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ORIGINAL ARTICLE – PANCREATIC TUMORS

Management of Acute Cholecystitis during Neoadjuvant Therapy in Patients with Pancreatic Adenocarcinoma

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ABSTRACT

Background. Patients with localized pancreatic cancer (PC) can develop acute cholecystitis during neoadjuvant therapy; optimal management remains undefined.

Methods. Consecutive patients with localized PC who had indwelling biliary stents and received neoadjuvant therapy were reviewed. Time from stent placement to the development of acute cholecystitis was calculated. Patients were categorized as having surgical versus nonoperative management of cholecystitis. Time to PC resection was defined as the time from the start of treatment to pancreatic resection.

Results. Of the 283 patients with indwelling biliary stents, acute cholecystitis occurred in 17 (6%) patients. The median time from the date of stent placement to the development of cholecystitis was 2.3 months [interquartile range (IQR) 4.6 months]. Acute cholecystitis was managed with cholecystostomy tube placement in 15 (88%) patients and cholecystectomy in 2 (12%). In total, 189 (67%) of the 283 patients completed all intended neoadjuvant therapy and surgery; 10 (59%) of the 17 patients with cholecystitis (10 of 15 managed with a cholecystostomy tube and 0 of 2 managed with cholecystectomy) and 179 (67%) of the 266 patients without cholecystitis ($p = 0.47$). The median time to PC resection was 3.2 months for the 179 patients without cholecystitis and 3.6 months for the 10 patients with cholecystitis ($p = 1.00$).

Conclusions. Acute cholecystitis occurred in 6% of patients with indwelling biliary stents during neoadjuvant therapy. Management with a cholecystostomy tube did not delay the completion of neoadjuvant therapy and surgery and should be considered the optimal management of this complication.

Over the past decade, the use of neoadjuvant therapy for patients with pancreatic cancer (PC) has increased due to data from single-institution experiences as well as a recent randomized controlled trial which demonstrated superior survival among patients who received neoadjuvant therapy and surgery compared with those treated with a surgery-first approach.[1–7] The majority of patients with operable PC present with obstructive jaundice and require endobiliary stent placement, as normalization of liver function tests is required to initiate optimal systemic therapy. Such patients may develop subsequent acute cholecystitis due to occlusion of the cystic duct by the biliary stent or tumor ingrowth, which may be accompanied by endobiliary stent occlusion. The incidence of acute cholecystitis following stent placement in a heterogenous population of patients with malignant biliary obstruction has been reported to range from 2 to 10%.[8,9]

In patients without PC, standard management of acute cholecystitis has included laparoscopic or open cholecystectomy. However, among patients with PC who are

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receiving neoadjuvant therapy, cholecystectomy risks the interruption of systemic chemotherapy or chemoradiation and may make a subsequent pancreaticoduodenectomy more difficult. The oncologic impact of an interruption in planned therapy is hard to quantitate, but one would assume a negative effect. Since cholecystitis may also be managed nonoperatively, an alternative treatment strategy is to place a cholecystostomy tube with a plan for future definitive cholecystectomy at the time of pancreaticoduodenectomy. We hypothesized that nonoperative management of cholecystitis with placement of a cholecystostomy tube would not delay the completion of neoadjuvant therapy and surgery. The goals of this study are to: (1) describe the incidence of acute cholecystitis among patients with localized PC who also had an endobiliary stent and received neoadjuvant therapy, and (2) compare the differences in the time to completion of all neoadjuvant therapy and surgery among patients who did and did not have cholecystitis.

METHODS

Study Subjects

This study was approved by the Medical College of Wisconsin (MCW) Institutional Review Board. Using a prospectively maintained database, consecutive patients with localized PC who received neoadjuvant therapy and surgery were identified from 2009 to 2016. Patients were included if they had biopsy-proven ductal adenocarcinoma of the pancreas and an indwelling biliary stent. Patients were excluded if they did not have biliary obstruction, did not receive neoadjuvant therapy, or had locally advanced or metastatic PC. Clinical stage was determined using objective radiographic criteria based on dual-phase computed tomography (CT) imaging, and patients were classified as resectable or borderline resectable (BLR) as previously described.[10] Neoadjuvant therapy consisted of chemotherapy alone, chemoradiation, or both chemotherapy and chemoradiation.

