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Incidence and Risk Factors of Acute Ischemic Cholecystitis after Transarterial Chemoembolization: Correlation with Cone Beam CT Findings

간동맥 화학 색전술 후 발생한 급성 담낭염의 발생률과 위험인자: Cone Beam CT 소견과의 상관관계

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Purpose Acute cholecystitis is a complication of transarterial chemoembolization (TACE) that occasionally requires surgical intervention. We aimed to analyze the incidence and risk factors of cholecystitis requiring surgical intervention in patients with embolic material uptake on cone beam CT (CBCT) performed immediately after various TACE procedures.

Materials and Methods After a retrospective review of 2633 TACE procedures performed over a 6-year period, 120 patients with embolic material retention in the gallbladder wall on CBCT immediately after TACE were selected. We analyzed the incidence of and risk factors for acute cholecystitis.

Results The overall incidence of acute cholecystitis requiring surgical intervention was 0.45% (12 of 2633 TACE procedures); however, it was present in 10% (12 of 120) of procedures that showed high-density embolic material retention in the gallbladder wall on CBCT performed immediately after TACE. Acute cholecystitis requiring surgical intervention occurred in eight patients (66.7%) who underwent direct cystic arterial embolization. Surgical intervention was performed 15 days (mean) after TACE.

Conclusion Most unintended chemolipiodol deposits in the gallbladder wall resolved without intervention or surgery. However, superselective direct cystic arterial chemoembolization was associated with a high incidence of acute cholecystitis requiring surgery, and patients who undergo this procedure should be closely monitored.

Index terms Transarterial Chemoembolization; Cone Beam Computed Tomography; Hepatocellular Carcinoma; Cholecystitis

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INTRODUCTION

Inadvertent reflux of chemoembolic agents into the cystic artery is not uncommon during transarterial chemoembolization (TACE), and may cause ischemic complications in the gallbladder (1-4). The incidence of acute ischemic cholecystitis after TACE rangess 0.3%–10% (5-10). One study reported that repeat chemoembolization procedures are a risk factor (1). The clinical outcomes of ischemic cholecystitis after TACE are controversial; some studies have reported necrotizing cholecystitis requiring interventional treatment or surgery (7-10), while another indicated no severe outcomes with conservative treatment (5).

Cone-beam CT (CBCT) technology is evolving rapidly and is widely used by interventional radiologists. CBCT aids not only in tumor targeting before treatment, but also in assessing the procedural success of TACE (11). The uptake of embolic material by the gallbladder wall can be easily confirmed using CBCT performed immediately after TACE. Thus, using post-procedural CBCT, it is possible to immediately evaluate the unintended uptake of embolic material by the gallbladder wall; such unintended uptake may be associated with the development of acute cholecystitis.

Several studies have analyzed the incidence and clinical outcomes of acute cholecystitis associated with TACE procedures. Some studies have reported a direct correlation between an inadvertent reflex to chemoembolic agents in the cystic artery and acute cholecystitis. Thus, in this study, we aimed to analyze the incidence of and risk factors for severe cholecystitis requiring surgical or interventional treatment in patients with embolic material uptake, as determined by CBCT performed immediately after TACE.

MATERIALS AND METHODS

STUDY POPULATION

In this ethics board-approved study, a retrospective review of 2633 TACE procedures from January 2015 to December 2020 was performed. Among these TACE procedures, 2122 were conventional TACE (c-TACE) and 511 were drug-eluting bead TACE (DEB-TACE) procedures. One hundred and twenty patients (85 male, 35 female; mean age 67.2 years) who showed high-density embolic material retention in the gallbladder wall on CBCT performed immediately after TACE were selected for analysis. A retrospective chart and image review of acute cholecystitis was performed for these 120 patients. One hundred eighteen patients underwent c-TACE, while two underwent DEB-TACE. Most patients had a Child–Pugh score (CPS) of A, although eight had CPS of B, and the underlying causes of hepatitis were hepatitis B virus (n = 93), hepatitis C virus (n = 10), and non-B/non-C (n = 17). The median number of prior TACE procedures was 4 (range, 1–24).

