



The Effect of Previous Cholecystectomy on Stage of Pancreatic Head Adenocarcinoma

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AS and ASK designed the study and performed the statistical analysis. Author MOK wrote the protocol, and wrote the first draft of the manuscript. Authors MOK and SGT managed the analyses of the study. Authors MOK and AS managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/41177

Editor(s):

(1) Syed Faisal Zaidi, Department of Basic Medical Sciences, College of Medicine, King Saud Bin Abdulaziz University-HS, National Guard Health Affairs, King Abdulaziz Medical City, Kingdom of Saudi Arabia.

Reviewers:

(1) Rahul Gupta, Synergy Institute of Medical Sciences, India.

(2) Pedro Uson, Hospital Israelita Albert Einstein, Brazil.

Complete Peer review History: <http://www.sciedomains.org/review-history/24469>

Received 18th February 2018

Accepted 24th April 2018

Published 5th May 2018

Original Research Article

ABSTRACT

Aim: A relationship between the history of cholecystectomy and risk of pancreas cancer has been previously shown. However, the effect of cholecystectomy on pathological features of pancreatic cancer has not been investigated yet. The aim of the study is to investigate the possible effect of cholecystectomy on tumor stage in patients who underwent Whipple procedure for pancreatic head adenocarcinoma.

Study Design: This is a retrospective clinical study.

Methodology: A total of 116 patients were included in the study. All patients were classified as patients who had a history of cholecystectomy (Group 1) and those without a history of cholecystectomy (Group 2). The two groups were compared with each other in terms of clinical and pathological characteristics.

Results: There were 48 (41.4%) females and 68 (58.6%) males, with an overall mean age of 60.7 years. Twenty-two (19%) patients had a history of cholecystectomy. The patients in Group 1 had a

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higher T-stage than patients in Group 2 ($p < 0.001$). The stage of tumor was also significantly different between the groups ($p < 0.001$).

Conclusion: This is the first study indicating the possible effect of previous cholecystectomy on tumor stage in pancreatic head cancer. Clinicians should be more careful in the evaluation of such patients to avoid a delay in the diagnosis.

Keywords: Cholecystectomy; pancreatic head adenocarcinoma; tumor stage; whipple procedure.

1. INTRODUCTION

Pancreas cancer is among the most frequent causes of cancer-related death worldwide [1]. Approximately 95% of pancreatic cancers are ductal adenocarcinomas arising from the exocrine part of the organ [2]. Head of the pancreas is the most common localisation of these cancers, with a five-year survival rate of 20% even in localised disease [3]. The reason for this poor prognosis is that these cancers are usually diagnosed at advanced stages due to the lack of specific symptoms and signs. Therefore, only one-fifth of the patients can be suitable for surgery at the time of diagnosis [4]. Although exact etiology is unclear, smoking, obesity, diabetes, chronic pancreatitis, and family history are the well-known risk factors [2,5]. Apart from those, the relationship between cholecystectomy and pancreatic carcinogenesis has become an interesting research topic for the past few decades. Despite several types of research with opposite results, a link between cholecystectomy and the risk of pancreas cancer has been shown in most of the studies [2,6-8]. However, to our knowledge, the effect of cholecystectomy on pathological features of pancreatic cancer has not been investigated to date.

In this study, we aimed to investigate the possible effect of cholecystectomy on tumor stage in patients who underwent Whipple procedure for pancreatic head adenocarcinoma.

2. MATERIALS AND METHODS

2.1 Patients and Study Design

One hundred and sixteen patients (aged ≥ 18 years) who underwent Whipple procedure for pancreatic head adenocarcinoma in a tertiary multidisciplinary hospital between 2010 and 2016 were included in the study. Informed consents were waived due to the retrospective nature of the study. Patients' age and gender, history of cholecystectomy (at least two years prior to diagnosis of pancreatic cancer), type of surgery, and pathological characteristics of the

tumor were recorded. All tumors were staged according to the current American Joint Committee on Cancer (AJCC) staging system [9]. All patients were classified into two groups: patients who underwent cholecystectomy (Group 1) and those without a history of cholecystectomy (Group 2). The patients who underwent cholecystectomy within two years prior to the diagnosis of pancreas cancer and who received neoadjuvant therapy were excluded from the study. The indication of cholecystectomy was gallstone in all patients.

2.2 Statistical Analysis

The Statistical package for social science (SPSS 21.0 software, IL-Chicago- USA) standard version was used for data analyses. The results of descriptive analysis were presented as mean \pm standard deviation (SD)/percentages for continuous variables and number/percentage for categorical variables. Mann Whitney U test, Fisher's exact test and Chi-square test were used to investigate the differences between the groups. Significance level was accepted as $p < 0.05$.

3. RESULTS AND DISCUSSION

3.1 Results

A total of 116 patients with a mean age of 60.7 years were included in the study. Among those, 22 (19%) had a history of cholecystectomy. All patients underwent Whipple procedure (pancreaticoduodenectomy) for a diagnosis of pancreatic head adenocarcinoma. The baseline patient characteristics and pathological features are presented in Table 1.

