Long-term survival of distal cholangiocarcinoma after pancreaticoduodenectomy combined with portal vein system resection and reconstruction

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Research

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Abstract

BACKGROUND:

Pancreaticoduodenectomy is the only definitively curative therapy for the long-term survival of distal cholangiocarcinoma patients. And the 5-year survival rate of distal cholangiocarcinoma after pancreatoduodenectomy ranged from 22–47%. Pancreatoduodenectomy combined with portal vein system resection and reconstruction for distal cholangiocarcinoma is rarely reported because it's not common. To our knowledge, only few reports have provided the detail outcome and long-term survival of distal cholangiocarcinoma after pancreaticoduodenectomy combined with portal vein system resection and reconstruction. Therefore, we developed a program to analysis the risk factors of prognosis for distal cholangiocarcinoma patients after pancreaticoduodenectomy, and to evaluate the vascular invasion type, operation procedure and long-term survival of patients with portal vein system invasion.

METHODS:

Retrospective reviewed for 123 distal cholangiocarcinoma patients after pancreatoduodenectomy between January 2011 and December 2019. Portal vein system invasion in 17 patients according to the pathology. Multivariable regression Cox models produced survival estimate to the distal cholangiocarcinoma patients. Then patients were grouped according to portal vein system invasion, and tumor-free and overall survival rates were investigated with the Kaplan-Meier analysis. Finally, the vascular invasion type and operation procedure were analyzed to the distal cholangiocarcinoma patients with portal vein system invasion.

RESULTS:

The 1-year, 3-year, 5-year overall survival rates of patients with distal cholangiocarcinoma after pancreatoduodenectomy were 75.2%, 37.1%, 31.5%. Multifactor Cox regression showed tumour differentiation degree ($RR = 1.440$, 95% CI : 1.009–2.055), portal vein system invasion ($RR = 1.860$, 95% CI : 1.057–3.275) and lymph node metastasis ($RR = 2.097$, 95% CI : 1.054–4.174) as independent risk factors for long-term survival. There were 17 patients underwent pancreatoduodenectomy combined with portal vein system resection and reconstruction. The patients with portal vein system invasion had larger tumor diameter, longer operation time, more blood transfusion rate and more lymph node metastasis rate than control group ($P < 0.05$). The 1-year, 2-year overall survival rates for patients without and with portal vein system invasion were 79.7%, 58.9% and 48.6%, 10.8% ($p = 0.000$). The median overall survival time for patients without and with portal vein system invasion were 49.1 and 14.2 months, respectively.

CONCLUSION:

The portal vein system invasion is an important independent risk factors for long-term survival to the patients with distal cholangiocarcinoma, and the long-term survival is poor. Pancreatoduodenectomy combined with portal vein system resection and reconstruction did not increase the incidence of perioperative complication rate and mortality. At present, surgery maybe still the only effective method for distal cholangiocarcinoma patients with portal vein system invasion.

Background

Cholangiocarcinoma is a rare malignancy and accounts for 2% of all malignancies [1]. Distal cholangiocarcinoma refers to the extrahepatic bile duct where the tumor below the confluence of the cystic duct, accounting for 20–40% of all cholangiocarcinoma [2–3]. Surgical resection by pancreaticoduodenectomy remains the only definitively curative therapy for the long-term survival of distal cholangiocarcinoma patients [4]. And the 5-year survival rate of distal cholangiocarcinoma after pancreaticoduodenectomy ranged from 22–47% [5–7].

Pancreatoduodenectomy combined with portal vein system resection and reconstruction for distal cholangiocarcinoma is rarely reported because it's not common. To our knowledge, only few reports have provided the detail outcome and long-term survival of distal cholangiocarcinoma after pancreaticoduodenectomy combined with portal vein system resection and reconstruction[8–9].

Therefore, we collectively reviewed 123 patients with distal cholangiocarcinoma after pancreaticoduodenectomy in our hospital, and there were 17 patients with portal vein system invasion. The aim of our study was to analyse the risk factors of prognosis for distal cholangiocarcinoma patients after pancreaticoduodenectomy, and to evaluate the vascular invasion type, operation procedure and long-term survival of patients with portal vein system invasion.

