

Missed Pancreaticobiliary Malignancy: The Flaw of the Expedited Cholecystectomy

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Abstract

Background: Early cholecystectomy has been recommended for patients with acute cholecystitis and gallstone pancreatitis. However, patients with pancreaticobiliary malignancy may present acutely with similar symptoms. We hypothesize that the diagnoses of these malignancies may potentially be delayed as an unintended consequence of expedited cholecystectomies. This study reviews a cohort of patients who underwent pancreaticoduodenectomy (PD) to identify those who underwent a separate cholecystectomy before their PD. **Methods:** We retrospectively reviewed 162 PDs performed between 2012 and 2022. Data collected included: demographics, disease etiology and the presence of cholelithiasis. We identified patients who had a previous cholecystectomy and the time elapsed before PD as well as procedures done during the interval. We reported detailed case summaries on those patients who had a cholecystectomy within 1 year of PD. **Results:** In the entire cohort, mean age was 65 years, 54% were males, and 83% had a malignant reason for PD. Thirty-one patients had cholelithiasis with 23 (14%) patients having had previous cholecystectomy. Six patients had cholecystectomy within 1 year of PD. They had the following malignancies: ampullary—3, pancreas—1, cholangiocarcinoma—1 and neuroendocrine—1. Four of these patients had expedited cholecystectomy on their index hospital admission and were later found to have a periampullary malignancy with further work up. **Conclusions:** Pancreaticobiliary malignancies can be difficult to diagnose, and surgeons should not overlook these potential diagnoses when considering expedited cholecystectomy. Future studies in large cohorts are needed to identify high risk candidates who should undergo more detailed testing to exclude malignancy before proceeding with cholecystectomy.

Keywords

Cholecystectomy, Periampullary Malignancy, Pancreas Malignancy, Pancreaticoduodenectomy

1. Introduction

Twenty million people in the United States have gallstones [1]. About 20% of these patients have episodes of biliary colic, with only 1% to 4% having complications such as acute cholecystitis, gallstone pancreatitis, choledocholithiasis, or gallstone ileus [1]. Ultimately, this leads to 700,000 cholecystectomies performed annually in the US, at a cost of \$6.5 billion [2]. Previous studies including several large systematic reviews have demonstrated that early cholecystectomy for acute cholecystitis is safe and results in decreased hospital length of stay [3]-[5]. This initiated the impetus for early cholecystectomy.

In patients with gallstone pancreatitis, the 2015 PONCHO trial demonstrated that same-admission cholecystectomy for patients with biliary pancreatitis reduced rates of 30-day readmission and recurrent pancreatitis, with additional cost savings and no increase in complications [6] [7]. Further randomized controlled trials have confirmed these findings [8]. In 2019, the Gallstone PANC trial again demonstrated that early cholecystectomy within 24 hours of admission in patients with mild gallstone pancreatitis reduced the need for biliary endoscopy, time to surgery, and hospital length of stay [9]. They concluded that the overall complication risk was low and cost analysis demonstrated an 81% reduction in 90-day health care system costs [10].

Unfortunately, many of the inflammatory conditions related to gallstones are also risk factors for pancreaticobiliary malignancy [11]. Additional risk factors such as diabetes, smoking, obesity, and advanced age that predispose one to gallstones are also associated with malignancy, which complicates this diagnosis [12]. With the increasing demand for early cholecystectomy, we hypothesize that the possibility of pancreaticobiliary malignancy may be overlooked. This study reviews a cohort of patients who underwent pancreaticoduodenectomy (PD) for any reason and identifies those patients who underwent cholecystectomy at a separate setting before the PD. We then performed a detailed evaluation of those cases who had a cholecystectomy within one year of the PD to determine if the expedited cholecystectomy may have potentially delayed the diagnosis of a more complex process.

2. Methods

This is a retrospective study of patients who underwent PD by a single surgeon at the Queens Medical Center during the time period 2012 to 2022. This medical center is the largest in the State of Hawaii and the tertiary referral center for complex gastrointestinal and hepatobiliary disease.

This study was approved by the University of Hawaii Institutional Review Board and a waiver of informed consent was obtained. We collected demographic data including age, gender, ethnicity and anthropomorphic information of height, weight and calculated body mass index and comorbid conditions including the presence of diabetes mellitus, hypertension, cardiac disease, pulmonary disease, chronic liver disease or any other previous malignancy. No funding was obtained for this project.

In terms of the current problem of pancreaticobiliary issue that required PD, we noted the diagnosis, stage, tumor characteristics and American Joint Committee on Cancer stage if malignant. We collected information on pre-operative stent placement, laboratory studies and tumor markers Carcinoembryonic Antigen (CEA) and Cancer Antigen 19-9 (CA 19-9) when available. All pathology reports were reviewed to identify those patients who had cholelithiasis.