Cholecystitis

Cholecystitis was defined by the presence of both clinical symptoms and radiographic findings. Clinical symptoms included right upper quadrant pain, fever (temperature > 38 °C), elevated white blood cell count ($> 10{,}000$ cell/μL), and a new elevation in liver function tests [aspartate transaminase (AST)/alanine transaminase (ALT) $> 2 \times$ upper limit of normal]. Radiographic findings included ultrasound or CT findings consistent with cholelithiasis, gallbladder wall thickening (≥ 5 mm), or pericholecystic fluid. Treatment of cholecystitis was categorized as surgical if the patient received a laparoscopic or open cholecystectomy and nonoperative if the patient was managed with a cholecystostomy tube. All patients with cholecystitis received antibiotics. Among patients who completed all neoadjuvant therapy and surgery, preoperative antibiotics consisted of intravenous ceftriaxone and metronidazole and were changed based on prior history of acute cholecystitis. Time to the development of acute cholecystitis was defined as the time from biliary stent placement to the date of diagnosis of cholecystitis. Time to completion of neoadjuvant therapy and surgery was calculated from the start of treatment to the date of surgery.

Statistical Analysis

Categorical variables were compared using the Fischer's exact or Chi squared test. The cumulative incidence of cholecystitis was calculated as the number of patients diagnosed with acute cholecystitis divided by the total cohort of patients. All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics and Neoadjuvant Therapy

An endobiliary stent was placed in 283 consecutive patients with localized PC who received neoadjuvant therapy. Of the 283 patients, 121 (43%) had resectable PC and 162 (57%) had BLR PC. The demographic data are summarized in Table 1. Of the 283 patients, 138 (49%) were female, and the median age at diagnosis for all patients was 65 years (IQR 13 years). Uncovered metal stents were placed in 171 (60%), covered metal stents were placed in 58 (20%), and 54 (19%) had the metal stent placed prior to referral without specification of the type of metal stent (covered vs. uncovered). Neoadjuvant therapy consisted of chemoradiation alone in 100 (35%) patients, chemotherapy in 45 (16%), and both in 137 (49%) patients. The average duration of neoadjuvant therapy for all patients who had chemoradiation, chemotherapy, or both chemoradiation and chemotherapy was 4.2 months (IQR 2.6 months), being 2.4, 2.3, and 6.0 months, respectively ($p < 0.001$).

The outcome of patients with and without acute cholecystitis is summarized in Fig. 1. Of the 283 patients, acute cholecystitis occurred in 17 (6%) patients. The median time to cholecystitis from date of stent placement was 2.3 months; 2 (12%) patients developed cholecystitis within the first week, while the remaining 15 (88%) developed cholecystitis at a median of 2.6 months

TABLE 1 Risk factors associated with cholecystitis

Variable	Total (n = 283)	No cholecystitis (n = 266)	Cholecystitis (n = 17)	p value
Female gender, n (%)	138 (49)	128 (48)	10 (59)	0.46
Charlson comorbidity index, median (IQR)	5 (3.5)	5 (2)	5 (3.5)	
Age, median (IQR), years	65 (13)	65.5 (14)	64 (10)	0.48
BMI, median (IQR), kg/m^2	26.63 (7.2)	26.43 (7.4)	27 (3.0)	0.21
Clinical stage, n (%)				0.80
Resectable	121 (43)	113 (42)	8 (47)	
Borderline resectable (BLR)	162 (57)	153 (58)	9 (53)	
Type of neoadjuvant therapy, n (%)				0.50
Chemotherapy	45 (16)	41 (15)	4 (24)	
Chemoradiation	100 (35)	96 (36)	4 (23)	
Both	137 (49)	129 (49)	8 (47)	
None	1 (0)	0 (0)	1 (6)	
Completed surgery, n (%)				0.47
Not resected	94 (33)	87 (33)	7 (41)	
Completed all intended therapy and surgery	189 (67)	179 (67)	10 (59)	