Patients And Methods

Patients

A retrospective analysis was made of 123 consecutive patients with distal cholangiocarcinoma who underwent pancreaticoduodenectomy from January 2011 to December 2019 in the Department of Hepatobiliary Surgery of our hospital. All of the patients were diagnosed with adenocarcinoma according to the pathology. And the patients with no invasion of major celiac arteries (hepatic artery / celiac trunk / superior mesenteric artery) or distant metastasis. There were also 17 patients were diagnosed with portal vein system invasion according to the pathology.

The patients including 72 (58.5%) males and 51 (41.5%) females, and the age of the patients ranged from 29 to 84 years (mean, 64.9 ± 9.2 years). Forty-two (34.1%) patients underwent percutaneous transhepatic cholangial drainage (PTCD) before operation, and 16 (13.0%) patients underwent endoscopic retrograde cholangiopancreatography (ERCP) before operation. The radiological information was acquired from the latest CT or MRI examination before operation.

This study was approved by the Ethics Committee of Beijing Chaoyang Hospital (acceptance number 2020-D-141). All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration.

Treatment and Follow-up

All of the patients underwent pancreatoduodenectomy. And regional lymph node dissection was performed routinely during the operation, including nodes along the common hepatic artery, nodes in the hepatoduodenal ligament, and anterior or posterior pancreatoduodenal nodes. And the portal vein system resection and reconstruction was performed to the patients with vascular invasion.

Patients were followed up by outpatient and telephone. Blood routine and blood biochemistry examination every one month, carbohydrate antigen 19 - 9 (CA19-9) and CT scan every 3 months for 2 years. Then CA19-9 and CT scan every 6 months above 2 years.

Statistical analysis

Catalogued data included general conditions (gender, age, diabetes history, smoking history, biliary drainage history, leukocyte, neutrophil ratio, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), direct bilirubin (DB), glutamyltranspeptidase (GGT), albumin (ALB), CEA, CA19-9), intraoperative conditions (operation time, bleeding volume, blood transfusion), pathological conditions (maximum tumor diameter, tumour differentiation degree, perineural invasion, portal vein system invasion, lymph node metastasis, T stage, R0 resection) and follow-up conditions (postoperative complication, postoperative chemotherapy, tumour recurrence and long-term survival) .

Endpoints for the current analysis was patient death or tumour recurrence. The normal distribution data was represented by mean $\pm$ SD, and comparisons were analyzed with the Student t-test according to data distribution. The non normal distribution data was represented by M (P25, P75)

, and comparisons were analyzed with the Mann-Whitney rank-sum test. Categorical variables were presented as number and percentage and were analyzed by Chi-square test or Fisher exact test, as appropriate.

Overall and tumour-free survival rates were calculated using the Kaplan-Meier method. Log-rank test was used to perform the univariate analysis, and Cox proportional hazard regression models were used for multivariate analysis. Those variables, which were found to be significant in univariate analysis, were further enrolled in the multivariate analysis.

A p value < 0.05 was considered statistically significant. The statistical measurements were performed using the SPSS 19.0 (IBM, Chicago, Illinois, USA) software program.

Results

Perioperative outcomes

All of the 123 patients successfully completed the operation. The amount of bleeding was 500 (400, 600) ml, 43 patients received blood transfusion, and the operation time ranged from 6 to 15 hours (mean, 9.8 ± 1.9 hours). R0 resection in 117 patients with the R0 rate of 95.1%. The tumor size ranged from 0.5 to 6.5 cm (mean, 2.2 ± 1.0 cm). Lymph node metastases in 51 patients with the rate of 41.5%. Portal vein system invasion in 17 patients according to the pathology.

In our group, 6 patients died during the perioperative period, and the perioperative mortality was 4.9%. The causes of deaths included haemorrhage 3 cases, myocardial infarction 1 case, pulmonary embolism 1 case and cerebral hemorrhage 1 case. There were 34 patients with postoperative complications, and the incidence rate was 27.6%. Among them, biochemical fistula in 14 (11.4%) cases, grade B pancreatic fistula in 7 (5.7%) cases, grade C pancreatic fistula in 5 (4.1%) cases, haemorrhage in 9 (7.3%) cases.