Our inclusion criteria involved all patients who underwent a PD from 2012-2022 performed by a single provider. Patient demographics, preoperative laboratory values, operative time and hospital length of stay were included in our analysis. We then identified all patients in the cohort who had a previous cholecystectomy before the date of the PD. We compared perioperative data between patients with a prior cholecystectomy to patients without a prior cholecystectomy using a t-test. The patients were then stratified by the timing of their previous cholecystectomy. Patients without a prior cholecystectomy were excluded in this part of the analysis. We reviewed previous pathology reports for the presence of cholelithiasis on these gallbladders. If reports were not available, we reviewed clinical information that noted the presence of cholelithiasis on imaging. We also noted the time (in days) between the prior cholecystectomy and the current PD. We evaluated those patients who had a cholecystectomy within 1 year of PD in greater detail by manual chart review. Specifically, we reviewed records for details that led up to the cholecystectomy including presenting symptoms, laboratory studies, imaging, endoscopy, and pathology on the removed gallbladder. Some of these cholecystectomies may have been performed at a community medical center and we used medical records that were provided to our center for referral for the PD. We then identified hospital readmissions, episodes of cholangitis and subsequent imaging and endoscopy that eventually lead to PD. One patient who had a prior cholecystectomy within one year was excluded in our review because his initial PD procedure was delayed due to severe pancreatitis.

3. Results

We identified 162 patients who underwent a PD during the time period January 2012 until December 2022. The mean age of the cohort was 65.0 ± 10.0 years with a slight male (54%) and Asian (61%) predominance. We found that 82% had a malignant process, mainly due to pancreas cancer (**Table 1**).

Table 1. Characteristics of entire cohort of patients who underwent pancreaticoduodenectomy.

Characteristics	Patients (n = 162)
Mean age (years)	65 $\pm$ 10 years
Males: Females	87 (54%): 75 (46%)
Race/Ethnicity	
Asian	99 (61%)

Continued

Caucasian	36 (22%)
Pacific Islander	23 (14%)
Other	4 (2%)
Diagnosis	
Pancreas Cancer	77 (44%)
Extrahepatic Cholangiocarcinoma	22 (14%)
Ampullary Cancer	18 (11%)
Pancreatic Cystic Neoplasm	18 (11%)
Other	27 (17%)
Number of Patients with Gallstones	31 (19%)
Number of Patients with Prior Cholecystectomy	23 (14%)
Mean time from Cholecystectomy to PD	12 ± 15 years

Nine patients (5.5%), had a history of pancreatitis before PD. Thirty-one patients (19%) had a history of gallstones with 23 (14%) of them having a cholecystectomy at a separate date before the PD. The mean time period from cholecystectomy to PD was 12.0 ± 15.0 years that ranged from 43 days to 40 years prior. We found that 6 patients had a cholecystectomy done over more than 12 years prior to PD, 5 patients had a cholecystectomy between 5 - 11 years prior to PD, 6 patients had a cholecystectomy between 1 - 4 years prior to PD, and 6 patients within 1 year of PD (**Figure 1**).

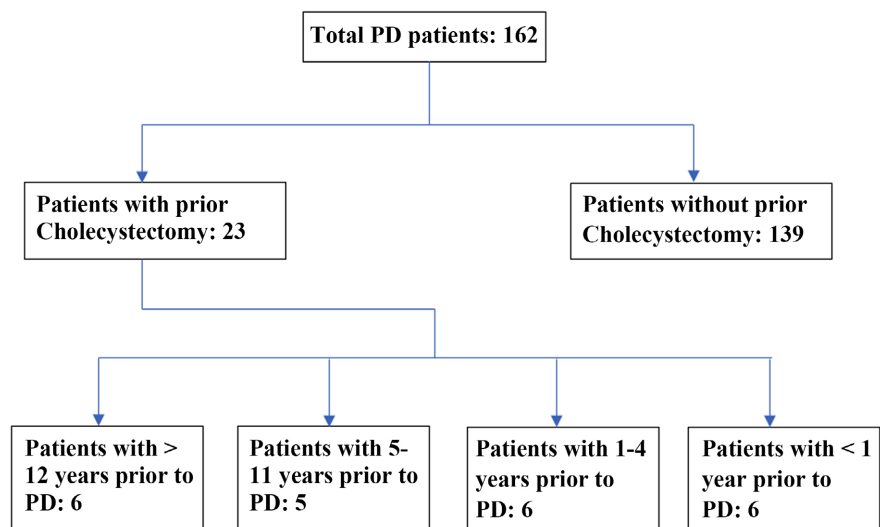


Figure 1. Distribution of patients who had prior cholecystectomy before pancreaticoduodenectomy by years between the procedures.

The following are case summaries of 5 cases who had a cholecystectomy within 1 year of PD. The pre-cholecystectomy image modalities are described in **Table 2**.

Table 2. Imaging modalities for five patients who had a cholecystectomy before PD stratified by Pre- and Post-Cholecystectomy.