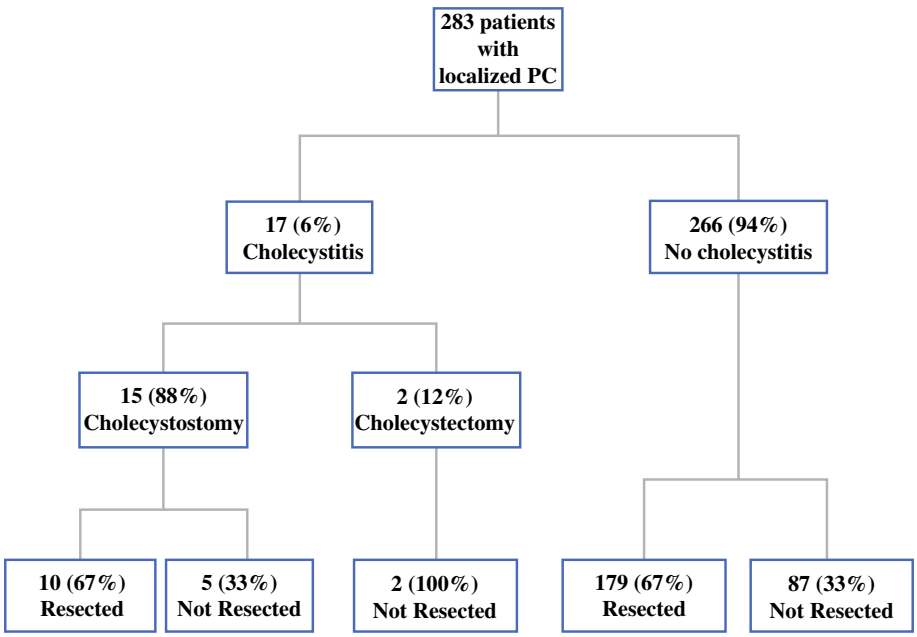

FIG. 1 CONSORT diagram of 283 patients receiving neoadjuvant therapy for pancreatic cancer

following stent placement. Of the 17 patients, 5 (29%) had a covered metal stent, 10 (59%) had an uncovered metal stent, and 2 (12%) had a metal stent without documentation of the specific type. There was no association between the development of cholecystitis and clinical stage of disease (p = 0.80) or type of neoadjuvant therapy (p = 0.50). Details regarding the treatment and outcomes of each patient with acute cholecystitis are summarized in Table 2.

Acute cholecystitis was managed nonoperatively with cholecystostomy tube placement in 15 (88%) of the 17 patients. The median length of hospital stay for these 15 patients was 3.5 days (IQR: 5 days), and 2 (13%) patients had one additional hospital readmission. The first patient had fever and drainage from the cholecystostomy tube site. The cholecystostomy tube was interrogated and replaced with immediate resolution of symptoms. The second patient had drainage around the cholecystostomy tube site secondary to a distal common bile duct stent occlusion. This resolved following additional endobiliary stent placement. Following cholecystostomy tube placement, 4 (27%) of the 15 patients received no further therapy and 11 patients resumed oncologic treatment within a median of 4 (IQR: 5) days. Of the four patients who did not receive further therapy, two patients had significant cardiovascular

TABLE 2 Details of patients who developed acute cholecystitis (n = 17)

