Original Article

Impact of prior cholecystectomy on perioperative outcomes after resection for pancreatic cancer: a single-center, retrospective cohort study in a Chinese population

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Background: Cholecystectomy is carried out as one of the most extensive abdominal surgery. Patients with a long-term history of cholecystectomy may have an increased risk of pancreatic cancer. However, it's uncertain whether prior cholecystectomy is associated with the outcome of patients with pancreatic cancer. This study was to demonstrate that prior cholecystectomy may lead to adverse perioperative outcomes in patients with pancreatic adenocarcinoma.

Methods: Retrospective study comprising 755 consecutive patients with pathological diagnosis of pancreatic adenocarcinoma in Pancreas Center of the First Affiliated Hospital of Nanjing Medical University (January 2010 to December 2015) was conducted. Demographic details, surgery, tumor stage, pathology and complications were assessed. Patients were divided into NPC (no prior cholecystectomy) group and PC (prior cholecystectomy) group. PC group consist of three subgroups: RC (recent cholecystectomy), LTC (long term cholecystectomy), MTC (medium term cholecystectomy) group.

Results: A total of 9.3% (70/755) of the patients underwent prior cholecystectomy, which was significantly more frequent than other operations. The rate is also abnormally higher than Chinese population (1.2%, 31/2,579). Five hundred and fifty-three patients with radical resection were selected. Compared to NPC group, PC group has more progressive tumor with relatively higher level of serum CA19-9 and possibly higher rate of lymph node metastasis. Further analysis showed that RC group had remarkably longer surgery time and more blood loss than NPC group. There was no significant difference of operative time and blood loss between LTC/MTC group and NPC group. Postoperatively, there was no statistical difference between LTC/MTC group and NPC group in complications as POPF (postoperative pancreatic fistula), DGE (delayed gastric emptying), hemorrhage and infection. There was also no notably difference in length of hospital stay these two groups.

Conclusions: There is an abnormally high proportion of patients with cholecystectomy history in Chinese patients with pancreatic cancer. Patients with recent cholecystectomy history may have adverse perioperative outcome.

Keywords: Cholecystectomy; pancreatic cancer; pancreatic fistula; pancreaticoduodenectomy

Received: 15 February 2018; Accepted: 13 March 2019; Published: 23 April 2019.
doi: 10.21037/apc.2019.03.01
View this article at: http://dx.doi.org/10.21037/apc.2019.03.01

Introduction

Pancreatic cancer is the seventh leading cause of cancer death in China with an overall 5-year survival rate as low as 7%. The poor prognosis is related to several factors, the most important of which may be the late stage when diagnosed (1). The etiology of pancreatic cancer has not been fully explored. Well-established risk factors for pancreatic cancer include cigarette smoking (2), chronic pancreatitis, diabetes (3), high body mass index (BMI) and centralized fat distribution (4). Moreover, physical inactivity, substance use, and even occupational exposure to certain pesticides are reported to be potential risk factors (5). Although some of the risk factors have been discovered as mentioned above, the etiology of pancreatic cancer has not been fully explored.

Cholecystectomy was reported to be related to increased risk of digestive tract cancer and liver cancer (6,7). There are a few studies that explored the relationship between prior cholecystectomy and pancreatic cancer with contradictory results, Schernhammer *et al.* (8) reported that subjects with gallstone diseases or cholecystectomy were more likely to have pancreatic cancer than those without. Interestingly, Talamini *et al.* reported different conclusion (9). A meta-analysis indicated that cholecystectomy is an independent risk factor for pancreatic carcinogenesis recently (10). However, there were significant between-study heterogeneity and modest publication bias in this current meta-analysis. Besides, the data is missing in Chinese mainland population. Therefore, more studies are needed for further elucidation.

Moreover, in a lot of cases, patients with pancreatic cancer who present with biliary symptoms may also undergo improper cholecystectomy and thus delay cancer diagnosis (11). However, it's uncertain whether prior cholecystectomy is associated with the outcome of patients with pancreatic cancer. The purpose of this study was to demonstrate that prior cholecystectomy may lead to adverse short outcome in patients with pancreatic adenocarcinoma.

Methods

Patients

A single-center study was conducted in order to determine the number of patients who had been diagnosed with pancreatic cancer from January 2010 to December 2015 as shown in *Figure 1*. The study protocol was approved by the review board of The First Affiliated Hospital of Nanjing Medical University. The pathological reports were re-evaluated to rule out patients with non-adenocarcinoma. As a result, 755 patients with pancreatic ductal adenocarcinoma (PDAC) were identified.