Patient	Imaging Modalities				
	Ultrasound	CT	MRI	ERCP	EUS
1 (Pre-Cholecystectomy)	US #1			ERCP #1	
1 (Post-Cholecystectomy)	US #2		MRCP #1	ERCP #2 ERCP #3	
2 (Pre-Cholecystectomy)	US #1	CT #1	MRCP #1		
2 (Post-Cholecystectomy)	US #2	CT #2		ERCP #1 ERCP #2	
3 (Pre-Cholecystectomy)	US #1	CT #1	MRCP #1	ERCP #1	
3 (Post-Cholecystectomy)		CT #2	MRCP #2	ERCP #2 ERCP #3 ERCP #4	EUS #1 EUS #2
4 (Pre-Cholecystectomy)	US #1				
4 (Post-Cholecystectomy)		CT #1	MRCP #1	ERCP #1 ERCP #2 ERCP #3	
5 (Pre-Cholecystectomy)	US #1		MRCP #1 MRCP #2		
5 (Post-Cholecystectomy)	US #2	CT #1	MRCP #3 MRCP #4 MRCP #5 MRCP #6	ERCP #1 ERCP #2 ERCP #3 ERCP #4 ERCP #5 ERCP #6	EUS #1

The reasons for PD included three ampullary adenocarcinomas, one cholangiocarcinoma, and one neuroendocrine tumor, summarized in **Table 3**.

Table 3. Summary of Pre-PD details on patients who underwent cholecystectomy within 1 year before PD.

Case	Cholangitis	CEA (U/mL)	CA 19-9 (U/mL)	Time Between Cholecystectomy and PD	Final Pathology
1	Yes	0.7	65	65 days	Ampullary adenocarcinoma 1.6 cm stage III
2	No	None	None	43 days	Large cell neuroendocrine tumor of pancreas, stage II
3	Yes	None	140	57 days	Cholangiocarcinoma, 2.0 cm stage IIB
4	No	3	40	213 days	Ampullary adenocarcinoma 3.2 cm, stage IB
5	Yes	<1.8	69	239 days	Ampullary adenocarcinoma 2.5 cm, stage IB

The sixth patient who had a cholecystectomy within 1 year of PD was found to have necrotizing pancreatitis at surgery and therefore received a cholecystectomy and delayed PD. The final pathology for this patient was pancreatic adenocarcinoma. When comparing perioperative data between patients with a prior cholecystectomy, only operative times were significantly different (**Table 4**).

Table 4. Perioperative comparison between pancreaticoduodenectomy patients with a prior cholecystectomy.

	No Cholecystectomy	Prior Cholecystectomy	P value
Age (years)	64.9 ± 10.8	66.4 ± 9.7	0.54
BMI	23.6 ± 4.9	24.4 ± 5.5	0.45
Tumor Size at Diagnosis (cm)	2.9 ± 1.9	3.2 ± 1.6	0.2
Preop Bilirubin (mg/dL)	3.25 ± 5.7	1.8 ± 2.6	0.18
Preop AST (IU/L)	54 ± 56	43 ± 34	0.85
Preop ALT (IU/L)	80 ± 100	49 ± 54	0.08
Preop Alkphos (IU/L)	212 ± 192	216 ± 223	0.81
Preop Albumin (gm/dL)	4 ± 1.1	3.9 ± 0.45	0.88
OR time (min)	281 ± 45	321 ± 45	0.0002
RBC Transfusions (units)	0.29 ± 1.1	0.45 ± 1.2	0.94
Hospital LOS (days)	11 ± 6	9 ± 5	0.52

Patients with a prior cholecystectomy had a mean operative time 40 minutes longer than patients without a previous cholecystectomy.

4. Case 1

A 48-year-old female presented with bloating and jaundice with bilirubin 6.0 mg/dL. An ultrasound (US) [#1] showed cholelithiasis with biliary dilation of 1.9 cm. Two stones were extracted with endoscopic retrograde cholangiopancreatography (ERCP) [#1] and 2 biliary stents were placed. Cytology on the biliary tissue was benign. She had two readmissions for pain and then underwent laparoscopic cholecystectomy 17 days after the ERCP. About a month later, a plastic stent was removed on ERCP [#2] and the cholangiogram showed choledocholithiasis with sludge. A sphincterotomy was done. A month later, she developed fever, chills, and hyperbilirubinemia to 6.5 mg/dL. A US [#2] showed dilated intrahepatic and extrahepatic ducts. A magnetic resonance cholangiopancreatography (MRCP) [#1] showed biliary obstruction with intrahepatic and extrahepatic dilation of 1.9 cm, no pancreatic mass, and no choledocholithiasis. A repeat ERCP [#3] showed purulent fluid, sludge, and an ampullary mass. Biopsy demonstrated ampullary cancer. CEA was normal and CA 19-9 was 65 U/mL. She underwent a PD 65 days after her laparoscopic cholecystectomy with pathology showing 1.6 cm poorly differentiated ampullary adenocarcinoma stage III.