Patient #	Treatment	Readmission	Resumed oncologic therapy	Pancreatic cancer resected	Reason not resected
Nonoperative management					
1	Cholecystostomy	No	Yes	Yes	N/A
2	Cholecystostomy	Yes—stent occlusion	Yes	Yes	N/A
3	Cholecystostomy	No	Yes	Yes	N/A
4	Cholecystostomy	No	Yes	Yes	N/A
5	Cholecystostomy	Repeat cholecystitis	Yes	Yes	N/A
6	Cholecystostomy	No	Yes	Yes	N/A
7	Cholecystostomy	No	Yes	Yes	N/A
8	Cholecystostomy	No	Yes	Yes	N/A
9	Cholecystostomy	No	Yes	Yes	N/A
10	Cholecystostomy	No	Yes	Yes	N/A
11	Cholecystostomy	No	No	No	Metastatic disease
12	Cholecystostomy	No	No	No	Performance status
13	Cholecystostomy	No	No	No	Performance status, cardiac arrest
14	Cholecystostomy	No	Yes	No	Performance status
15	Cholecystostomy	No	No	No	Performance status
Surg					
16	Cholecystectomy	Yes	No	No	Perioperative death
17	Cholecystectomy	No	No	No	Local disease progression

events (ventricular fibrillation and worsening congestive heart failure, respectively) which precluded consideration of eventual surgery and two patients experienced a significant decline in performance status which precluded further therapy.

Of the 17 patients who developed cholecystitis, 2 (12%) patients underwent laparoscopic cholecystectomy. One patient developed acute cholecystitis prior to starting neoadjuvant therapy but after being seen at our institution, at which time the treatment plan was developed. Within 1 week of laparoscopic cholecystectomy performed at an outside institution, she developed acute mental status changes and was found to have had a right thalamic intraparenchymal and intraventricular hemorrhage, from which she did not recover. How her death on postoperative day 6 was related to the laparoscopic cholecystectomy was not clear, and an autopsy was not performed. The second patient developed acute cholecystitis during induction chemotherapy and underwent a laparoscopic cholecystectomy. Following the surgical procedure, her performance status and nutritional status deteriorated. She received one additional cycle of chemotherapy but then was unable to tolerate any additional treatment. She developed local disease progression as well as ascites and cachexia and was ultimately referred to hospice care.

The impact of acute cholecystitis on the completion of oncologic care is summarized in Fig. 2. In total, 189 (67%) of the 283 patients completed all intended neoadjuvant therapy and surgery: 10 (59%) of the 17 patients with cholecystitis and 179 (67%) of the 266 patients without cholecystitis (p = 0.47). Of the 15 patients managed nonoperatively, 5 (33%) did not complete neoadjuvant therapy and surgery, due to cardiovascular comorbidities (n = 2), decline in performance status (n = 2), and metastatic disease progression (n = 1). Neither patient who had a cholecystectomy completed neoadjuvant therapy and surgery. Of the 189 patients who completed all intended neoadjuvant therapy and surgery, the median time to surgery was 3.2 months for the 179 patients without cholecystitis and 3.6 months for the 10 patients with cholecystitis (p = 1.00). Of the 189 patients, 17 (9%) patients had a Clavien–Dindo classification grade 3 complication, and this was not different between patients who did and did not have acute cholecystitis during neoadjuvant therapy (0/10 vs. 17/179, p = 0.67). Infectious complication of any type occurred in 31 (17%) of patients without prior cholecystitis, as compared with 1 (6%) among patients with prior cholecystitis (p = 0.50).

DISCUSSION

To the best of the authors' knowledge, this is the first report describing nonoperative management of acute cholecystitis in patients receiving neoadjuvant therapy for operable PC. In a cohort of 283 consecutive patients who *all* had a metal stent placed for biliary obstruction, 6%

