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The Incidence of Ischemic Cholecystitis after Prophylactic Cystic Artery Embolization: A Single-Center Retrospective Study

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Abstract

Background Prophylactic cystic artery embolization (CAE) is used to prevent radiation cholecystitis in patients undergoing transarterial radioembolization (TARE), but the incidence of ischemic cholecystitis following CAE remains unclear.

Purpose This retrospective study aimed to determine the incidence of ischemic cholecystitis after prophylactic CAE prior to TARE.

Methods The medical records of 22 patients who underwent CAE prior to TARE between 2002 and 2021 were reviewed. Patients were assessed for evidence of acute cholecystitis and gallbladder imaging changes after the procedure.

Results Four out of the 22 patients (18.2%) developed cholecystitis after CAE, and two of these patients showed evidence of microsphere deposition consistent with radiation cholecystitis. Excluding these two patients, the incidence of ischemic cholecystitis was 9.1%. Additionally, 8 out of 22 patients (36.4%) developed gallbladder imaging changes after the embolization.

Conclusion The incidence of ischemic cholecystitis following CAE is comparable, if not greater than the risk of radiation cholecystitis without prophylactic embolization. Further research is necessary to better understand the risk factors associated with the development of cholecystitis after CAE and to inform recommendations for future preventative measures.

Keywords
- ischemic cholecystitis
- cystic artery embolization
- complications

Introduction

Nontarget embolization during tansarterial radioembolization (TARE) of liver malignancies can result in serious complications such as radiation cholecystitis, gastrointestinal radiation ulcers, or pancreatitis.[1–10] To avoid these complications, arteries such as the right gastric artery, gastroduodenal artery, and cystic artery (CA) can be prophylactically embolized.[7] Alternatively, TARE can be performed safely in most cases by delivering the radioembolic material distal to the origin of the undesired arteries. This might not be possible in certain anatomic variations such as the

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origination of the CA from the distal right hepatic artery in a patient undergoing right lobar TARE. In this case, prophylactic cystic artery embolization (CAE) can be performed to prevent radiation cholecystitis.[5] While CAE can prevent radiation cholecystitis, it may result in ischemic cholecystitis, another serious adverse event that can result in significant morbidity and mortality. The purpose of this study is to determine the incidence of ischemic cholecystitis after prophylactic CAE.

Reported gallbladder (GB) deposition of radio-labeled 99m Tc-MAA detected on pre-TARE treatment mapping ranges from 8 to 32.3% depending on the proximity of the CA to the TARE treatment site.[11] The reported incidence of radiation cholecystitis without prophylactic CAE ranges from 0.6 to 5.4%.[8,9] Although radiation cholecystitis is associated with high morbidity and mortality rates, advances in radioembolization techniques could eliminate the need for prophylactic CAE prior to TARE. Moreover, given the potential complications of CAE, particularly ischemic cholecystitis due to GB infarction, even when collaterals from the GB bed are present,[12,13] it is important to consider the risks and benefits of the procedure. The incidence of cholecystitis after CAE remains uncertain, with previous research reporting rates ranging from 2.2 to 9%.[7,12,13] In this study, we aim to contribute valuable insights to the existing limited literature on the safety of CAE. Specifically, we investigate the incidence of ischemic cholecystitis following CAE, shedding light on potential risks associated with this intervention.

Methods

Institutional Review Board approval was obtained and requirements for obtaining patient consent were waived at their discretion. Patients who underwent CAE from 2001 to 2020 were retrospectively reviewed through medical charts. Information regarding embolization timing and material, postprocedural symptoms, imaging changes before and after embolization, and histopathological reports were collected and analyzed. Imaging reports were reviewed for findings associated with acute or chronic cholecystitis (GB wall thickening, pericholecystic fluid, fat stranding, discontinuity of the GB wall, GB calcifications). When inconsistencies were found between imaging reports and the medical record, images were accessed via the Carestream PACS (Carestream Health, Rochester, New York, United States) and re-evaluated by a board-certified interventional radiologist. Histopathology slides were retrieved from storage and reinterpreted by a surgical pathologist.