5. Case 2

A 70-year-old male who presented with abdominal pain and 15 pounds weight loss. The bilirubin was 4.4 mg/dL and the lipase was >3000 IU/L. A US [#1] revealed mildly dilated intrahepatic ductal dilation and a common bile duct (CBD) measuring 8 - 10 mm without stones. A computed tomography (CT) scan [#1] and MRCP [#1] showed mild peripancreatic fat stranding and a mildly dilated CBD, 9 mm, with no distal obstructing lesion and normal intrahepatic ducts. This was thought to be due to gallstone pancreatitis and the patient underwent a laparoscopic cholecystectomy during the same hospitalization. Intraoperative cholangiogram did not show stones and contrast flowed into the duodenum, but the ampulla appeared slightly narrowed. His jaundice persisted and both US [#2] and repeat CT [#2] scan showed a questionable mass at the head of the pancreas with mildly dilated CBD and pancreatic duct. He underwent ERCP [#1] and stent placement 4 days after the cholecystectomy. The ampulla appeared to have fullness and biopsy showed high grade adenocarcinoma with ulceration and neuroendocrine features. An additional ERCP [#2] was performed for stent exchange. He underwent PD 43 days after the cholecystectomy for a 2.5 cm neuroendocrine tumor of the pancreas, stage III.

6. Case 3

A 55-year-old female presented with fever, chills, epigastric pain, bilirubin 11.8 mg/dL, and lipase mildly elevated at 81 U/L. US [#1] and CT [#1] scan showed cholelithiasis, no cholecystitis, intra- and extrahepatic biliary ductal dilation to 14 mm. An ERCP [#1] showed a normal major papilla, but a localized indeterminate biliary stricture in the lower bile duct concerning for an obstructing stone vs stricture. A plastic stent was placed and a sphincterotomy was performed. A postoperative MRCP [#1] was performed that showed mild intrahepatic bile duct dilation, an 8 mm CBD and no choledocholithiasis. Laparoscopic cholecystectomy was done 2 days later during the index admission. The bilirubin on postoperative day 1 decreased to 2.3 mg/dL, and she was discharged. She returned to the hospital 1 day after being discharged with bilirubin 10.3 mg/dL and lipase 634 U/L. The repeat CT [#2] scan showed persistent dilation of the CBD, but no choledocholithiasis. An endoscopic ultrasound (EUS) [#1] showed multiple stones in the CBD and peripancreatic changes consistent with acute pancreatitis. An ERCP [#2] was performed that removed purulent fluid and stones in the CBD consistent with cholangitis. Three weeks later she was admitted again with fevers and ERCP [#3] demonstrated occluded stents and choledocholithiasis. Cholangioscopy showed a localized biliary stricture. Biopsies were negative for malignancy. EUS [#2] was also repeated and showed a 6 mm subtle mass, which was biopsied. Another ERCP [#4] was done a few weeks later showing a patent sphincterotomy, an edematous major papilla, and pancreatic head stenosis. A new pancreatic and biliary stent was placed. A follow up MRCP [#2] showed mild biliary ductal dilation with focal area of narrowing in the distal

CBD, but no discrete biliary or ampullary mass. The biopsy from the EUS was positive for cholangiocarcinoma. CA 19-9 was 140 U/mL. After a negative metastatic work up and 57 days after her laparoscopic cholecystectomy, she underwent a PD for a 2.0 cm cholangiocarcinoma, stage IIB.

7. Case 4

A 65-year-old male presented with abdominal pain, and fever. Bilirubin was 1.8 mg/dL. Lipase was normal. US [#1] showed a distended gallbladder with sludge and a 7 mm stone, as well as mildly dilated intrahepatic and extrahepatic ducts measuring 8 mm. Laparoscopic cholecystectomy was performed on the same day as the US. This was complicated by a bile leak. An ERCP [#1] with sphincterotomy and plastic stent placement was done 2 weeks later. Two months later a follow up ERCP [#2] showed the papilla was bulging suggestive of an ampullary lesion, biopsy showed atypical superficial fragments of a villous adenoma. About 4 months later, he returned to the hospital with abdominal pain, bilirubin elevated at 3 mg/dL. The CT [#1] scan and MRCP [#1] showed dilation of extrahepatic ducts and a 2.3 polypoid mass at the level of the ampulla that projected into the second portion of the duodenum. The bilirubin the next day increased to 6.8 mg/dL. A repeat ERCP [#3] was done and a 1.1 cm malignant mass was seen at the ampulla. Biopsy showed adenocarcinoma. CEA was normal and CA 19-9 was 40 U/mL. He underwent PD for an ampullary adenocarcinoma, stage IB which was performed 213 days after his laparoscopic cholecystectomy.