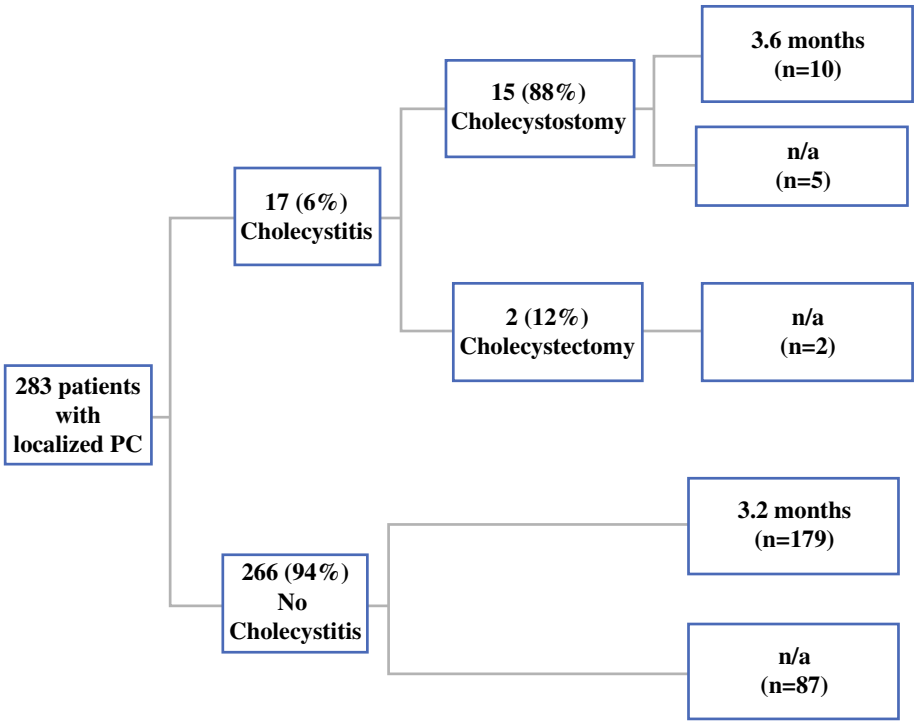

FIG. 2 Impact of treatment for cholecystitis on oncologic care

developed acute cholecystitis during neoadjuvant therapy. We observed that nonoperative management with a cholecystostomy tube and antibiotics was not an impediment to completing all intended neoadjuvant therapy and surgery. Of the 15 patients who had nonoperative management, only 5 (33%) did not undergo successful pancreaticoduodenectomy; one patient had metastatic disease, and the remaining four had significant comorbidities or a decline in performance status, such that they could not complete any further therapy. While the development of cholecystitis may have contributed to their decline, all four patients had successful resolution of the inflammatory changes seen on imaging and their clinical symptoms related to the right upper quadrant of the abdomen completely resolved. Neoadjuvant treatment sequencing has been well shown to successfully dichotomize the population of patients with operable PC into those who will, and will not, benefit from surgery. Underlying comorbidities and performance status are difficult to evaluate at one point in time (at diagnosis); patient selection for surgery becomes much more accurate when serial assessments are made, as occurs during neoadjuvant therapy. The ability of patients to pass the "stress test" of neoadjuvant anticancer therapy before being considered for major surgery is one reason why the morbidity and mortality of pancreatectomy are very low at our institution.

Nonoperative management of acute cholecystitis in patients receiving chemotherapy or chemoradiation has been our practice for the past 25 years. This philosophy evolved due to the concern that an operation could delay or impede the delivery of systemic therapy. This practice began before the advent of laparoscopic cholecystectomy, at which time general anesthesia and an open incision would have required that chemotherapy be stopped for a minimum of 2–3 weeks. With the advent of laparoscopic cholecystectomy, our practice has not changed, especially in patients who may require a pancreaticoduodenectomy, as a subsequent portal dissection may be made more difficult by a laparoscopic (or potentially open) cholecystectomy. In addition, the technical advances in interventional radiology have made cholecystostomy tube placement a relatively quick and safe procedure. Chemotherapy can often be resumed within a few days, and for those patients receiving chemoradiation, an interruption of the radiation schedule may be limited to one or two fractions. Importantly, the progressive enlargement of the obstructed gallbladder can lead to unfavorable changes in the position of the adjacent pancreas and associated vessels when patients are receiving highly conformal chemoradiation. This must be identified and corrected as soon as possible to avoid a marginal miss of the tumor or increased radiation dose to adjacent normal organs. Insertion of the cholecystostomy catheter does not create the need for replanning of the radiation course. For patients who develop cholecystitis following the completion of chemoradiation during the 4–6 weeks prior to surgery, a trial of antibiotic therapy without cholecystostomy tube may be reasonable, especially in patients without

