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Incidence and Consequence of Nontarget Embolization Following Bland Hepatic Arterial Embolization

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Abstract

Purpose Estimate the incidence of nontarget embolization (NTE) as identified on immediate post-hepatic artery embolization CT.

Materials and Methods Two hundred hepatic embolizations performed with particles alone (bland embolization) in 147 patients between August 16, 2013 and August 26, 2014 with immediate post-procedure CT were retrospectively reviewed. Arterial anatomy, vessels treated, imaging findings of NTE, patient demographics, length of hospital stay following embolization, and procedure-related complications were recorded. The data were analyzed using two-sided *t*-tests and chi-squared tests.

Results Evidence of NTE was seen on post-procedure CT in 64 of 200 cases (64/200, 32%). Six organs were affected, with 69 discrete sites in 64 patients. The majority (49/69, 71.0%) involved the gallbladder. The mean length of hospital stay (LOS) for patients with and without NTE was 2.9 ± 1.5 nights (range 1–7) and 2.9 ± 2.3 nights (range 0–21), respectively ($P = 0.81$). NTE was more common following embolization of replaced or accessory hepatic vessels. There were three complications in the NTE group (3/64, 4.7%) following the embolization procedure, one of which was cholecystitis directly related to NTE. The other two were one incidence each of contrast-induced nephropathy and pneumonia. In the group without NTE, seven complications occurred (7/136, 5.1%, $P = 0.889$), including one death resulting from hepatic failure, two gastrointestinal bleeds, two hepatic abscesses, flash pulmonary edema, and pancreatitis.

Conclusion Unanticipated NTE is not uncommon after bland hepatic artery embolization, particularly after treating accessory or replaced vessels, but does not increase complications or LOS.

Level of Evidence Level 2b, Retrospective Cohort.

Keywords Hepatic malignancy · Embolization · Complication

Introduction

When confined to the liver, unresectable primary and metastatic tumors may be treated with transarterial therapy, including hepatic artery embolization (HAE), chemoembolization using either conventional TACE (cTACE) or drug-eluting beads (DEB-TACE), and radioembolization (TARE). All have an acceptable safety profile, and each has its associated procedural and peri-procedural complications [1]. One potential complication occurs when the embolic particle travels outside of the desired treatment zone, termed nontarget embolization (NTE). We began performing HAE in rooms with integrated multidetector CT scanners in 2008. The value of immediate CT after HAE in predicting response to treatment based on retention of contrast within the target tumor had been demonstrated

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[2], as seen with lipiodol [3]. We observed operator unanticipated extrahepatic deposition of contrast material following embolization which was presumably secondary to NTE. Clinical sequelae seemed rare, and we hypothesized that CT allowed for recognition of NTE that would otherwise have been clinically occult and that might not be associated with adverse clinical outcome. The purpose of this study was to estimate the incidence of NTE after HAE based on the immediate post-embolization CT and examine the effect on complication rate and length of hospital stay.

Materials and Methods

Study Design

This study was conducted under a waiver from the Institutional Review Board allowing for retrospective collection and study of the existing data. The requirement for informed consent was waived. All embolizations performed for the treatment of liver tumors in a combined angiography/CT room between August 2013 and August 2014 were retrospectively reviewed. Patients were excluded if no post-embolization CT was available for review.

Embolization Technique

HAE was performed by experienced, fellowship-trained interventional radiologists (6–29 years) as selectively as possible, typically with coaxial microcatheters. All patients received peri-procedural antibiotics: cefazolin or clindamycin and gentamicin if the patient was allergic to cefazolin. Patients with a contaminated biliary tree (drainage catheter, stent across the ampulla, or surgical biliary bypass) received cefotetan intended to provide broad-spectrum coverage that was continued while the patient was an inpatient. Those patients were then sent home on ciprofloxacin and metronidazole for 5 days.

The embolization technique has been well described [4]. Via a common femoral artery approach, angiography is performed through a diagnostic catheter with investigation of replaced or accessory hepatic arteries when present. Potential extrahepatic vessels providing tumor blood supply are studied when appropriate (right inferior phrenic or intercostal arteries, for example). CTA was not routinely performed during the study period. A microcatheter is used to catheterize vessels supplying the target tumor as selectively as possible, taking care to avoid reflux into nontarget branches. Embolization is performed with hydrophilic microspheres alone (bland embolization) until complete stasis (5 cardiac beats) is achieved in the targeted vessel(s). The microspheres are mixed with nonionic iodinated contrast material so that delivery can be monitored fluoroscopically. Typically, embolization is performed with 40–120 µm particles in hepatic vessels and 100–300 µm particles in extrahepatic vessels. Following embolization, an immediate non-contrast CT scan of the abdomen is obtained to evaluate the distribution of contrast trapped within the tumors, presumably a surrogate for embolic particle distribution and predictor of treatment effect. This concept is supported by the correlation between contrast retention and response to treatment [2].