Data was aggregated from patient charts for statistical analysis. Patients were divided into the cholecystitis (+) group; the broader imaging changes (+) group for those who had GB changes on follow-up imaging indicating GB injury, which included the cholecystitis (+) patients; and the imaging changes (-) group.

Patient Characteristics

CAE was performed in 22 patients between 2001 and 2020. Eleven patients were male, and 9 patients were female, with an average age of 56.4 years. Most patients undergoing prophylactic CAE for planned Resin right lobar TARE had metastatic disease to the liver ($n = 18$), 14 of which had colorectal cancer, followed by one patient each with esophageal cancer, pancreatic adenocarcinoma, endometrial cancer, and nonsmall cell lung cancer. Two patients had a primary hepatic malignancy treated with glass TARE, one with hepatocellular carcinoma, and one with cholangiocarcinoma.

Procedure

Informed consent was obtained for all procedures. All patients were evaluated in outpatient clinic with standard clinical, laboratory, and imaging workup. All procedures were performed under moderate sedation and common femoral artery access. All patients underwent mapping with radio-labeled 99m Tc-MAA for right lobar TARE.

In all treated cases, the radioembolic delivery was performed with the tip of the microcatheter proximal to the origin of the CA. The CA was either embolized during presphere mapping or prior to Y90 delivery if GB uptake was observed on single-photon emission computerized tomography (SPECT). Embolization was performed using coils ($n = 21$), and Gelfoam ($n = 1$). The endpoint of embolization was flow reduction or near stasis.

Results

Of the 22 patients who underwent CAE, four (18.2%) went on to develop clinically significant cholecystitis that required treatment. Two of them required cholecystostomy tube placements, which were removed after 8 weeks, one required a cholecystostomy tube placement followed by a cholecystectomy, and one patient required a cholecystectomy procedure. Four additional patients (18.2%) had GB changes on follow-up imaging performed 1 to 3 months post-CAE, only two of which had transient symptoms that did not require treatment (►**Table 1**).

One patient developed acute severe abdominal pain shortly after CAE performed immediately prior to right lobar TARE (►**Fig. 1** and ►**Fig. 2**). The symptoms improved but started to worsen 48 hours later. Imaging confirmed acute cholecystitis. The cholecystitis was treated with antibiotics and cholecystostomy tube placement. The cholecystostomy tube was removed after 8 weeks. The subsequent left lobar treatment was delayed for 12 weeks after the right lobar treatment to allow for recovery from the acute cholecystitis. In another patient, abdominal pain started immediately after CAE performed during mapping procedure and worsened over the next 16 days. Imaging confirmed acute cholecystitis, and a cholecystostomy tube was inserted, leading to symptom relief. The TARE procedure was deferred due to inability to deliver tumoricidal dose to the tumor. The tube was successfully removed after 8 weeks. The third patient underwent CAE with coils on the same day as the TARE procedure. Post-TARE imaging showed no significant GB wall activity. The patient developed abdominal pain on day 2 postprocedure, which significantly worsened on day 30. Imaging

Table 1 Patients who developed imaging changes with or without cholecystitis

Patient	Diagnosis	Sex	Age (years)	Embolization material	Embolization timing	Cholecystitis	Cholecystitis management
1	CRC	M	70	Coils	Mapping	No	No
2	CRC	F	52	Coils	Mapping	No	No
3	CRC	F	60	Coils	TARE	No	No
4	Endometrial cancer	F	60	Coils	TARE	No	No
5	CRC	F	74	Coils	TARE	Yes	Cholecystostomy tube placement at day 38 followed by cholecystectomy at day 58
6	Cholangiocarcinoma	F	65	Coils	Mapping	Yes	Cholecystostomy tube placement at day 16
7	Pancreatic adenocarcinoma	M	48	Coils	TARE	Yes	Cholecystostomy tube placement at day 2
8	CRC	M	49	Coils	Mapping	Yes	Cholecystectomy at day 280

Abbreviations: CRC, colorectal cancer; TARE, transarterial radioembolization.