cholelithiasis. However, these patients would need to be closely monitored to avoid potential complications that could arise from inadequate treatment. For patients who are more than 6 weeks from surgery, conservative management with an antibiotics-alone approach carries considerable risk of recurrent cholecystitis. In a meta-analysis of 12 prospective randomized controlled trials comparing early versus late cholecystectomy for acute cholecystitis with over 500 patients, 9% of patients randomized to conservative management (consisting of fluid resuscitation and antibiotics alone) failed to respond or developed early complications during the first admission. In addition, 15% of patients who initially responded to conservative management had recurrent symptoms, and 26% of these patients required urgent or emergent surgery.[11] In a Cochrane Review comparing early versus delayed cholecystectomy in patients with acute cholecystitis, 18% of patients developed relapse of symptoms while awaiting delayed cholecystectomy.[12]

In general, self-expanding metal stents have been the preferred method of biliary drainage in patients who receive neoadjuvant therapy, as the patency rates are significantly better than those of silastic/polyethylene stents.[13] Complications associated with metal stents include stent occlusion, migration, and kinking, all of which can contribute to the development of cholecystitis or cholangitis.[14,15] Fortunately, stent-associated complications are relatively infrequent and most can be managed nonoperatively. At our institution there is consensus among our advanced gastroenterologists and surgeons to utilize uncovered metal stents over covered metal stents during the neoadjuvant period due to a lower rate of stent migration. Historically, acute cholecystitis has been observed in 3% of patents with percutaneous transhepatic biliary drainage.[16] In the modern era of self-expanding stents, the incidence of stent-associated acute cholecystitis among patients with localized or metastatic periampullary tumors ranges from 6 to 10%.[8,9,17] In the largest reported series of patients who had a metal stent placed for a malignant distal biliary obstruction, 26 (6.9%) of 376 developed acute cholecystitis and all were successfully managed nonoperatively, including 4 with antibiotics alone, 12 with percutaneous gallbladder aspiration, 8 with a cholecystostomy tube, and 2 patients with endoscopic transpapillary gallbladder drainage.[17]

Within the context of patients who receive oncologic therapy, nonoperative management is particularly attractive to prevent any lapse in treatment sequencing. We observed no statistically significant difference in time to surgery between the patients without cholecystitis and the patients with cholecystitis who were managed nonoperatively. We were unable to determine the effects of cholecystectomy on time to surgery, as neither of the two patients who underwent cholecystectomy successfully completed all intended therapy. While cholecystectomy provides a permanent correction of cholecystitis, surgery may delay neoadjuvant therapy, prevent patients from completing therapy, or make a subsequent portal dissection more difficult. Cholecystostomy tube placement is minimally invasive and would not be expected to cause a significant delay in pancreatic cancer therapy. However, procedure-related complications may rarely occur, and when they do, it is usually within the first few days.[18] Complications include procedure-related sepsis (0.9%), bleeding (0.4–1.9%), or bile leak (1.9–2.4%).[18] However, cholecystostomy tube placement is a reliable and proven method for the resolution of the clinical symptoms and radiographic findings associated with acute cholecystitis, and almost all patients experience resolution of their symptoms after the procedure.[19]

The main limitation of this study is the small sample size of patients who underwent surgical management of cholecystitis. Of the 17 patients who developed cholecystitis, only 2 were treated with a cholecystectomy, and both were treated at referring hospitals, reflecting our bias for nonoperative management of biliary stent-associated cholecystitis. The remaining 15 patients were treated with cholecystostomy tube placement. Importantly, we can confirm that cholecystostomy is safe and effective for the management of biliary stent-associated cholecystitis and remains our preferred approach to this complication in patients who are under active anticancer treatment.

CONCLUSIONS

Acute cholecystitis occurred in 6% of patients with pancreatic adenocarcinoma following biliary stent placement. Placement of a cholecystostomy tube for the management of acute cholecystitis did not significantly delay the completion of intended neoadjuvant therapy and surgery and is an effective alternative to cholecystectomy for this patient population.

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DISCLOSURES None.

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