Data extraction

Data collected include demographics (age, sex), detailed history (prior surgery, time from cholecystectomy to diagnosis), comorbidities (hypertension, diabetes), intraoperative factors (operation time, estimated blood loss), follow-up vital status, which were acquired from the patients' clinical notes, operative records, anesthetic charts, and radiologic and pathological reports. Patients with history of cholecystectomy were divided into NPC (no prior cholecystectomy) group and PC (prior cholecystectomy) group. PC group consists of three subgroups: RC (recent cholecystectomy: within 24 months prior to the diagnosis of pancreatic cancer), LTC (long term cholecystectomy: longer than 10 years prior to the diagnosis of pancreatic cancer), MTC (medium term cholecystectomy: longer than 24 months and within 10 years to the diagnosis of pancreatic cancer).

Definitions

All the patients enrolled were initially arranged for surgery. Pancreaticoduodenectomy or distal pancreatectomy with or without vascular reconstruction were performed on resectable or borderline resectable patients. POPF was defined and graded according to criteria proposed by the International Study Group on Pancreatic Fistula (ISGPF) as amylase-rich fluid (more than three-fold greater than the upper limit of serum amylase level) of any measurable volume on or after postoperative day. Delayed gastric emptying (DGE) and postoperative hemorrhage (PPH) were defined and graded using the schema proposed by the International Study Group of Pancreatic Surgery (ISGPS). PPH represented all of the postoperative episodes of hemorrhage.

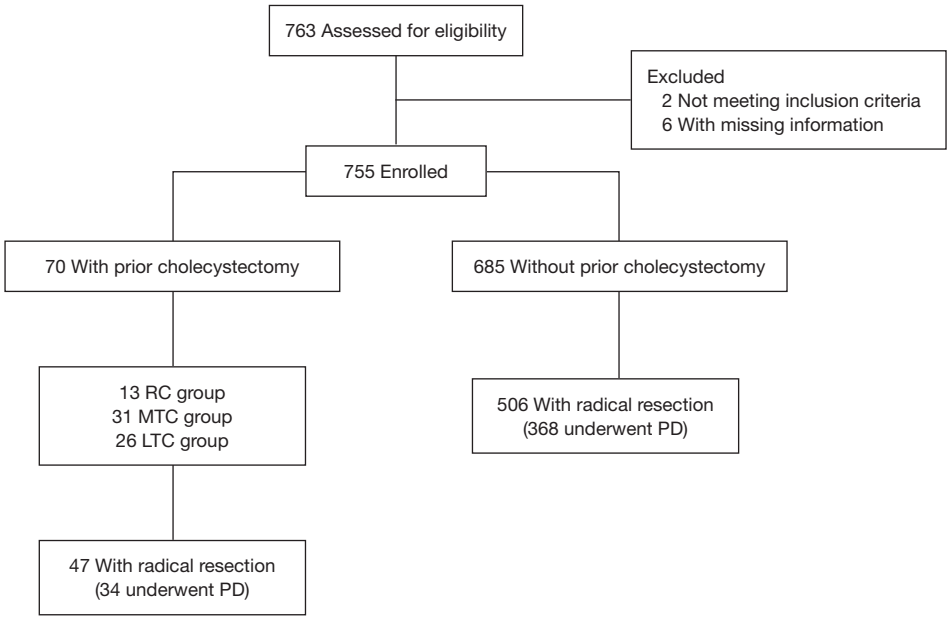

Figure 1 Flow chart of patient enrollment and analysis. RC, recent cholecystectomy; MTC, medium term cholecystectomy; LTC, long term cholecystectomy; PD, pancreaticoduodenectomy.

Statistical analysis

Statistical analyses were performed using SPSS® version 21.0 (IBM, Armonk, New York, USA). Fischer exact, χ^2 and *t*-tests were used to test the significance of differences between patients with cancer undergoing a previous cholecystectomy with those who did not where appropriate. Logistic regression analysis was performed to adjust the P value of risk factors. P<0.05 was considered a significant difference.

Table 1 Surgical history of patients with PDAC

History of surgery	Male (n=462)	Female (n=293)
Cholecystectomy	29	41
Appendectomy	25	15
Thyroidectomy	6	9
Gynecological operation	–	42
Mastectomy	–	7

PDAC, pancreatic ductal adenocarcinoma.