8. Case 5

A 76-year-old female who presented with abnormal liver tests underwent MRCP [#1] which showed a distended gallbladder with mild pericholecystic fluid, CBD 9 mm with a 2 - 3 mm filling defect and a 6 mm pancreatic duct. She later presented with right upper abdominal pain and a low-grade fever. Bilirubin was 2.2 mg/dL. Lipase was elevated at 81 U/L. She had a US [#1] and MRCP [#2] which showed gallbladder wall thickening with a trace of pericholecystic fluid, mild dilation of the CBD to 8 mm, no filling defects, 4 - 5 mm pancreatic duct, and no pancreatic mass. A laparoscopic cholecystectomy was performed on the same day. Intraoperative cholangiogram showed a dilated CBD, no filling defects and adequate flow into the duodenum. Pathology showed acute cholecystitis. Five days later, a repeat US [#2] showed a 12 mm CBD, with mild dilation of the pancreatic duct. About a month later, she was readmitted for sepsis and an MRCP [#3] showed CBD dilation to 12 - 13 mm, no choledocholithiasis, and pancreatic ductal dilation to 10 mm. The EUS [#1] showed dilation in the main bile duct to the level of the ampulla. The ampulla biopsy was benign. The pancreatic duct also appeared dilated, but no pancreatic mass was seen. The next day, the patient returned to the hospital with fever. Another MRCP [#4] now showed worsening biliary and pancreatic ductal dilation. An ERCP [#1] showed a bulging major papilla. A sphincterotomy was performed and pancreatic/biliary

stents were placed. The ampulla biopsy was again benign. A week later, she presented with hematochezia with a hemoglobin of 5.6 g/dL and lipase 1400 U/L. The CT-arteriogram showed no active bleeding. The ERCP [#2] showed a patent sphincterotomy and an irregular distal bile duct, concerning for an ampullary tumor. The stent was replaced and the duct was swept of clots and sludge. The cytology was negative. Her bleeding resolved and she was discharged after a few days. The next month, an ERCP [#3] showed a patent sphincterotomy, and cholangioscopy was performed. All biopsies and cytology remained negative. Serum IgG4 was also normal. The following next months, she had a subsequent MRCP [#5] and ERCP [#4] showing unchanged dilation of hepatic and pancreatic ducts and no suspicious pancreatic mass. Repeat cholangioscopic biopsies and brushings were all negative. Three months later she returned to the hospital with bilirubin 6.3 mg/dL. The CT [#1] suggested an occluded stent and ERCP [#5] confirmed this. Another sphincterotomy was performed and a stent was replaced. All cytology was negative. Later that month, her bilirubin levels were elevated at 4 mg/dL. The MRCP [#6] showed interval worsening of the biliary and pancreatic ductal dilation, as well as a new 14 mm non-enhancing cyst in the pancreatic head, but no discrete pancreatic mass. An ERCP [#6] the next day showed a partially occluded biliary stent with sludge and purulent fluid. Again, a single biliary stricture was found in the lower third of the main bile duct, but this time the biopsy showed adenocarcinoma. CEA was normal, and CA 19-9 levels were 69 U/mL. She underwent PD for an ampullary adenocarcinoma, which was 239 days after her laparoscopic cholecystectomy.

9. Discussion

Multiple studies have demonstrated that cholecystectomy on the index admission for gallstone pancreatitis is safe, cost effective, and minimizes recurrence of symptoms [6]-[10]. Since the PONCHO trial was published in 2015, same-admission cholecystectomy has essentially become the standard of care. While there are clear benefits to this approach, there are situations in which a prompt cholecystectomy may potentially neglect to appreciate other more complicated and sometimes malignant conditions.

Although pancreatic cancer does not typically present with acute pancreatitis, a meta-analysis by Liu *et al.* demonstrated an association of acute pancreatitis and pancreatic malignancy [11]. A comparative study was done with a cohort of 1504 patients diagnosed with pancreatic cancer comparing those with an episode of acute pancreatitis, and those without a history of pancreatitis [12]. They found that 18 patients or 1.2% of the cohort had pancreatic cancer presenting with acute pancreatitis [12]. The time from pancreatitis to diagnosis ranged from less than 1 month to 48 months, with 15 patients presenting within 1 year. A Surveillance, Epidemiology and End-Results (SEER) study reported that acute pancreatitis and pancreatic malignancy occurs in 5.3% of cases [13]. One of our patients presented with acute pancreatitis without choledocholithiasis on MRCP

and yet this was presumed to be gallstone pancreatitis with a passed stone. Thus, a same admission cholecystectomy was performed. It was not until after the pancreatitis improved and the hyperbilirubinemia persisted that a pancreatic malignancy was more evident on imaging. This highlights the association between pancreatitis and underlying pancreas cancer, as well as the importance of considering the possibility of malignancy in patients with an unclear etiology for pancreatitis.