This study was approved by our Institutional Review Board, which waived the requirement for written informed consent (IRB No. KC22RASI0521).

IMAGING TECHNIQUES

Within 2 weeks before the TACE procedure, all patients underwent contrast-enhanced (CT or MRI) imaging of the liver using our institution's routine protocol. During TACE, at least

two CBCT scans were performed. Initial CBCT was performed at the level of the common hepatic artery before chemoembolization to accurately characterize the tumor and detect tumor-feeding arteries. Completion CBCT was performed immediately after chemoembolization to evaluate the uptake of chemoembolic agents. Routine follow-up imaging studies were performed 1 month later to assess evaluation using contrast-enhanced CT or MRI. However, if the patient had severe abdominal pain, an emergency CT scan was performed before the routine follow-up. Cross-sectional images were independently analyzed by one of four diagnostic radiologists. Acute cholecystitis was diagnosed based on the clinical symptoms and typical CT findings of gallbladder distention, wall thickening, mucosal hyperenhancement, and/or pericholecystic fat stranding or fluid (7). Two radiologists with 3 and 15 years of experience in interventional radiology, respectively, independently reviewed the CBCT images. Differences in interpretation were resolved by consensus. Completion CBCT images were reviewed to determine whether there was uptake of embolic material by the gallbladder wall.

TACE TECHNIQUES

All TACE procedures were performed by two interventional radiologists with 8 and 15 years of experience, respectively. c-TACE was performed using standard angiographic techniques with a chemolipiodol mixture and gelatin particles (EG-GEL, 150–350 μm; Engain Co., Seongnam, Korea). The chemolipiodol mixture contained 10 mg of doxorubicin (Adriamycin RDF; Ildong, Seoul, Korea) mixed with 1 mL of nonionic contrast media and 2 mL of iodised oil (Lipiodol; Guerbet, Rue Paul Langevin, France). Doxorubicin (10–30 mg) was used in the TACE procedures. DEB-TACE was performed using DC Beads (Biocompatibles, Surrey, UK), and 50 mg of doxorubicin was loaded per vial. DEB particles were 70–150 μm or 100–300 μm in diameter. Gelatin particles were not used in DEB-TACE. The position of the catheter before the injection of chemoembolic agents was at the lobar or multisegmental level in patients with multiple, large, or bilateral hepatocellular carcinomas (HCCs), and a superselective maneuver was used in patients with a few small HCCs. If the tumor had a cystic arterial supply, cystic artery embolization was performed after consultation with a clinician. No nontarget embolization protection device was used. The endpoints of embolization were complete stasis for c-TACE and near stasis for DEB-TACE. All patients underwent a final CBCT immediately after TACE (Fig. 1).