Results

Clinical characteristics

Among 755 patients with pathology diagnosis of PDAC, 9.3% (70/755) of the patients underwent prior cholecystectomy (15 days to 30 years), which is more frequent than other prior operations include gynecological operation (42/755), appendectomy (40/755), thyroidectomy (15/755) and mastectomy (7/755) as shown in (*Table 1*). The rate of prior cholecystectomy in PDAC patients is also significantly higher than that of Chinese population (31/2,579) (*Table 2*) (12). The baseline clinicopathological characteristics for each group were compared as shown in *Tables 3*,*4*. There were 462 men and 293 women were pathologically diagnosed with PDAC. Of the 755 patients, 70 (9.3%) underwent prior cholecystectomy (PC group) and 685 (90.7%) have no history of cholecystectomy (NPC group). There was no significant difference in age, history of alcohol use and smoking, diabetes, AJCC stage and resection rate between PC group and NPC group. There were statistical differences in gender and hypertension between the two groups. Notably, the CA19-9 level was significantly higher in PC group (*Table 3*). Univariable and multivariable logistic regression analysis for associations between preoperative risk factors and CA19-9 higher than 100 showed that prior cholecystectomy was risk factor for a CA19-9 level higher than 100 (*Table 4*).

Operative characteristics and postoperative data

For patients who underwent radical resection, it was

Table 2 Prior cholecystectomy compared with Chinese population

History of cholecystectomy	PDAC patients	Chinese population	P
With prior cholecystectomy	70 (9.3%)	31 (1.2%)	<0.001
No prior cholecystectomy	685 (90.7%)	2,548 (98.8%) (12)	

PDAC, pancreatic ductal adenocarcinoma.

Table 3 Basic demographics and perioperative characteristics

Characteristics	PC group (n=70)	NPC group (n=685)	P
Sex (M/F)	29/41	433/252	0.000
Age (y)	65.6±8.8	61.7±10.1	
≥70	20	157	0.301
<70	50	528	
Time prior to cholecystectomy			–
≥10 years	26	–	
≥2 years, <10 years	31	–	
<2 years	13	–	
History			
Smoking	18	171	0.885
Alcohol	11	114	1.000
Comorbidities			
Diabetes	18	121	0.107
Hypertension	20	114	0.020
AJCC stage			
1/2	41	423	0.608
3/4	29	262	
CA19-9			
≥100	50	397	0.030
<100			
Radical resection	47	506	1.000

Table 4 Prior cholecystectomy and higher CA19-9 at surgery

Characteristics	Univariable		Multivariable	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Sex: male *vs.* female	0.86 (0.64–1.16)	0.320		
Age: ≥70 *vs.* <70	1.51 (1.06–2.14)	0.022	1.47 (1.04–2.10)	0.031
Prior cholecystectomy: yes *vs.* no	1.80 (1.05–3.10)	0.033	1.74 (1.01–3.00)	0.045
AJCC stage: 3/4 *vs.* 1/2	0.93 (0.69–1.25)	0.619		

PDAC patients (n=755). PDAC, pancreatic ductal adenocarcinoma.

Table 5 Operative characteristics and postoperative data of LTC/MTC group

Variables	Patients with LTC/MTC	Patients with NPC	P
Operative time (min)	234.7±108.5	235.7±77.7	0.714
Blood loss (mL)	327.6±455.0	310.5±276.2	0.331
Pancreatic fistula			
Absent	30	433	0.268
Present	8	73	
Delayed gastric emptying			
Absent	33	429	0.732
Present	5	77	
Hemorrhage			
Absent	35	475	0.931
Present	3	31	
Infection			
Absent	32	463	0.222
Present	6	43	
Hospital stay (day)	19.05±6.58	20.93±9.94	0.368

LTC, long term cholecystectomy; MTC, medium term cholecystectomy; NPC, no prior cholecystectomy.

suggested that there was no significant difference of operative time and blood loss between LTC/MTC group and NPC group (*Table 5*). Postoperatively, there was no statistical difference between LTC/MTC group and NPC group in complications as POPF, DGE, hemorrhage and infection. There was also no notably difference in length of hospital stay of these two groups.

However, RC group had remarkably longer surgery time and more blood loss than NPC group (*Table 6*) while other parameters as POPF, DGE, hemorrhage and infection and LOS showed no difference. Subgroup analysis for patients who underwent PD (*Table 7*) showed that the rate of postoperative infection is significantly higher in LTC/MTC patients. However, other characteristics still indicate no remarkable difference.

Comparison of pathological characteristics

Five hundred and fifty-three of the 755 patients who underwent radical resection were selected, of whom the pathological data was complete. There is no statistical difference of tumor differentiation, tumor size, nerve invasion and artery invasion between patients with LTC/MTC group versus NPC (*Table 8*). Patients with prior cholecystectomy had a trend for higher rate of lymph node metastasis than those without. However, no statistical significance was observed. Further subgroup analysis for LTC and MTC group showed no significant difference either (*Tables 9,10*).