Prognostic outcomes

The final follow-up date is April 2020, and the median follow-up length is 41.0 months. Two patients missed follow-up. Finally, 115 patients were studied of long-term survival. The 1-year, 3-year, 5-year tumour-free and overall survival rates of all patients were 67.0%, 36.0%, 27.1% and 75.2%, 37.1%, 31.5% (Fig. 1A and 1B). The median tumour-free and overall survival time were 38.2 and 44.7 months, respectively.

Risk factors for long-term survival of distal cholangiocarcinoma after pancreatoduodenectomy

In the 115 patients, univariate analysis identified neutrophil ratio, CA19-9, tumour differentiation degree, perineural invasion, portal vein system invasion and lymph node metastasis as the risk factors for long-term survival of distal cholangiocarcinoma patients after pancreatoduodenectomy (Table 1). And multifactor Cox regression showed tumour differentiation degree ($RR= 1.440$, 95% CI : 1.009–2.055), portal vein system invasion ($RR= 1.860$, 95% CI : 1.057–3.275) and lymph node metastasis ($RR= 2.097$, 95% CI : 1.054–4.174) as independent risk factors for long-term survival (Table 2).

Table 1. Risk factors for long-term survival of distal cholangiocarcinoma patients after pancreatoduodenectomy by univariate analysis

les	No. patients	1-year survival (%)	3-year survival (%)	Median survival (month)	P value
r	70	75.6	42.6	41.4	0.905
ale	45	74.8	31.2	44.7	
ear)	60	77.8	37.3	47.4	0.409
	55	72.3	36.7	37.7	
es	31	76.1	37.4	45.3	0.753
	84	74.8	37.0	41.5	
	37	79.8	31.2	32.0	0.441
	78	73.2	38.8	48.4	
drainage	51	77.4	32.4	43.3	0.860
	64	73.4	41.4	43.1	
yte (*10 ⁹)	104	74.6	34.7	42.5	0.179
	11	81.8	68.2	60.2	
ophil ratio (%)	90	82.3	39.5	47.7	0.038
	25	49.6	27.9	32.0	
/L)	61	69.2	40.8	40.2	0.122
	54	82.4	46.1	35.8	
/L)	30	82.5	34.5	43.1	0.896
	85	72.5	37.9	42.4	
/L)	29	76.7	43.7	44.5	0.630
	86	74.7	35.9	43.0	
mol/L)	17	94.1	62.7	57.2	0.062
	98	71.6	33.3	41.2	
nol/L)	11	90.9	63.6	34.3	0.196
	104	73.3	35.0	43.0	
J/L)	9	76.2	40.6	26.6	0.896
	106	75.2	37.3	44.7	
ug/ml)	101	75.9	41.3	47.3	0.073
	14	70.7	10.5	24.6	
9 (U/ml)	40	86.7	52.3	50.9	0.031

	75	68.9	29.1	38.0	
ion time (h)	49	76.0	43.9	43.9	0.372
	66	74.7	33.2	41.2	
ing volume (ml)	53	72.3	38.0	45.3	0.883
	62	77.8	36.9	43.4	
ransfusion	39	69.5	30.5	35.1	0.078
	76	78.0	39.5	43.4	
ntiation	29	85.2	50.8	52.6	0.016
	51	77.3	34.8	43.5	
erate	35	63.5	28.6	31.3	
diameter (cm)	44	88.5	38.9	46.4	0.162
	71	66.0	35.8	41.3	
ural invasion	104	73.6	32.4	38.4	0.015
	11	90.9	90.9	93.0	
vein system	16	48.6	-	14.2	0.000
n	99	79.7	42.4	49.1	
	47	63.5	19.0	27.5	0.000
node metastasis	68	83.0	50.7	55.5	
	110	74.9	38.2	45.4	0.464
ection	5	80.0	20.0	23.4	
	2	100	100	-	0.281
	11	90.9	47.1	48.7	
	102	72.9	34.8	42.4	
	28	73.5	26.0	31.4	0.250
erative	87	75.9	40.1	47.9	
cation	37	77.8	38.4	40.2	0.784
	78	73.7	36.3	41.0	
erative					
therapy					