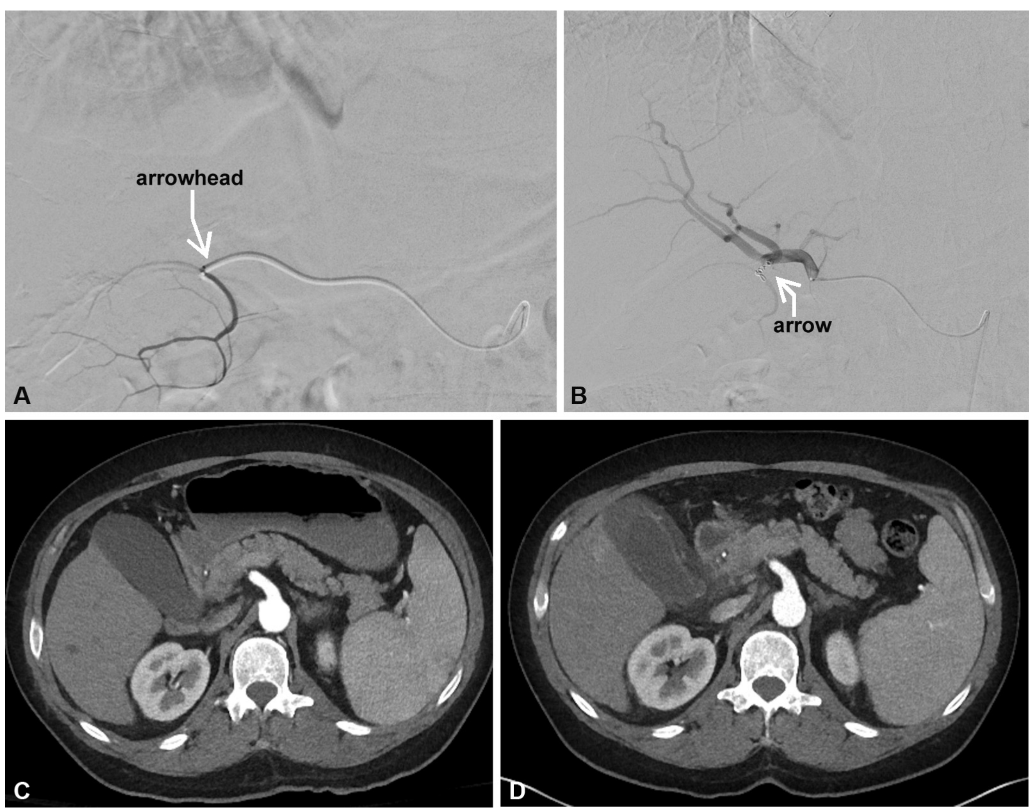

Fig. 1 Development of acute cholecystitis after prophylactic cystic artery embolization (CAE). Patient with a history of metastatic pancreatic cancer who underwent prophylactic CAE due to gallbladder uptake observed on pre-embolization mapping with Tc-99m MAA. (**A**) Digital subtraction angiography (DSA) after selective cannulation of the CA (arrowheads). (**B**) DSA of the right hepatic artery demonstrating minimal CA flow after embolization with a ruby coil (arrow). (**C**) Axial contrast-enhanced computed tomography (CECT) of the abdomen was performed few hours after the embolization due to acute pain demonstrated normal appearing gallbladder. (**D**) CECT of the abdomen performed 2 days after CAE due to worsening pain demonstrated gallbladder wall thickening, mucosal enhancement, and pericholecystic fluid consistent with acute cholecystitis.