Ampullary and carcinoid tumors have been reported to present with pancreatitis or jaundice primarily in case reports [14]-[21]. Although the exact rate of ampullary tumors presenting as acute cholecystitis is unknown, we report that 3 out of our 18 patients with ampullary cancer presented with cholecystitis within one year of their episode of cholecystitis. Therefore, it is conceivable that this is occurring more often than recognized. Additionally, these 3 patients with ampullary cancer required multiple ERCP procedures with negative pathology results before the diagnosis was made.

The diagnosis of cholangiocarcinoma is often difficult and has similar risk factors that can lead to pancreatitis [22]. Cholangiocarcinoma often presents insidiously with jaundice or indeterminate strictures. In a retrospective study from 2017 to 2021, a definitive tissue diagnosis of cholangiocarcinoma was achieved in only 14% [23]. Many of these cases require repeat endoscopic procedures and close follow-up before the diagnosis can be made, similar to other cancers [24] [25]. Consensus guidelines have recommended that advanced endoscopists should repeat these studies and should monitor these patients closely [26]. Navvethen *et al* showed that 79% of patients were diagnosed with malignancy within the 0 - 6 month time frame, while only 13.1% were found to have a malignancy at the 7 - 12 month period [27]. They found no malignancy after a 36 month evaluation [27]. Even if not malignant, these strictures may represent other inflammatory cholangiopathies which do have malignant potential.

Diagnosis of pancreaticobiliary malignancy can be difficult as these malignancies mimic the presentation of benign etiologies. The 2019 American Society for Gastrointestinal Endoscopy recommends ERCP evaluation for possible choledocholithiasis if there is a stone on imaging, clinical ascending cholangitis, or a total bilirubin > 4 mg/dL with a dilated CBD [28]. Although MRCP is considered to be superior to CT and US, this imaging modality remains fallible. The sensitivity and specificity are reported as high as 95% - 100% for diagnosing benign and malignant conditions [29]. In our series, all 5 patient had a dilated CBD > 8 mm on imaging, but only two patients had initial bilirubin > 6 mg/dL and underwent ERCP for choledocholithiasis. However, malignancy was not discovered until after cholecystectomy and subsequent tests. In fact, these 5 patients underwent 8 US, 6 CT scans, 11 MRCPs, and 18 ERCP procedures before the diagnosis of malignancy was obtained.

Perhaps a more thoughtful approach might include obtaining tumor markers in select cases. Interestingly, four of the five patients who had tumor mark-

ers performed before PD had mild elevation in CA 19-9. However, Ca 19-9 can also be normal in some patients with malignancy and can also be elevated with biliary obstruction alone even without malignancy, so the benefit of more liberal use of these tumor markers in this situation is unclear and would need further investigation. Perhaps jaundice or biliary ductal dilation with other clinical risk factors such as advanced age, weight loss, and the absence of stone disease may presage a less obvious malignancy, but this too would need further exploration.

Unfortunately, patients with severe acute cholecystitis may truly need an urgent cholecystectomy to avoid septic consequences despite the underlying undiagnosed malignancy. In our cohort of 162 patients who underwent PD, 19% had cholelithiasis and were at risk for such a presentation. However, a cholecystectomy shortly before a second more definitive operation may potentially increase morbidity, complexity, and cost, in addition to delaying the diagnosis of a malignancy. While our series is small, a previous cholecystectomy did increase the operative time for the PD by 40 minutes.

This study is limited in that it is from a single center and is merely a case series from the perspective of patients who received a PD at a tertiary referral center during an 11-year period. Cholecystectomies were sometimes performed at community hospitals on neighboring islands which may account for the inconsistent work up and potential delays. In addition, we may have underestimated this problem, as this study does not account for patients with pancreaticobiliary tumors who did not undergo PD for other reasons.