Discussion

This study reports a surprisingly high incidence of cholecystectomies prior to diagnosis of pancreatic cancer in Chinese mainland population for the first time. Cholecystectomy is extensively performed in Chinese patients because of high incidence of gallstone and the great safety and feasibility of laparoscopic cholecystectomy. For patients with pancreatic cancer, the rate is even higher. Part of the reason is that symptoms such as upper abdominal pain or even jaundice can concur with frequent diseases such as cholecystolithiasis. Moreover, laparoscopic cholecystectomy is the treatment of choice for the vast majority of patients with symptomatic cholecystolithiasis. However, a major drawback remains the lack of visceral palpation of the abdominal organs. Indeed, several case reports have indicated that this disadvantage of laparoscopic cholecystectomy can lead to missing diagnosis and a fatal delay in the diagnosis

Table 6 Operative characteristics and postoperative data of RC group

Variables	Patients with RC	Patients with NPC	P
Operative time (min)	262.6±83.3	235.7±77.7	0.164
Blood loss (mL)	450.00±180.28	310.5±276.2	0.010
Pancreatic fistula			
Absent	7	433	0.857
Present	2	73	
Delayed gastric emptying			
Absent	7	429	0.911
Present	2	77	
Hemorrhage			
Absent	8	475	1.000
Present	1	31	
Infection			
Absent	8	463	0.395
Present	1	43	
Hospital stay (day)	23.40±6.67	20.93±9.94	0.110

RC, recent cholecystectomy; NPC, no prior cholecystectomy.

Table 7 Subgroup analysis for patients undergone PD

Variables	PD patients with LTC/MTC	PD patients with NPC	P
Operative time (min)	257.9±118.5	250.0±79.1	0.622
Blood loss (mL)	398.2±524.5	332.9±297.9	0.517
Pancreatic fistula			
Absent	19	313	0.056
Present	8	55	
Delayed gastric emptying			
Absent	22	300	1.000
Present	5	68	
Hemorrhage			
Absent	25	342	1.000
Present	2	26	
Infection			
Absent	21	333	0.048
Present	6	35	
Hospital stay (day)	19.48±7.36	21.42±10.38	0.385

PD, pancreaticoduodenectomy; NPC, no prior cholecystectomy; LTC, long term cholecystectomy; MTC, medium term cholecystectomy.

Table 8 Comparison of pathological characteristics between LTC/MTC and PC group

Variables	Patients with LTC/MTC		Patients with NPC		P
	n	%	n	%	
Histological grade					
Well/moderately	17	44.7	188	37.2	0.352
Poorly	21	55.3	318	62.8	
Tumor size					
≤3 cm	19	50	242	47.8	0.796
>3 cm	19	50	264	52.2	
Nerve invasion					
Absent	12	31.6	127	25.1	0.377
Present	26	68.4	379	74.9	
Lymph node metastasis					
Absent	14	36.8	268	53.0	0.055
Present	24	63.2	238	47.0	
Arterial invasion					
Absent	33	86.8	435	86.0	0.881
Present	5	13.2	71	14.0	

LTC, long term cholecystectomy; MTC, medium term cholecystectomy; NPC, no prior cholecystectomy.

Table 9 Comparison of pathological characteristics between LTC and PC group

Variables	Patients with LTC		Patients with NPC		P
	n	%	n	%	
Histological grade					
Well/moderately	11	47.8	188	37.2	0.301
Poorly	12	52.2	318	62.8	
Tumor size					
≤3 cm	11	47.8	242	47.8	0.970
>3 cm	12	52.2	264	52.2	
Nerve invasion					
Absent	9	39.1	127	25.1	0.139
Present	14	60.9	379	74.9	
Lymph node metastasis					
Absent	9	39.1	268	53.0	0.188
Present	14	60.9	238	47.0	
Arterial invasion					
Absent	21	91.3	435	86.0	0.642
Present	2	8.7	71	14.0	

LTC, long term cholecystectomy; NPC, no prior cholecystectomy.