Table 2
Risk factors for long-term survival of distal cholangiocarcinoma patients after pancreatoduodenectomy by multivariate Cox regression

Variables	<i>RR</i>	95% <i>CI</i>	P value
Neutrophil ratio	1.555	0.876–2.760	0.131
CA19-9	1.364	0.766–2.430	0.292
Differentiation	1.440	1.009–2.055	0.045
Perineural invasion	3.972	0.530-29.771	0.180
Portal vein system invasion	1.860	1.057–3.275	0.032
Lymph node metastasis	2.097	1.054–4.174	0.035

Clinical features of patients with portal vein system invasion

All of the 123 patients were divided into portal vein system invasion group and control group according to the presence or absence portal vein system invasion. The clinical features comparison between the two groups were shown in Table 3. The patients with portal vein system invasion had larger tumor diameter, longer operation time, more blood transfusion rate and more lymph node metastasis rate than control group ($P < 0.05$). However, pancreatoduodenectomy combined with vascular resection and reconstruction did not increase the incidence of perioperative complication rate and mortality.

Table 3

Clinical features comparison between the portal vein system invasion group and control group

Variables	portal vein system invasion group (n = 17)	control group (n = 106)	P value
Age(year)	62.4 ± 9.8	65.7 ± 8.9	0.164
Leukocyte (*10 ⁹)	6.5 ± 1.7	6.8 ± 2.3	0.651
Neutrophil ratio (%)	69.1 ± 9.1	66.3 ± 10.5	0.300
ALB (g/L)	34.1 ± 4.4	34.4 ± 6.2	0.848
ALT (U/L)	111.0(41.0, 159.0)	65.5(34.0, 151.3)	0.473
AST (U/L)	67.0(32.0, 120.0)	58.0(37.8, 103.0)	0.815
TB (μmol/L)	117.1(30.3, 224.9)	105.9(33.6, 216.8)	0.823
DB (μmol/L)	109.0(25.5, 202.2)	81.1(21.9, 167.2)	0.731
GGT (U/L)	396.0(151.0, 706.0)	370.0(129.0, 772.5)	0.988
CEA (ng/ml)	2.5(1.9, 3.2)	2.2(1.3, 3.4)	0.162
CA19-9 (U/ml)	80.2(37.4, 410.9)	53.1(25.5, 170.8)	0.270
Tumor diameter (cm)	3.0 ± 1.4	2.1 ± 0.9	0.001
Bleeding volume (ml)	600.0(400.0, 1500.0)	500.0(400.0, 600.0)	0.288
Operation time (h)	11.8 ± 2.2	9.5 ± 1.6	0.000
ICU stay (day)	4.0(2.0, 6.0)	2.0(1.0, 4.0)	0.060
Postoperative hospital stay (day)	21.0(17.0, 26.0)	21.0(16.0, 26.0)	0.953
Gender (%)			
Male	12(70.6)	60(56.6)	0.277
Female	5(29.4)	46(43.4)	
Diabetes history (%)			
Yes	4(23.5)	30(28.3)	0.907
No	13(76.5)	76(71.7)	
Smoking history (%)			
Yes	5(29.4)	33(31.1)	0.887

Variables	portal vein system invasion group (n = 17)	control group (n = 106)	P value
No	12(70.6)	73(68.9)	
Biliary drainage history (%)			
Yes	9(52.9)	49(46.2)	0.607
No	8(47.1)	57(53.8)	
Blood transfusion (%)			
Yes	10(58.8)	33(31.1)	0.026
No	7(41.2)	73(68.9)	
Differentiation (%)			
Poor	7(41.2)	29(27.4)	0.497
Moderate	7(41.2)	51(48.1)	
Well	3(17.6)	26(24.5)	
Perineural invasion (%)			
Yes	17(100)	91(85.8)	0.209
No	0(0)	15(14.2)	
Lymph node metastasis (%)			
Yes	13(76.5)	38(35.8)	0.002
No	4(23.5)	68(64.2)	
Resection (%)			
R0	16(94.1)	101(95.3)	1.000
R1	1(5.9)	5(4.7)	
T stage (%)			
T1	0(0)	2(1.9)	0.254
T2	0(0)	13(12.3)	
T3	17(100)	91(85.8)	
Postoperative complication (%)			
Yes	3(17.6)	31(29.2)	0.484