10. Conclusion

We present a case series of patients who underwent cholecystectomy within one year of PD and four of the five cases had an expedited cholecystectomy after the recent guidelines were published. The study illustrates the potential flaws of always aiming for prompt cholecystectomy. Because pancreaticobiliary malignancy can present insidiously and may evade modern imaging and pathology, further studies are needed on large cohorts of patients who had a cholecystectomy followed by subsequent diagnosis of a malignancy. It will also be helpful to identify clinical factors which can alert the surgeon to a potentially more complex pathology so a more thorough and deliberate evaluation can be considered before surgical intervention.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Hassler, K.R., Collins, J.T., Philip, K., *et al.* (2023) Laparoscopic Cholecystectomy. StatPearls. <https://www.ncbi.nlm.nih.gov/books/NBK448145/>
- [2] Shaffer, E.A. (2005) Epidemiology and Risk Factors for Gallstone Disease: Has the Paradigm Changed in the 21st Century? *Current Gastroenterology Reports*, **7**, 132-140. <https://doi.org/10.1007/s11894-005-0051-8>
- [3] Cao, A.M., Eslick, G.D. and Cox, M.R. (2015) Early Cholecystectomy Is Superior to Delayed Cholecystectomy for Acute Cholecystitis: A Meta-Analysis. *Journal of Gastrointestinal Surgery*, **19**, 848-857. <https://doi.org/10.1007/s11605-015-2747-x>
- [4] Gurusamy, K.S. and Samraj, K. (2006) Early versus Delayed Laparoscopic Cholecystectomy for Acute Cholecystitis. *The Cochrane Database of Systematic Reviews*, No. 4, CD005440. <https://doi.org/10.1002/14651858.CD005440.pub2>
- [5] Gurusamy, K.S., Davidson, C., Gluud, C. and Davidson, B.R. (2013) Early versus Delayed Laparoscopic Cholecystectomy for People with Acute Cholecystitis. *Cochrane Database of Systematic Reviews*, No. 6, CD005440. <https://doi.org/10.1002/14651858.cd005440.pub3>
- [6] da Costa, D.W., Bouwense, S.A., Schepers, N.J., Besselink, M.G., van Santvoort, H.C., van Brunshot, S., *et al.* (2015) Same-Admission versus Interval Cholecystectomy for Mild Gallstone Pancreatitis (PONCHO): A Multicentre Randomised Controlled Trial. *The Lancet*, **386**, 1261-1268. [https://doi.org/10.1016/s0140-6736\(15\)00274-3](https://doi.org/10.1016/s0140-6736(15)00274-3)
- [7] da Costa, D.W., Dijkstra, L.M., Bouwense, S.A., Schepers, N.J., Besselink, M.G., van Santvoort, H.C., *et al.* (2016) Cost-Effectiveness of Same-Admission versus Interval Cholecystectomy after Mild Gallstone Pancreatitis in the PONCHO Trial. *British Journal of Surgery*, **103**, 1695-1703. <https://doi.org/10.1002/bjs.10222>
- [8] Noel, R., Arnelo, U., Lundell, L., Hammarqvist, F., Jumaa, H., Enochsson, L., *et al.* (2018) Index versus Delayed Cholecystectomy in Mild Gallstone Pancreatitis: Results of a Randomized Controlled Trial. *HPB*, **20**, 932-938. <https://doi.org/10.1016/j.hpb.2018.03.016>
- [9] Mueck, K.M., Wei, S., Pedroza, C., Bernardi, K., Jackson, M.L., Liang, M.K., *et al.* (2019) Gallstone Pancreatitis: Admission versus Normal Cholecystectomy—A Randomized Trial (Gallstone PANC Trial). *Annals of Surgery*, **270**, 519-527. <https://doi.org/10.1097/sla.0000000000003424>
- [10] Isbell, K.D., Wei, S., Dodwad, S.M., Avritscher, E.B., Mueck, K.M., Bernardi, K., *et al.* (2021) Impact of Early Cholecystectomy on the Cost of Treating Mild Gallstone Pancreatitis: Gallstone PANC Trial. *Journal of the American College of Surgeons*, **233**, 517-525. <https://doi.org/10.1016/j.jamcollsurg.2021.06.023>
- [11] Liu, J., Wang, Y. and Yu, Y. (2020) Meta-Analysis Reveals an Association between Acute Pancreatitis and the Risk of Pancreatic Cancer. *World Journal of Clinical Cases*, **8**, 4416-4430. <https://doi.org/10.12998/wjcc.v8.i19.4416>
- [12] Minato, Y., Kamisawa, T., Tabata, T., Hara, S., Kuruma, S., Chiba, K., *et al.* (2013) Pancreatic Cancer Causing Acute Pancreatitis: A Comparative Study with Cancer Patients without Pancreatitis and Pancreatitis Patients without Cancer. *Journal of Hepato-Biliary-Pancreatic Sciences*, **20**, 628-633. <https://doi.org/10.1007/s00534-013-0598-y>
- [13] Kirkegård, J., Gaber, C., Lund, J.L., Hinton, S.P., Ladekarl, M., Heide-Jørgensen, U., *et al.* (2020) Acute Pancreatitis as an Early Marker of Pancreatic Cancer and Cancer Stage, Treatment, and Prognosis. *Cancer Epidemiology*, **64**, Article ID: 101647. <https://doi.org/10.1016/j.canep.2019.101647>