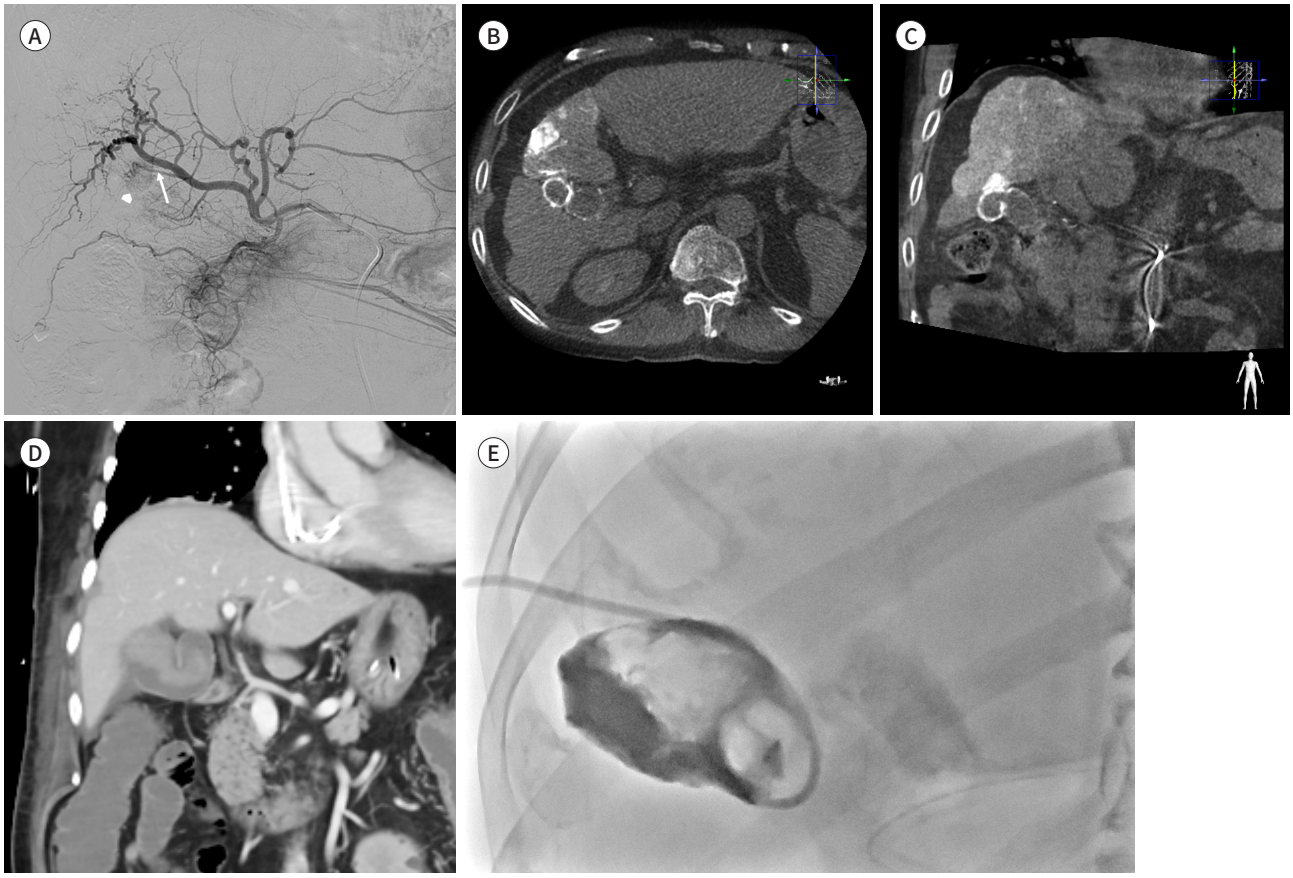
STATISTICAL ANALYSIS

Statistical analyses were performed using the IBM SPSS Statistics software for Windows (version 23.0; IBM Corp., Armonk, NY, USA). Continuous variables are expressed as means and standard deviations. Logistic regression was used to investigate the correlation between various factors and incidence of acute cholecystitis. The significance level for all analyses was set at $p < 0.05$. All statistical analyses were performed by an independent investigator.

RESULTS

In a review of 2633 TACE procedures, 120 patients presented with high-density embolic material retention in the gallbladder wall on postinterventional CBCT. Unintended embolic material retention was observed in various catheter positions, including lobar treatment in

Fig. 1. A 64-year-old male with a small hepatocellular carcinoma lesion in segment 4.
A. Common hepatic angiogram showing a small, stained tumor (arrowhead). Note the cystic arterial tumor supply (arrow).
B. Postprocedural CBCT after direct cystic arterial chemoembolization showing uptake of embolic material by the gallbladder wall as well as the tumor.
C. Coronal image of postprocedural CBCT.
D. An imaging finding consistent with the patient's clinical picture of acute cholecystitis at 5 days after transarterial chemoembolization.
E. Tubogram after percutaneous cholecystostomy tube placement showing obstruction of the cystic duct and a large hemorrhage.
CBCT = cone beam CT