Patients who had a history of cholecystectomy were compared with those who had not a history of cholecystectomy, in terms of clinical and pathological characteristics (Table 2). The two patient groups were similar in age ($p = 0.166$) and gender ($p = 0.156$). Almost all patients in Group 1 had T3-4 tumors on final pathological examination whereas these tumors were found

Table 1. The baseline patient characteristics and pathological features (n=116)

Characteristics	n (%)
Age (year)	60.7±11.5 (36-84)
Gender (female/male)	48 (41.4%)/68 (58.6%)
Diagnosis	pancreatic head adenocarcinoma (100%)
Type of surgery	whipple procedure (100%)
History of cholecystectomy	22 (19%)
Stage of tumor	
stage i	36 (31%)
stage ii	46 (39.7%)
stage iii	34 (29.3%)

Age was presented as mean±SD; other variables were presented as n (%)

Table 2. The comparison of clinicopathological characteristics between patients with a history of cholecystectomy and patients without a history of cholecystectomy

Characteristics	Group 1 (n=22)	Group 2 (n=94)	p
Age (year)	62.2±12.8 (38-84)	60.4±11.2 (36-84)	0.166
Gender			0.156
female	6 (27.3%)	42 (44.7%)	
male	16 (72.7%)	52 (55.3%)	
T (tumor)			<0.001
t1	0 (0%)	16 (17%)	
t2	2 (9.1%)	34 (36.2%)	
t3	6 (27.3%)	24 (25.5%)	
t4	14 (63.6%)	20 (21.3%)	
N (node)			0.075
n0	14 (63.6%)	78 (74.6%)	
n1	8 (36.4%)	16 (19.4%)	
Stage			<0.001
stage 1	0 (0%)	36 (29.2%)	
stage 2	8 (36.4%)	38 (37.3%)	
stage 3	14 (63.6%)	20 (27.6%)	

Age was presented as mean±sd; other variables were presented as n (%)

only in 20.1% of the patients in Group 2. Statistically, patients with a history of cholecystectomy had a higher T-stage in comparison to patients without a history of cholecystectomy ($p<0.001$). N-stage was not found significantly different between the two groups ($p=0.075$). The stage of tumor was significantly different in patients of Group 1 compared with those in Group 2 ($p<0.001$).

3.2 Discussion

Cholecystectomy is one of the most widely performed operations worldwide. Its incidence increases with aging as observed in pancreas cancer [10]. At this point, the question is whether the high frequency of cholecystectomy in patients with pancreatic cancer is a normal finding because of high global incidence, or cholecystectomy is really a risk factor affecting pancreatic carcinogenesis. In most of the studies

on this issue, a significant relationship was found between history of cholecystectomy and pancreatic cancer [7,8,11]. In a meta-analysis by Lin et al. [12], a 23% excess risk of pancreatic cancer was reported in patients with a history of cholecystectomy. In our study, such a statistical evaluation could not be performed due to the absence of a control group. Additionally, the relationship between cholecystectomy and pancreatic cancer was not the primary goal of this study. However, the rate of cholecystectomy in our study population was consistent with those reported in other similar clinical studies [7]. Cholecystectomy was also found to be associated with increased risk of other gastrointestinal cancers such as gastric cancer, colorectal cancer, and liver cancer [8,12,13]. However, there are also several studies that revealed no association between cholecystectomy and pancreatic cancer or other gastrointestinal cancers [6,14,15]. Various

characteristics such as the ethnicity of the study population or the study design may contribute to the discrepant findings. In our opinion, one of the reasons for these conflicting findings is the different time intervals between cholecystectomy and diagnosis of pancreas cancer. As carcinogenesis is a process involving numerous complex events, it is expected that a certain period is necessary for a carcinogenic effect after cholecystectomy. However, the time interval between cholecystectomy and pancreatic cancer diagnosis was not considered in most of those studies [14-16]. Moreover, in a recent study, there was no time trend for the associations between gallstones or cholecystectomy and noncardia gastric cancers, rectal cancers, and pancreatic cancers [8]. In order to minimize the potential negative effect of this condition on the statistical outcomes, the patients who had undergone cholecystectomy over two years before cancer diagnosis were only included in our study.

The underlying mechanisms for the effect of cholecystectomy in pancreatic carcinogenesis are not well defined. Increased secondary bile acids or metabolites after cholecystectomy have been accused for carcinogenesis in various organs including liver, colon, and pancreas [17, 18]. In addition to its carcinogenic effect, bile can cause inflammation, a well-known mechanism of carcinogenesis, in epithelial surfaces outside of the gallbladder [8,19]. The other hypothesis is that the increased level of cholecystokinin after cholecystectomy stimulates cancer cell growth and initiates carcinogenesis in pancreas [20].

The clinical picture of pancreas cancer is often non-specific, and depends on the size and location of the tumor. Although abdominal pain, anorexia, weight loss, nausea, and weakness are the most common symptoms in all types of pancreatic cancer, a palpable but nontender gallbladder in a jaundiced patient, known as Courvoisier's sign, is up to 55 percent sensitive for malignant obstruction of the bile duct, primarily indicating pancreatic head adenocarcinoma [21]. Our hypothesis was also based on this characteristic feature of pancreatic head cancer.

This study has some limitations. First of all, it was conducted in a single center, which may limit the generalization of the results. A relatively small sample size is another limitation of this work, which make it difficult to interpret subgroup findings. Additionally, the study population only

consisted of patients who had undergone Whipple procedure for pancreatic head adenocarcinoma, therefore the patients who could not be operated due to metastatic disease or unresectable tumor were not included in the study. Finally, the present work only focused on the affect of cholecystectomy on tumor size and stage, thus different potential confounding factors such as smoking, alcohol use, diabetes, and obesity were not taken into account in the statistical evaluation.

4. CONCLUSION

In conclusion, this is the first study indicating the possible effect of the previous cholecystectomy on tumor stage in pancreatic head cancer. Clinicians should be more careful in the evaluation of such patients to avoid a delay in the diagnosis, which is highly associated with poor prognosis. Larger studies with different patient populations should confirm the results from the present study. Further studies may also be helpful to determine such association between cholecystectomy and pancreatic body/tail cancers.

CONSENT

Informed consents were waived due to the retrospective nature of the study.

ETHICAL APPROVAL

As per international standard or university standard written ethical permission has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:

The peer review history for this paper can be accessed here:
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