup>2</sup>						
< 18	6	4.008 (0.000-8.701)	0.939			
18-25	54	6.998 (5.147-8.849)				
> 25	9	7.721 (1.548-13.894)	0.548			
Smoke						
No	50	7.031 (4.606-9.455)				
Yes	19	5.979 (0.607-11.352)	0.317			
ASA						
I	21	9.988 (3.524-16.452)				
II-III	48	6.998 (3.803-10.193)	0.273			
Primary tumor location						
Head/neck	53	6.998 (4.910-9.086)				
Body/tail	16	7.129 (3.438-10.820)	0.762			
CA19-9, U/mL						
≤ 400	40	7.984 (6.454-9.513)				
> 400	29	4.008 (2.832-5.185)	0.042	1.398	0.773-2.527	0.267
CA125, U/mL						
≤ 62	32	9.035 (7.052-11.017)				
> 62	37	4.008 (2.801-5.215)	0.003	2.601	1.403-4.823	0.002
CEA, U/mL						
≤ 5	42	7.721 (6.340-9.102)				
> 5	27	5.191 (1.847-8.535)	0.320			
Fibrinogen, g/L						
≤ 4.0	50	7.129 (5.373-8.886)				
> 4.0	19	5.191 (2.575-7.807)	0.533			
NLR						
≤ 5	59	7.031 (5.123-8.939)				
> 5	10	4.008 (0.000-9.812)	0.495			
PLR						
≤ 150	36	7.031 (4.545-9.517)				
> 150	33	5.979 (3.287-8.672)	0.851			
PNI						
> 45	42	7.129 (6.237-8.022)				
≤ 45	27	5.848 (3.396-8.300)	0.890			
Platelet						
≤ 250 × 10 <sup>9</sup> /L	53	6.998 (5.018-8.978)				
> 250 × 10 <sup>9</sup> /L	16	7.097 (0.957-13.236)	0.993			
Jaundice						
No	34	7.721 (4.540-10.901)				
Yes	35	6.998 (3.593-10.403)	0.446			
Biliary drainage						
No	45	7.129 (5.245-9.014)				
Yes	24	5.027 (1.872-8.181)	0.878			
Bilirubin, μmol/L						
≤ 50	58	6.998 (4.918-9.078)				
> 50	11	7.031 (1.408-12.651)	0.448			
Albumin, g/L						
> 35	42	7.097 (4.893-9.300)				
≤ 35	27	5.027 (2.171-7.882)	0.799			
Diabetes mellitus						
No	39	6.998 (4.177-9.819)				
Yes	30	6.998 (4.424-9.572)	0.300			
Pancreatitis						
No	42	5.979 (4.876-9.186)				
Yes	27	6.998 (2.516-11.480)	0.789			



**Table 7 Comparison of perioperative parameters in different cohorts of patients undergoing surgery**

Parameter	No. of patients		P value
	Simultaneous resections (Group A) n = 30	Pancreatectomy alone (Group C) n = 138	
Mean operative time, min	344.3	380.5	0.494
Median blood loss, mL	400	400	0.780
Intra-operative RBC transfusion	12	61	0.691
Complication			
Pancreatic fistula	9	22	0.072
Any other	13	44	0.230
Biliary fistula	0	0	
Chylous fistula	1	3	
Delayed gastric emptying	4	10	
Intra-abdominal infection	6	28	
Gastrointestinal hemorrhage	0	1	
Cerebral infarction	1	0	
Pneumonia	1	2	
Post-operative diabetes mellitus			0.602
Dissolved	7	15	
New-onset	6	12	
Persistent	6	22	
Re-admission	2	4	
In-hospital mortality	0	0	
Hospital stay, d	18	19	0.479

pros and cons of. Accurate detection of liver metastases from PDAC and proper selection of patients who are likely to benefit from simultaneous curative resections for primary PDAC and synchronous liver metastasis are a great challenge for individualized therapy for PDAC. As pancreatectomy is performed with relatively high morbidity and mortality, assessment of unresectability of synchronous liver metastases under the circumstance of resectable primary PDAC, needs an objective standard using a series of pre-operative clinical parameters. In the present study, we identified a pre-operative serum signature of CA125 levels over 38 U/mL as one of the predictors for synchronous liver metastasis from PDAC. Serum CA125 levels over 62 U/mL were found not only to imply unresectability for synchronous liver metastasis, but also to indicate a poor survival for PDAC patients with synchronous liver metastasis. These suggest that PDAC patients with synchronous liver metastasis predicted by serum CA125 levels over 38 U/mL could be appropriate for and, more importantly, benefit from the simultaneous resections if serum CA125 levels range between 38 U/mL and 62 U/mL.