- [14] Rafiullah, and Tanimu, S. (2014) Adenomyomatous Hyperplasia of the Ampulla of Vater Presenting as Acute Pancreatitis. *BMJ Case Reports*, **2014**, bcr2013203151. <https://doi.org/10.1136/bcr-2013-203151>
- [15] Kwon, T., Park, D.H., Shim, K.Y., Cho, H., Park, J.H., Lee, S., *et al.* (2007) Ampullary Adenomyoma Presenting as Acute Recurrent Pancreatitis. *World Journal of Gastroenterology*, **13**, 2892-2894. <https://doi.org/10.3748/wjg.v13.i20.2892>
- [16] Hammarstrom, L., Holmin, T. and Stenram, U. (1997) Adenomyoma of the Ampulla of Vater: An Uncommon Cause of Bile Duct Obstruction. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques*, **7**, 388-393. <https://doi.org/10.1097/00019509-199710000-00006>
- [17] Guzzardo, G., Kleinman, M.S., Krackov, J.H. and Schwartz, S.I. (1990) Recurrent Acute Pancreatitis Caused by Ampullary Villous Adenoma. *Journal of Clinical Gastroenterology*, **12**, 200-202. <https://doi.org/10.1097/00004836-199004000-00020>
- [18] Dixon, J.M., Chapman, R.W. and Berry, A.R. (1987) Carcinoid Tumour of the Ampulla of Vater Presenting as Acute Pancreatitis. *Gut*, **28**, 1296-1297. <https://doi.org/10.1136/gut.28.10.1296>
- [19] Berk, T., Friedman, L.S., Goldstein, S.D., Marks, G.P. and Rosato, F.E. (1985) Relapsing Acute Pancreatitis as the Presenting Manifestation of an Ampullary Neoplasm in a Patient with Familial Polyposis Coli. *The American Journal of Gastroenterology*, **80**, 627-629.
- [20] Petrou, A., Bramis, K., Williams, T., Papalambros, A., Mantonakis, E. and Felekouras, E. (2011) Acute Recurrent Pancreatitis: A Possible Clinical Manifestation of Ampullary Cancer. *JOP. Journal of the Pancreas*, **12**, 593-597.
- [21] Souaf, I., Znati, K., Chahbouni, S., Hafid, I., Ameurtesse, H., Hammam, N., *et al.* (2014) Signet Ring Cell Carcinoma of Ampulla of Vater: Report of a Rare Malignancy and Literature Review. *Case Reports in Clinical Medicine*, **3**, 145-148. <https://doi.org/10.4236/crcm.2014.33035>
- [22] Petrick, J.L., Yang, B., Altekruse, S.F., Van Dyke, A.L., Koshiol, J., Graubard, B.I., *et al.* (2017) Risk Factors for Intrahepatic and Extrahepatic Cholangiocarcinoma in the United States: A Population-Based Study in SEER-Medicare. *PLOS ONE*, **12**, e0186643. <https://doi.org/10.1371/journal.pone.0186643>
- [23] Tag-Adeen, M., Malak, M., Abdel-Gawad, M., Abu-Elfath, A., Eldamarawy, R.H., Alzamzamy, A., *et al.* (2023) Clinical Characteristics, Risk Factors and Diagnostic Outcomes of Patients Presented with Indeterminate Biliary Stricture: A Multicenter Study. *Frontiers in Medicine*, **9**, Article 1018201. <https://doi.org/10.3389/fmed.2022.1018201>
- [24] Hashimoto, N. (2016) Prevention and Management of Periapillary Tumors in Familial Adenomatous Polyposis. *Open Access Library Journal*, **3**, 1-5. <https://doi.org/10.4236/oalib.1102338>
- [25] Nielson, C.B. and Vincek, V. (2018) Malignant Melanocytic Matricoma and Criteria for Malignancy. *Open Journal of Pathology*, **8**, 94-100. <https://doi.org/10.4236/ojpathology.2018.83011>
- [26] Angsuwatcharakon, P., Kulpatcharapong, S., Moon, J.H., Ramchandani, M., Lau, J., Isayama, H., *et al.* (2022) Consensus Guidelines on the Role of Cholangioscopy to Diagnose Indeterminate Biliary Stricture. *HPB*, **24**, 17-29. <https://doi.org/10.1016/j.hpb.2021.05.005>
- [27] Navaneethan, U., Njei, B., Lourdasamy, V., Konjeti, R., Vargo, J.J. and Parsi, M.A. (2015) Comparative Effectiveness of Biliary Brush Cytology and Intraductal Biopsy for Detection of Malignant Biliary Strictures: A Systematic Review and Me-

ta-Analysis. *Gastrointestinal Endoscopy*, **81**, 168-176.

<https://doi.org/10.1016/j.gie.2014.09.017>

- [28] Buxbaum, J.L., Abbas Fehmi, S.M., Sultan, S., Fishman, D.S., Qumseya, B.J., Cortessis, V.K., *et al.* (2019) ASGE Guideline on the Role of Endoscopy in the Evaluation and Management of Choledocholithiasis. *Gastrointestinal Endoscopy*, **89**, 1075-1105.E15. <https://doi.org/10.1016/j.gie.2018.10.001>
- [29] Singh, A. (2014) Diagnostic Accuracy of MRCP as Compared to Ultrasound/ct in Patients with Obstructive Jaundice. *Journal of Clinical and Diagnostic Research*, **8**, 103-107. <https://doi.org/10.7860/jcdr/2014/8149.4120>