Variables	portal vein system invasion group (n = 17)	control group (n = 106)	P value
No	14(82.4)	75(70.8)	
Perioperative death (%)			
Yes	1(5.9)	5(4.7)	1.000
No	16(94.1)	101(95.3)	

Method of portal vein system resection and reconstruction

The location of portal vein system invasion by distal cholangiocarcinoma was showed in Fig. 3, and the location mainly contains portal vein (PV, n = 6), junction of portal vein and superior mesenteric vein (SMV, n = 7) and superior mesenteric vein (n = 4). The method of portal vein system resection and reconstruction was showed in Table 4. Wedge resection followed by primary closure was performed in 4 patients. Segmental resection was performed in 6 patients with PV or SMV invasion, and 4 patients were reconstructed by end-to-end anastomosis, 2 patients were reconstructed by the venous allograft with shape of "I". Segmental resection was performed in 7 patients with junction of PV and SMV invasion, and the venous allograft with shape of "Y" were used to reconstruction.

Table 4
Resection and reconstruction method of portal vein system invasion

Method	PV invasion (n = 6)	SMV invasion (n = 4)	junction of PV and SMV invasion (n = 7)
Resection			
Wedge	1	3	0
Segmental	5	1	7
Reconstruction			
Primary closure	1	3	0
End-to-end	3	1	0
Venous allograft	2	0	7

Prognostic outcomes of patients with portal vein system invasion

The final follow-up date is April 2020, one patient was dead during the perioperative period in the 17 distal cholangiocarcinoma patients with portal vein system invasion. Finally, 16 patients were studied of long-term survival. The 1-year, 2-year, 3-year tumour-free survival rates for patients without and with portal vein system invasion were 73.3%, 53.2%, 40.5% and 31.3%, -, - (p = 0.000, Fig. 2A). And the 1-year, 2-year,

3-year overall survival rates were 79.7%, 58.9%, 42.4% and 48.6%, 10.8%, - ($p = 0.000$, Fig. 2B). The median tumour-free, overall survival time for patients without and with portal vein system invasion were 42.0, 49.1 and 10.2, 14.2 months, respectively.

Discussion

At present, the optimum treatment of distal cholangiocarcinoma is still based on surgery, and pancreatoduodenectomy is the standard operation [10–11]. Andrianello et al. [12] reviewed the data of 1490 cases of distal cholangiocarcinoma after pancreatoduodenectomy in the United States. The overall median survival time is 31 months, and the 1-year and 3-year survival rates are 89% and 40%, respectively. Our research showed the 1-year and 3-year survival rates were 75.2% and 37.1%.

Because of the lack of effective adjuvant therapy, it is very important to determine the risk factors of survival before operation for the long-term prognosis of patients. Our study showed tumour differentiation degree, portal vein system invasion and lymph node metastasis as independent risk factors for long-term survival. It's known to all that tumour differentiation degree and lymph node metastasis are the important risk factors for the long-term survival [13–17]. But previous studies have not paid enough attention because the portal vein system invasion is not common in distal cholangiocarcinoma. So the portal vein system invasion is not included as the standard of T stage in the 8th AJCC TNM classification system. The portal vein system invasion rate was reported to range from 6.2–9.4% in patients with distal cholangiocarcinoma [8–9, 18]. Maeta et al. [8] reviewed 453 patients with distal cholangiocarcinoma who underwent pancreatoduodenectomy in 31 medical center, the portal vein system invasion rate was 6.8% (31/453) among them. The portal vein system invasion rate was 13.8% in our study, and it is similar to the previous reports. We thought the reason for the low portal vein system invasion rate is that the distal bile duct is surrounded by the pancreas anatomically.