Since CA125 has been extensively used as a biomarker of various types of cancers, its diagnostic and prognostic values are gradually attracting great attention for PDAC. Recently it was reported in a two-center clinical study that elevated serum CA125 levels were more pronounced in patients with the metastasis-associated burden, especially liver metastasis<sup>[17]</sup>. Elevated serum CA125 levels in patients with gastric adenocarcinoma were also observed with the presence of peritoneal metastases and lymph

node metastases<sup>[31,32]</sup>. On the contrary to the similar elevated serum CA19-9 levels in all stages of PDAC, serum CA125 levels for PDAC with distant metastasis were shown to be higher than that for early or locally advanced PDAC<sup>[33]</sup>. Our result indicated that patients with PDAC were more likely to have synchronous liver metastasis if serum CA125 level exceeded 38 U/mL instead of serum CA19-9 level higher than 1000 U/mL. Thus, it is inferred that serum CA125 levels are insensitive to primary PDAC.

In addition to differential diagnosis, serum CA125 levels reflected the extent of liver metastases as well. We found that the median serum CA125 levels of unexpected liver metastases was lower than that of detected liver metastases (52 U/mL vs 72 U/mL,  $P = 0.009$ ). The median serum CA125 levels of liver metastases with fewer than 5 nodules smaller than 3 cm, or more than 3 nodules larger than 3 cm, or intermediate nodules was, respectively, 37 U/mL, 67 U/mL and 486 U/mL<sup>[17]</sup>. Of note, even though patients received curative resection for primary PDAC and post-operatively displayed a decrease in serum CA19-9 level, an early distant metastasis and poor survival still troubled those who did not experience a decrease in serum CA125 levels<sup>[17,18]</sup>, as we observed. Furthermore, CA125 expression in PDAC was also found to directly correlate with tumor stage, grade and metastasis<sup>[34,35]</sup>, and to increase along with loss of differentiation of PDAC<sup>[35]</sup>, which denotes the tendency for distant metastasis<sup>[36,37]</sup>. Primary PDAC expressed CA125 under the same intensity as metastatic lesions did, demonstrating the maintenance of PDAC for CA125 expression during the metastatic process<sup>[35]</sup>. Therefore, we believe that CA125 is an effective pre-operative factor for monitoring synchronous liver metastasis from PDAC.

Given that CA19-9 can be influenced by obstructive jaundice or pancreatitis<sup>[38]</sup> and cannot be detected due to lack of the Lewis antigen<sup>[39]</sup>, CA125 characterized by secretory stability is considered more suitable for objective judgement. Regarding the unresectability of cancer, CA125 has been widely utilized as the therapeutic strategy<sup>[40-44]</sup>. Compared with CA19-9, the most common tumor marker evaluated in patients with PDAC, CA125 as a predictor for unresectability of primary PDAC had a superior ROC area of 0.81, with a cutoff level of 19.7U/mL<sup>[45]</sup>. Moreover, elevated CA125 levels over the selected threshold could distinguish factually unresectable PDAC from equivocally resectable PDAC judged by multidetector CT<sup>[45]</sup>. In the present study, we analyzed a series of clinical parameters, including tumor markers, and found that serum CA125 levels over 62 U/mL might signify unresectability of synchronous liver metastasis even if primary PDAC could be curatively resected at a R0 status. Considering that serum CA125 levels also implied the extent of liver metastasis<sup>[17]</sup> and that the location and number of liver metastases determined

**Table 8** Survival data from published studies with simultaneous resections of primary pancreatic ductal adenocarcinoma and synchronous liver metastasis

	Simultaneous resections		Palliative surgical bypass or chemotherapy		Pancreatectomy alone		P value
	Median (mo)	n	Median (mo)	n	Median (mo)	n	
Adam <i>et al</i> <sup>[57]</sup> (2006)	NA <sup>1</sup>	41	-	-	-	-	-
Yamada <i>et al</i> <sup>[58]</sup> (2006)	15.0	6	-	-	-	-	-
Gleisner <i>et al</i> <sup>[59]</sup> (2007)	5.9	17	-	-	-	-	-
Shrikhande <i>et al</i> <sup>[60]</sup> (2007)	7.9	10	-	-	-	-	-
De Jong <i>et al</i> <sup>[51]</sup> (2010)	17.7	NA	-	-	17.9	NA	0.730
De Jong <i>et al</i> <sup>[61]</sup> (2010)	13.0 <sup>2</sup>	14	-	-	-	-	-
Dünschede <i>et al</i> <sup>[49]</sup> (2010)	8.0	9	11	5	-	-	-
Seelig <i>et al</i> <sup>[62]</sup> (2010)	11.8	4	-	-	-	-	-
Klein <i>et al</i> <sup>[50]</sup> (2012)	13.0	7	-	-	26.5	13	NA
Tachezy <i>et al</i> <sup>[63]</sup> (2016)	14.5	69	7.5	69	-	-	< 0.001