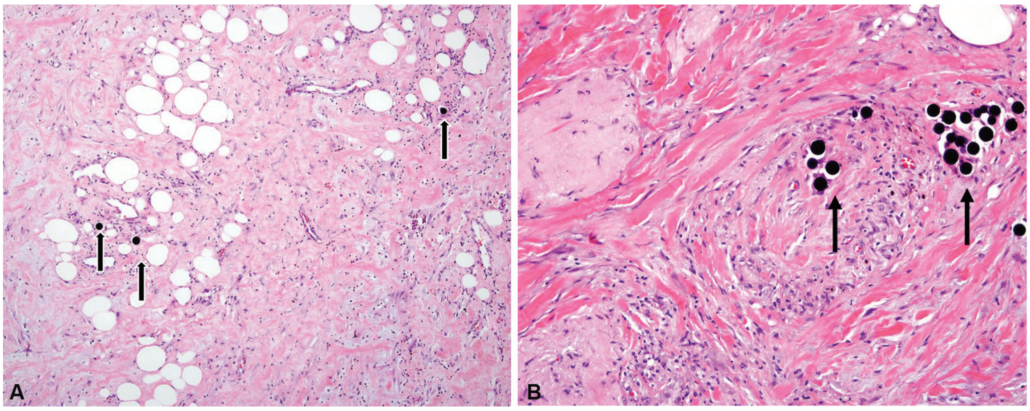

Fig. 2 Surgical histopathology of the gallbladder demonstrating radiation cholecystitis despite prophylactic cystic artery embolization (CAE). Patient with history of metastatic colorectal cancer who developed symptoms of chronic cholecystitis following transarterial radioembolization with Y90 microspheres. Cholecystectomy was performed at 280 days post-CAE, and surgical histopathology demonstrated diffuse microsphere deposition throughout the gallbladder with acute and chronic changes consistent with radiation cholecystitis. Sample slides are provided in the panels above. (**A**) Microsphere deposition (arrows) with dense keloidal fibrosis and ectatic vascular spaces. (**B**) Microsphere deposition within a blood vessel with resultant thrombosis.

confirmed acute cholecystitis, and a cholecystostomy tube was placed. Eventually, a cholecystectomy was performed, revealing evidence of radiation cholecystitis on histopathology. In the fourth patient, abdominal pain developed few days after CAE performed at the same setting with TARE. The pain remained persistent for months. Imaging showed diffuse GB wall thickening, Cholecystectomy was performed at day 280, resulting in complete resolution of abdominal pain. Surgical pathology confirmed acute and chronic cholecystitis with microsphere deposition.

Discussion

In our study, the incidence of cholecystitis was 18.2% (4/22) in those who underwent CAE for prophylaxis prior to TARE. For the cholecystitis (+) group, symptoms of cholecystitis began hours to 30 days post-CAE, with three of four patients undergoing a GB intervention within 2 months, while the fourth patient delayed surgery until 280 post-CAE. For the two patients who underwent cholecystectomy, surgical pathology specimens demonstrated microsphere deposition throughout the GB wall with acute and chronic inflammatory changes concerning for radiation cholecystitis ►**Fig. 2**. Three of the four patients underwent GB intervention within 2 months, whereas the fourth patient delayed surgery until 280 post-CAE. In the two patients who underwent cholecystectomy, surgical pathology specimens indicated the deposition of microspheres throughout the GB wall, accompanied by acute and chronic inflammatory changes suggestive of radiation cholecystitis. We hypothesize that ischemia secondary to CAE may have contributed to the development of cholecystitis in these patients. The partial embolization of the CA might have increased the risk of complete arterial occlusion by the Y90 spheres, resulting in mixed ischemic and radiation cholecystitis.

The GB and cystic duct are supplied primarily by the CA, most commonly arising off the right hepatic artery, with some collateral blood supply arising from hepatic arterial perforators within the GB fossa.[14,15] There are several reasons why prophylactic CAE may fail in preventing nontarget radioembolization, including incomplete CAE, CA recanalization, or the presence of two CAs. Piasecki et al found that 29.6% (16/54) of patients who underwent CAE had radioactive uptake in the GB wall on SPECT after TARE, 40% of which had two CAs.[16] For our two patients who developed radiation cholecystitis, one had post-CAE angiography consistent with incomplete CAE, while there was no clear etiology for CAE failure in the other patient.

No pathologic specimens were obtained for the remaining two patients in the cholecystitis (+) group who both underwent cholecystostomy tube placement. However, several factors suggest ischemia as the primary cause in these patients. Patient #1 exhibited symptoms within 2 hours after CAE and TARE, and a post-TARE Bremsstrahlung scan showed no radioactivity. One patient developed acute cholecystitis symptoms shortly after CAE and before TARE, confirming the ischemic etiology of the cholecystitis. Excluding the two presumed radiation cholecystitis cases, the incidence of presumed ischemic cholecystitis following CAE in our study is 9.1% (2/22).