64 patients, multisegmental embolization in 38, direct cystic arterial embolization in 12, and a superselective approach in 6. The anterior and posterior branches of the right hepatic artery were superselected. The overall incidence of acute cholecystitis requiring surgical intervention after TACE was 0.45% (12/2633). Among the 120 patients with embolic material retention on CBCT, the incidence of acute cholecystitis requiring surgical intervention was 10% (12/120). There were no significant differences in age, sex, CPS, viral markers, or the number of previous TACE sessions between all patients and the surgical intervention group. Only cystic artery embolization showed statistically significant differences between the two groups (odds ratio: 52; 95% confidence interval: 10.92–247.8; $p < 0.001$). A total of 2–6 mL of lipiodol was used for all TACE procedures. There was no significant difference in the amount of lipiodol administered between the patient and surgical intervention groups. Table 1 summarizes the variables of the two groups and includes the statistical analysis. Twenty-seven of 120 patients showed typical CT findings of acute cholecystitis on follow-up images. However, the symptoms in 15

of these patients subsided with medication alone and did not require intervention or surgery. Twelve patients whose symptoms did not subside with medical treatment underwent surgical intervention (cholecystectomy [*n* = 9] and percutaneous cholecystostomy with delayed cholecystectomy [*n* = 3]). Surgery was the most common intervention, performed in eight patients (66.7%) who underwent direct cystic arterial embolization and three who underwent lobar or multisegmental treatment. Surgery was performed 15 days (mean duration) after TACE. All patients who underwent cholecystectomy were discharged without major complications and proceeded to the next TACE session uneventfully. In all patients without surgical intervention, the lipiodol was washed out in the follow-up CT after 1–2 months. Diffuse gallbladder wall thickening also improved on follow-up CT. Cholecystitis occurred in one of the six patients who received superselected TACE; the patient underwent superselected TACE of the posterior branch of the right hepatic artery. The patient characteristics and TACE procedures are summarized in Table 2. The origin of the cystic artery was evaluated in 120 patients using CBCT. In almost all cases, the cystic artery originated from the right hepatic artery; in two cases, it originated from an aberrant right hepatic artery. Unintended embolization occurred in conventional anatomy.

Table 1. Variables of Patients Showing Embolic Material Retention of the Gallbladder Wall on Cone Beam CT

Characteristic	All Patient	Surgical Intervention	*p*-Value
Age	67.2 ± 10.1	63.4 ± 9.9	0.408
Sex			0.107
Male/female	85 (70.9)/35 (29.1)	9 (10.5)/3 (8.6)	
Child-pugh score			0.217
A/B/C	112 (93.3)/8 (6.7)/0	10 (8.9)/0/0	
Viral maker			0.513
HBV/HCV/negative	93 (77.5)/10 (8.3)/17 (14.2)	9 (9.6)/3 (30)/0	
Sessions of prior TACE	4.9 ± 3.4	2.6 ± 1.7	0.787
< 3 times	25 (20.8)	6 (24.0)	
≥ 3 times	95 (79.2)	6 (6.0)	
Catheter position			
Lobar	64 (53.3)	1 (1.5)	0.562
Right	60 (50.0)	1 (1.6)	
Left	4 (3.3)	0 (0)	
Multisegment	38 (31.7)	2 (5.2)	0.466
Superselective	6 (5.0)	1 (16.7)	0.058
Cystic artery directly	12 (10.0)	8 (66.7)	< 0.001
Type of chemoembolization			0.848
c-TACE	118 (98.3)	11 (9.3)	
DEB-TACE	2 (1.7)	1 (50.0)	
Lipiodol (mL)	4.5 ± 1.4	4.1 ± 1.2	0.513

Data are presented as mean ± standard deviation or *n* (%).
cTACE = conventional TACE, DEB = drug-eluting bead, HBV = hepatitis B virus, HCV = hepatitis C virus, TACE = transarterial chemoembolization

Table 2. Characteristics of Patients with Acute Cholecystitis Requiring Surgical Intervention