<sup>1</sup>Five-year survival of 20% was provided; <sup>2</sup>The median survival of 25 patients with pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma.

the feasibility and method of surgery<sup>[46]</sup>, our findings were quite deducible and rational. Taken together with predictability of synchronous liver metastasis by serum CA125 level over 38 U/mL, a narrow range of serum CA125 level from 38 U/mL to 62 U/mL denoted simultaneous resectability of primary PDAC and synchronous liver metastasis.

In spite of uneventful curative resections, prolonged survival does not necessarily belong to all patients. On one hand, it was demonstrated that resected patients with pre-operative serum CA125 levels over 18.4 U/mL survived less than half of the life time as those with lower serum CA125 levels (11.3 mo vs 25.3 mo)<sup>[17]</sup>. More importantly, unlike CA19-9, no discrepancies of predictability by CA125 were found in PDAC patients with hyperbilirubinemia<sup>[47]</sup>. It was determined in the two-center clinical study that the combination of CA19-9 over 1000 U/mL and either CA125 or CEA indicated a worse surgical outcome, with a median survival of 7.0 mo vs 18.2 mo for the validation cohort from our hospital<sup>[18]</sup>. In addition, as a good response to curative surgery, decreasing CA125 levels after pancreatectomy were associated with longer survival time as well (40.8 mo vs 14.6 mo)<sup>[17]</sup>. Our data also reflected that patients with elevated serum CA125 levels did not display a survival advantage following the simultaneous resections. Associated with the incidence of liver metastasis, co-expression of CA125 and mesothelin could signify unfavorable outcome in PDAC patients (19.0 mo vs 34.8 mo)<sup>[48]</sup>. In this study, we showed that pretreatment serum CA125 level over 62 U/mL was useful for indicating a worse outcome for PDAC patients with synchronous liver metastasis. These imply that our surgical option for primary PDAC and synchronous liver metastasis determined by serum CA125 levels does have an impact on patient survival and that the simultaneous curative resections do improve clinical outcome. Aggressive therapeutic regimens may be more advantageous in patients with lower serum CA125 levels.

On the other hand, Dünschede *et al*<sup>[49]</sup> claimed

shorter survival in patients with synchronous liver metastasis undergoing simultaneous resections than in those treated by gemcitabine (8.0 mo vs 11 mo) despite no statistical differences. However, resection for metachronous liver metastases instead of gemcitabine might extend survival in highly selected patients. Meanwhile, Klein *et al*<sup>[50]</sup> reported that no similar survival was achieved by pancreatectomy and simultaneous liver resection for PDAC, albeit at a R0 status, compared with pancreatectomy for non-metastasized PDAC (13.0 mo vs 26.5 mo)<sup>[50]</sup> (Table 8). On the contrary, we showed that the survival of PDAC patients with synchronous liver metastasis who underwent simultaneous curative resections (15.7 mo) was not only longer than that of those who underwent palliative surgical bypass alone (4.4 mo) but also similar to that of patients with non-metastasized PDAC who underwent curative pancreatectomy alone (16.9 mo). Such discrepancy with the previous two studies can be explained by inconspicuous residual lesion after liver resection misjudged by pre-operative or intra-operative assessment. In accordance with our data, De Jong *et al*<sup>[51]</sup> demonstrated that overall survival appeared not to be different in the patients who underwent PD and liver-directed therapy compared with those with no evidence of liver metastasis who underwent PD (17.7 mo vs 17.9 mo). Therefore, our result of Cox regression analysis showing that serum CA125 levels less than 62 U/mL were independently associated with a prolonged survival, justified our criterion of serum CA125 level as appropriate for simultaneous resections for primary PDAC and synchronous liver metastasis, and certified its benefit for survival of patients with synchronous liver metastasis from PDAC.

Now that pancreatectomy itself is associated with significant morbidity and mortality, a simultaneous liver resection may carry the extraneous risks influencing overall survival, such as bile leak, hemorrhage, or liver abscess<sup>[52,53]</sup>. The risk of developing a liver abscess reached nearly 40%-50%

for liver-directed therapy radiofrequency ablation of liver tumors in patients with a biliary tract procedure such as an enterobiliary anastomosis or biliary stenting<sup>[54]</sup>. As for liver resection for metastasized PDAC, it is noteworthy that the construction of a biliary-enteric anastomosis during PD may be one of the induction factors of a liver abscess. The development of post-operative complications has been found to be detrimental to survival and to lead to early recurrence in PDAC patients<sup>[55,56]</sup>. However, our study found no liver-specific complications caused by liver resection and no more severe pancreatic fistula caused by pancreatectomy, suggesting relative safety of simultaneous resections with similar morbidity compared with standard pancreatectomy alone.