Therefore, only a few studies have reported the relationship between the portal vein system invasion and the long-term survival. Miura et al. [9] reviewed 129 patients with distal cholangiocarcinoma who underwent pancreatoduodenectomy. Eight patients were diagnosed with the portal vein system invasion, and the 3-year survival rate was 17% which was lower than the patients without the portal vein system invasion (50%, $P < 0.01$). And multifactor Cox regression showed the portal vein system invasion was the only independent risk factor for long-term prognosis. Bahra et al. [18] reported the median survival time was 11.2 months in the 9 patients of distal cholangiocarcinoma with the portal vein system invasion. Our study also showed the poor survival of the portal vein system invasion patients with the median survival time was 14.2 months. And we also found the portal vein system invasion patients had larger tumor diameter and more lymph node metastasis rate than the patients without the portal vein system invasion. So we thought the reason of portal vein system invasion is related to the aggressive and behaviour of the tumor itself.

Although the long-term survival of distal cholangiocarcinoma patients with portal vein system invasion is poor, surgery may still be the only effective method because the lack of evidence-based adjuvant

treatment options [19]. The key of pancreatoduodenectomy combined with portal vein system resection is how to reconstruct the portal vein system safely [20]. Our experience is the reasonable reconstruction method should be selected according to the range, length and anastomotic tension of the resected vessels. Primary closure is suitable for wedge resection. End-to-end anastomosis is a good choice for segmental resection, but it's not suitable for a wide range segmental resection with high anastomotic tension. So we used the cold storage venous allograft to reconstruct the portal vein system for the patients with a wide range vascular segmental resection. And it's still another problem to the patients with junction of PV and SMV invasion. We used the cold storage venous allograft with shape of "Y" to reconstruct the portal vein system, in order to recover the blood flow of spleen vein. Our study showed pancreatoduodenectomy combined with portal vein system resection and reconstruction had longer operation time and more blood transfusion rate than the control group ($P < 0.05$). However, it did not increase the incidence of perioperative complication rate and mortality. And we also found no complication relate to the venous allograft.

The limitation of our study is a retrospective analysis. And we don't have enough evidence that surgery is the best treatment for the distal cholangiocarcinoma patients with portal vein system invasion because there are too few chemotherapy patients. Furthermore, we also don't have a control group of non-surgical patients with portal vein system invasion. Nevertheless, our study is the largest single center sample of distal cholangiocarcinoma patients who underwent pancreatoduodenectomy combined with portal vein system resection and reconstruction.

Conclusions

In conclusion, the portal vein system invasion is an important independent risk factors for long-term survival to the patients with distal cholangiocarcinoma, and the long-term survival is poor. There is no high-level evidence-based medical basis for the best treatment because there are few clinical reports of distal cholangiocarcinoma patients with portal system invasion [21]. And it is also not clear whether it can improve the long-term survival by adjuvant therapy. In the present study, surgery maybe still the only effective method for these patients [22].

Declarations

Ethics approval and consent to participate:

Our research was approved by the Ethics Committee of Beijing Chaoyang Hospital with the approval number of 2020-D-141.

Consent for publication:

Written informed consent for publication was obtained from all participants.

Availability of data and materials:

We do not wish to share our data because it is personal. We can provide it if the editor needs it, but we refuse to share the data publicly.

Competing interests:

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Authors' contributions:

HQ proposed the study. LSC performed the research and wrote the first draft. All authors contributed to the design and interpretation of the study and to further drafts. HQ is the guarantor.

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Figures

Figure 1

The tumour-free (A) and overall (B) survival curves for all patients.

Figure 2

The location of portal vein system invasion by distal cholangiocarcinoma: A(portal vein), B(junction of portal vein and superior mesenteric vein) and C(superior mesenteric vein). T: tumor; PV: portal vein; SMV: superior mesenteric vein; SV: splenic vein.

Figure 3

The tumour-free (A) and overall (B) survival curves for patients with or without portal vein system invasion.

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