Patients No.	Age (Years)	Sex	Viral Marker	Sessions of Prior TACE	Child-Pugh Score	Level of Embolization	Type of Chemoembolization	Operation Period after TACE (Days)
1	77	Male	HBV	6	5	Cystic artery	c-TACE	28
2	64	Female	HBV	1	5	Cystic artery	c-TACE	22
3	59	Male	HBV	3	5	Multisegment	c-TACE	23
4	69	Female	HBV	2	5	Cystic artery	DEB-TACE	3
5	59	Male	HCV	1	5	Cystic artery	c-TACE	5
6	69	Male	HBV	4	5	Cystic artery	c-TACE	20
7	79	Male	HCV	1	5	Superselective	c-TACE	11
8	63	Female	HCV	1	6	Multisegment	c-TACE	3
9	41	Male	HBV	3	5	Right lobar	c-TACE	31
10	64	Male	HBV	3	5	Cystic artery	c-TACE	14
11	57	Male	HBV	5	5	Cystic artery	c-TACE	4
12	60	Male	HBV	1	5	Cystic artery	c-TACE	20

cTACE = conventional TACE, DEB = drug-eluting bead, HBV = hepatitis B virus, HCV = hepatitis C virus, TACE = transarterial chemoembolization

DISCUSSION

Several previous studies have reported that acute cholecystitis after TACE occurs in 0.3%–10% of cases (5-10). Recently, Wagnetz et al. (1) reported that 4.9% of 246 patients developed acute cholecystitis after 355 TACE procedures. All symptomatic patients were treated conservatively without surgical or radiologic interventions. After radioembolization, Atassi et al. (12) reported a 0.6% incidence of radiation-induced cholecystitis requiring cholecystectomy, a 1.8% incidence of abnormal enhancement of the gallbladder wall on follow-up imaging, and a 0.9% incidence of gallbladder wall disruption without symptoms. The incidence of acute cholecystitis after TACE or radioembolization is low. However, previous studies have only analyzed the incidence of acute cholecystitis, regardless of the actual uptake of embolic material into the gallbladder wall. Currently, because TACE is mostly performed using a superselective approach, unintended uptake is not expected. Thus, this study is meaningful in that we evaluated the actual uptake of embolic material in the gallbladder wall using CBCT and predicted the incidence of acute cholecystitis in patients with embolic material uptake. CBCT using a flat-panel detector is an alternative approach for obtaining cross-sectional images during TACE. CBCT performed before and after TACE not only helps in the detection of tumors and tumor-feeding arteries, but can also be used to confirm that the endpoint of TACE has been reached (13). By intraprocedural monitoring of the embolized area, the uptake of the embolic material by the gallbladder wall can be easily confirmed, making it possible to directly correlate this factor with the development of acute cholecystitis. In this study, the incidence of acute cholecystitis requiring surgical intervention was 0.45%, similar to that reported in previous studies (5-10). However, among patients with CBCT-confirmed embolic material retention in the gallbladder wall, the incidence of acute cholecystitis was 10%. These results suggest that CBCT can predict patients at high risk of biliary injury. Anatomically, the cystic artery originates from the right hepatic artery and divides anteriorly and posteriorly to supply the