The current study had several limitations. Despite a time span of 8 years, only a relatively small sample size of patients was identified as having primary PDAC and synchronous liver metastasis who underwent either simultaneous resections or palliative surgical bypass. As such, this study had limited statistical power. Meanwhile, there may have been selection bias in whether PDAC patients with synchronous liver metastasis were chosen for surgery. For example, if some PDAC patients with resectable tumor of body or tail of the pancreas and unresectable synchronous liver metastases did not present with biliary or upper digestive obstruction, they usually underwent gemcitabine-based chemotherapy instead of palliative surgical bypass first and were excluded from our study. In addition, the focus of our study was the impact of pre-operative factors on diagnosis of liver metastasis and selection of suitable patients for simultaneous resections, which overlooks the influence of intra- or post-operative factors on overall and recurrence-free survival. Furthermore, the role of serum CA125 levels in clinical prediction for metachronous liver metastasis from PDAC was not investigated and hence cannot provide guidance for all patients with liver metastasis from PDAC.

In conclusion, diagnosis and treatment of liver metastasis from PDAC must be individualized in the era of precision medicine because of its highly malignant biological behavior. Serum CA125 level over 38 U/mL predicts synchronous liver metastasis from PDAC, and serum CA125 level over 62 U/mL is associated with unresectability of metastatic disease burden. The criterion set up by serum CA125 levels facilitates the careful diagnosis of synchronous liver metastases from PDAC pre-operatively and the prudent selection of appropriate patients for simultaneous resections for primary PDAC and synchronous liver metastasis for the sake of prolonged survival and substantially reduced morbidity or mortality. Therefore, simultaneous resections for primary PDAC and synchronous liver metastasis are justified by prolonged survival in patients selected by serum CA125. It is foreseeable that the indication for the simultaneous resections for precisely diagnosed liver-metastasized PDAC will be

extended with the development of surgical techniques and thus more PDAC patients will have a clear survival benefit.

## COMMENTS

### Background

Approximately 50% of new pancreatic ductal adenocarcinoma (PDAC) cases are discovered to have distant metastases. The doctrine that the presence of liver metastasis from resectable PDAC contradicts a curative resection and indicates a palliative surgical bypass, deprives patients of an incremental benefit from simultaneous curative resections for primary and metastatic PDAC. Diagnosis of synchronous liver metastasis from PDAC and assessment of unresectability are still challenging to surgeons.

### Research frontiers

The two-center clinical study we were involved in reported that elevated serum CA125 levels are more pronounced in patients with the metastasis-associated burden. On the contrary to the similar elevated serum CA19-9 levels in all stages of PDAC, serum CA125 levels for PDAC with distant metastasis were higher than that for early or locally advanced PDAC. Serum CA125 levels also imply the extent of liver metastasis, and the location and number of liver metastases determine the feasibility and method of surgery. Therefore, we hypothesized that CA125 might be an effective pre-operative factor for monitoring synchronous liver metastasis from PDAC, and that CA125 could predict unresectability of synchronous liver metastasis.

### Innovations and breakthroughs

PDAC patients with synchronous liver metastasis predicted by serum CA125 levels over 38 U/mL might be appropriate for and, more importantly, benefit from simultaneous resections if serum CA125 levels range between 38 U/mL and 62 U/mL. The survival of PDAC patients with synchronous liver metastasis who underwent simultaneous curative resections was not only longer than that of those who underwent palliative surgical bypass alone but also similar to that of patients with non-metastasized PDAC who underwent curative pancreatectomy alone.

### Applications

The criterion set up by serum CA125 levels facilitates the careful judgement of occurrence of synchronous liver metastases from PDAC, and the prudent selection of appropriate patients for simultaneous resections for primary PDAC and synchronous liver metastasis, for the sake of prolonged survival and substantially reduced morbidity or mortality.

### Terminology

Liver metastasis is a remarkable preference of PDAC to disseminate due to its portal venous blood draining and lymphatic spread, and drastically reduces the survival of patients with PDAC. Simultaneous curative resection is an unconventional surgical option for synchronous liver metastasis, which requires further justification by prolonged survival, a longer recurrence-free interval and, at least, no more surgical-related morbidity and mortality.

### Peer-review

This research is original and very interesting for publication.

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