Table 10 Comparison of pathological characteristics between MTC and PC group

Variables	Patients with MTC		Patients with NPC		P
	n	%	n	%	
Histological grade					
Well/moderately	8	53.3	188	37.2	0.453
Poorly	7	46.7	318	62.8	
Tumor size					
≤3 cm	8	53.3	242	47.8	0.696
>3 cm	7	46.7	264	52.2	
Nerve invasion					
Absent	3	20.0	127	25.1	0.870
Present	12	80.0	379	74.9	
Lymph node metastasis					
Absent	5	33.3	268	53.0	0.130
Present	10	66.7	238	47.0	
Arterial invasion					
Absent	12	80.0	435	86.0	0.817
Present	3	20.0	71	14.0	

MTC, medium term cholecystectomy; NPC, no prior cholecystectomy.

of abdominal malignancies (11,13,14). In addition to missing diagnosis, presenting signs and symptoms including jaundice, abdominal pain, nausea, and dark urine could be simply caused by PDAC instead of cholecystolithiasis where misdiagnosis could be involved. A recent study showed that initial misdiagnosis of patients with proximal PDAC is associated with delay in diagnosis and higher risk of locally advanced or advanced disease at time of PDAC diagnosis (15). Also, longer time from symptom onset to diagnosis has been shown to be an independent risk factor for survival in a previous study (16). Therefore, the missing diagnosis and (or) misdiagnosis may happen in PDAC patients with recent cholecystectomy. But whether long term history of cholecystectomy can affect the progression and prognosis in PDAC patients is still uncertain although some studies have given vague answers (17,18).

In this study, we found that patients with prior cholecystectomy may have more chance for the invasion of lymph node, which is strongly associated with adverse outcome. Patients with prior cholecystectomy have higher level of serum CA19-9, which is also an important prognostic factor for the survival of PDAC patients. Therefore, these two points give us confidence that the history of cholecystectomy may be an adverse prognostic factor for PDAC (19,20).

The mechanism behind this fact is still unclear. Animal models suggest that cholecystectomy can promote the proliferation of pancreatic acinar cells by increased the level of cholecystokinin (CCK). On the other hand, it has been suggested that metabolism of bile salts is enhanced after cholecystectomy. Secondary bile acids or metabolites may have carcinogenic effects on the colon, liver, and pancreas (21).

In addition, cholecystectomy may suppress the normal inhibitory effect of CCK on the sphincter of Oddi (22). The presence of gallstones, on the other hand, appears to be associated with chronic pancreatitis (23), which increase the risk of pancreatic cancer. However, the strength of the association remains uncertain because of the retrospective design of most analyses.

The difference of the operative characteristics and postoperative data among the subgroups is not very

notable. However, it indicated that patients with recent cholecystectomy seem to have more blood loss in operation, which is not hard to conceive because a recent operation obviously makes the resection even more difficult. The lack of visceral palpation during laparoscopic cholecystectomy presents an imminent problem for laparoscopic surgery in general and might be one reason for the undetected pancreatic cancers in our study. In addition, there is also a weak difference in the postoperative infection rate between LTC group and NPC group who had PD for treatment. However, we cannot rule out the possibility of the bias of this study for this discovery.

A limitation of this study was that we only analyzed patients from one single surgical center. Perhaps, some patients' status post recent cholecystectomy were not amenable to curative resection secondary to local invasion or metastatic disease and thus were excluded from our analysis. Also, the survival information is absent in this study due to the unfinished follow up, which should have improved the quality for this research.

Conclusions

This report demonstrates that there is an abnormally high proportion of patients with cholecystectomy history in patients with pancreatic cancer in Chinese population, which needs validation in further epidemiological studies. Prior cholecystectomy may result in substantially higher level of serum CA19-9 when diagnosed and higher rate of lymph node invasion which may compromise the prognosis and survival of PDAC patients. Also, PDAC patients with recent cholecystectomy history may have adverse outcome because of the delay of diagnosis and the higher rate of complications caused by higher degree of difficulty for surgery, which calls for more caution for elderly patients with upper abdominal pain or jaundice.

Acknowledgments

Funding: This study was funded by the National Natural Science Foundation of China (No. 81672449), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD, JX10231801), Jiangsu Key Medical Discipline (General Surgery, ZDXKA2016005), the Natural Science Foundation of Jiangsu Province (BK20161590), the Innovation Capability Development Project of Jiangsu Province (BM2015004), and the Talents Planning of Six Summit Fields of Jiangsu Province (WSW-019).

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Yingbin Liu and Wei Gongi) for the series "The 8th Annual International Surgery Forum" published in *Annals of Pancreatic Cancer*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ apc.2019.03.01). The series "The 8th Annual International Surgery Forum" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the review board of The First Affiliated Hospital of Nanjing Medical University (No. 2016-SR-094). Informed consent was waived due to the retrospective nature of the study.

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doi: 10.21037/apc.2019.03.01
Cite this article as: Yin L, Liu X, Liu T, Fu Y, Peng Y, Ding D, Lu Z, Gao W, Wu J, Jiang K, Wei J, Miao Y. Impact of prior cholecystectomy on perioperative outcomes after resection for pancreatic cancer: a single-center, retrospective cohort study in a Chinese population. Ann Pancreat Cancer 2019;2:4.