gallbladder (14, 15). This may explain the high incidence of cystic artery embolization when approaching the proximal right hepatic or proper hepatic arteries. In our case, most of the cystic arteries originated from the right hepatic arteries, and unintended embolization occurred in this conventional anatomy. However, variations in the cystic arteries, such as those originating from the left hepatic, proper hepatic, or superior mesenteric arteries, have been reported (14, 15). Thus, unintended embolization of the cystic artery may occur whenever lobar or multisegmental treatment is performed. In this study, 120 of 2633 patients who underwent TACE showed high-density embolic material retention by the gallbladder wall on postinterventional CBCT. Most patients underwent chemoembolic agent infusion over a wide area using a lobar or multisegmental approach, whereas 12 underwent direct cystic arterial embolization and 6 underwent superselective embolization. Nevertheless, only 3 of the 102 patients who underwent lobar or multisegmental treatment showed acute cholecystitis requiring surgical intervention in this study. This suggests that most embolic material retention by the gallbladder wall after lobar TACE is self-limiting and does not require intervention or surgery. In all patients without surgical intervention, lipiodol was washed out in the follow-up CT after 1–2 months. Transient gallbladder wall thickening also improved on follow-up CT, similar to that reported in previous studies (16). Acute cholecystitis requiring surgical intervention was common, and occurred significantly more frequently in patients who underwent direct cystic arterial embolization than in those who underwent other types of arterial embolization. In our case, cholecystitis occurred in one of the two patients who received DEB-TACE. Cholecystitis may occur due to embolic particle deposition during DEB-TACE (17). Previously, the risk of cholecystitis was known to be high with DEB-TACE. However, a recent multicenter study reported no significant difference from c-TACE (16, 18). Identifying the feeding artery of the tumor using CBCT and performing superselective embolization can reduce the incidence of cholecystitis. In addition, "completion CBCT" can be used to predict patients at high risk of cholecystitis. By closely monitoring these patients, the morbidity and mortality associated with cholecystitis after TACE can be reduced.

In addition to the intrinsic limitations of any retrospective study, this study had several other limitations. First, as the number of patients treated with DEBs was small, our ability to evaluate the relationship between DEB-TACE and the incidence of acute cholecystitis was limited. Second, the number of patients with acute cholecystitis requiring surgical intervention was low. In conclusion, after lobar treatment, most cases of unintended deposition of chemoembolic agents in the gallbladder wall were self-limiting and did not require nonconservative treatment. However, patients who underwent direct cystic arterial chemoembolization showed a high incidence of acute cholecystitis requiring intervention or surgery; this patient population should be closely monitored.

Author Contributions

Conceptualization, K.J.Y., O.J.S., K.S.H.; data curation, K.J.Y., O.J.S., K.S.H.; formal analysis, K.J.Y., O.J.S., K.S.H.; funding acquisition, K.J.Y., O.J.S.; investigation, K.J.Y., O.J.S., C.H.J.; methodology, K.J.Y., O.J.S.; project administration, K.J.Y., O.J.S.; resources, K.J.Y., O.J.S.; software, K.J.Y., O.J.S.; supervision, K.J.Y., O.J.S., C.H.J.; validation, K.J.Y., O.J.S., C.H.J.; visualization, K.J.Y., O.J.S.; writing—original draft, K.J.Y., O.J.S.; and writing—review & editing, K.J.Y., O.J.S.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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간동맥 화학 색전술 후 발생한 급성 담낭염의 발생률과 위험인자: Cone Beam CT 소견과의 상관관계

김종영 · 오정석* · 천호종 · 김수호

목적 급성 담낭염은 간동맥 화학 색전술 후에 발생하는 비교적 드물지 않게 발생하는 합병증이며, 대부분 수술적 혹은 중재적 치료 없이 호전된다. 간동맥 화학 색전술 직후에 촬영한 cone beam CT 소견을 이용하여, 수술적 혹은 중재적 치료를 필요로 하는 담낭염의 발생률과 위험인자를 분석하고자 하였다.

대상과 방법 본 연구에서는 6년 동안 시행된 2633건의 간동맥 화학 색전술에 대해 후향적으로 분석하였다. 그중 시술 직후에 촬영한 cone beam CT에서 담낭에 색전 물질이 남아 있는 120명을 선택하여 급성 담낭염의 발생률과 위험인자에 대해 분석하였다.

결과 수술적 혹은 중재적 치료를 필요로 하는 담낭염의 전체 발생률은 0.45%였다. 색전 물질이 남아 있는 환자들 중에서는 10%에서 담낭염이 발생했다. 담낭염이 발생한 12명 중 8명은 담낭동맥의 색전술을 받은 환자들이었다.

결론 대부분의 담낭의 색전물질 침적은 추가적인 치료를 필요로 하지 않고 호전되지만, 담낭동맥의 색전술을 받은 경우에는 담낭염의 발생률이 높아 면밀한 모니터링이 필요하다.

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