Four additional patients had evidence of GB changes on follow-up imaging after CAE concerning for subclinical GB injury. Two of these patients experienced transient right upper quadrant abdominal pain post-CAE that was managed conservatively. Abnormal GB appearance on cross-sectional imaging is relatively common among patients with hepatic metastatic disease and underlying hepatic dysfunction. According to Sag et al, only 39% of patients exhibited a normal-appearing GB by standardized criteria prior to TARE.[17,18] These data highlight the importance of clinical correlation for signs and symptoms associated with cholecystitis, as sole reliance on imaging findings would lead to unnecessary intervention exposing patients to risk of complications associated with cholecystectomy or cholecystostomy tube placement.

In the study by McWilliams et al, the safety and efficacy of proximal catheter-directed arterial embolization (CAE) were assessed in 46 patients, of whom 11 were treated with coils and 35 with Gelfoam.[7] The study identified transient right upper quadrant pain and a positive Murphy's sign in two patients who were managed conservatively, and one patient required cholecystectomy due to acute cholecystitis (2.2% incidence). In a retrospective study conducted by Powerski et al, a comparison was made between 37 patients who underwent right TARE proximal to the CA without CAE, and 68 patients who underwent TARE with CAE.[14] The rates of cholecystitis in those who underwent TARE with CAE (2.7%) did not show a significant difference compared to those who underwent TARE without CAE (2.9%). It is noteworthy that the incidence of cholecystitis observed in our study is remarkably higher than what has been reported in the available literature. This discrepancy might be attributed to statistical variation or could be indicative of differences in institutional practices related to the diagnosis and management of acute cholecystitis.

Although radiation-induced cholecystitis is a concerning complication of radioembolization, with reported rates ranging from 0.6 to 5.4%, preventive measures such as prophylactic CAE may not always yield favorable clinical outcomes.[8,9] There are potential risks associated with CAE, including the possibility of vascular injury, prolonged procedure time, increased radiation dose, and additional costs. Moreover, CAE has the potential to compromise the GB's ability to withstand further embolic load from TARE, thereby increasing the risk of acute ischemic and/or radiation cholecystitis. Additionally, CAE could lead to the formation of difficult-to-embolize collateral vessels, which could further elevate the risk of radiation-induced cholecystitis in cases where repeat TARE is required, and microspheres cannot be delivered distal to the origin of these collateral vessels.[19,20] Acute ischemic cholecystitis can pose significant challenges within the TARE treatment pathway, as evident in our study, leading to notable delays in the administration of right lobar TARE and subsequent left lobar TARE. These delays arise from the need to resolve cholecystitis or adapt treatment schedules to accommodate both interventions. Nevertheless, these time lapses may negatively impact malignancy treatment outcomes.

Our study has certain limitations that warrant consideration. First, the retrospective nature of the design, along with the absence of a comparative group undergoing TARE without CAE, and the relatively small sample size might have constrained the statistical power of our findings. Additionally, distinguishing between radiation and ischemic cholecystitis can be challenging, given the overlap in clinical presentation. Follow-up imaging and clinical visits were not standardized across patients, which may have introduced variability into our results. Moreover, due to a lack of pathologic specimens obtained from patients who underwent cholecystostomy tube placement, as well as from those who showed imaging changes, we cannot confirm the presence of GB ischemia definitively.

Given comparable incidence rates of radiation and ischemic cholecystitis in our population despite prophylactic embolization, as well as other potential harms and limitations associated with prophylactic CAE, our study suggests that prophylactic CAE is probably unnecessary and potentially harmful performed prior to TARE.

Ethical Approval

Study informed consent is not required. Institutional Review Board (IRB) approval was obtained.

Informed Consent

This study has obtained IRB approval from The University of Iowa IRB and the need for informed consent was waived.

Conflict of Interest

None declared.

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