Data Collection and Definitions

CT images were reviewed by two authors, interventional radiologists, blinded to the angiographic findings, and evaluated for NTE. If there was any uncertainty, a third interventional radiologist reviewed the images to reach consensus. Procedural specifics were obtained from the report. Sites of NTE were noted, along with hepatic arterial anatomy, embolized vessels, and other procedural details. When selective embolization of segments in both hemilivers was performed, this was recorded as “bilateral.” Single-setting bilateral lobar (whole-liver) embolization was not performed. The hospital electronic medical record was reviewed to obtain patient demographic information and hospital course details. Length of hospital stay, which was defined as the number of nights spent in the hospital, was recorded. Complications related to the embolization procedure were noted and graded according to the latest Cirse Quality Assurance Document and Standards for Classification of Complications: The Cirse Classification System [5]. Routine follow-up imaging in patients with evidence of NTE following embolization was reviewed.

Data Analysis

Excel was used to perform statistical analysis (Microsoft, Redmond, WA). Two-sided *t*-tests and chi-squared tests were employed for statistical analyses.

Results

A total of 206 hepatic embolizations were performed in a combined room during the year, and 200 procedures performed on 147 patients were included in this review. Four cases were excluded for lack of immediate post-procedure CT, one because an adrenal metastasis was embolized concurrently, and another since an extended hospital stay was for social reasons. Following 200 procedures, 64 patients had NTE on the post-procedure CT (64/200, 32%). Patient demographics are shown in Table 1 and diagnoses in Table 2. The NTE group mean age was 59.3 ± 14.5 years (range 20–85 years) and 64.1 ± 12.3 years (range

Table 1 Patient demographics

	All patients $N = 200$	Nontarget embolization $N = 68$	No nontarget embolization $N = 132$	P
Age (years)	62.5 ± 13.2	59.3 ± 14.5	64.1 ± 12.3	0.015
Sex				
M	140 (70.0%)	44 (68.8%)	96 (70.6%)	0.791
F	60 (30.0%)	20 (31.2%)	40 (29.4%)	
Laterality of embolization				
Right	102 (51.0%)	37 (57.8%)	65 (47.8%)	0.357
Left	59 (29.5%)	15 (23.4%)	44 (32.4%)	
Bilateral	39 (19.5%)	12 (18.8%)	27 (19.9%)	
Accessory, replaced, or extrahepatic vessel embolized	39 (19.5%)	20 (31.3%)	19 (14.0%)	0.004
Microcatheter used	186 (93.0%)	59 (92.2%)	127 (93.4%)	0.757
Concurrent procedure				
Ablation	43 (21.5%)	7 (10.9%)	36 (26.5%)	0.013
Biopsy	17 (8.5%)	5 (7.8%)	12 (8.8%)	0.811

Table 2 Diagnosis

Diagnosis	Cases
Hepatocellular carcinoma	99 (49.5%)
Metastatic neuroendocrine tumor	74 (37.0%)
Metastatic GIST	6 (3.0%)
Metastatic leiomyosarcoma	5 (2.5%)
Metastatic renal cell carcinoma	3 (1.5%)
Cholangiocarcinoma	3 (1.5%)
Other	10 (5.0%)

Table 3 Sites of nontarget embolization

Site	Cases
Gallbladder	49 (71.0%)
Stomach	6 (8.7%)
Right adrenal gland	6 (8.7%)
Duodenum	4 (5.8%)
Right diaphragm	2 (2.9%)
Pancreas	2 (2.9%)

31–92 years) in those without NTE ($P = 0.015$). In the NTE group, 20 patients had an accessory, replaced, or extrahepatic vessel embolized (20/64, 31.3%), compared to 19 patients (19/136, 14.0%) without NTE ($P = 0.004$). Seven patients in the NTE group had an ablation performed in the same setting immediately following the embolization (7/64, 10.9%), compared to 36 patients (36/136, 26.5%) without NTE ($P = 0.013$). Microcatheters were used in the majority of cases (186/200, 93.0%). There was no significant difference between groups with regard to sex, side of the liver embolized, whether a microcatheter was used, or whether a concurrent liver biopsy was performed. Additionally, there was no significant difference between the groups with regard to performance of lobar embolization. Fourteen of the NTE group patients underwent lobar treatment (14/64, 21.9%), compared to 33 patients (33/136, 24.3%) without NTE ($P = 0.710$).

The mean length of stay was 2.9 ± 1.5 nights (range 1–7 nights) in the NTE group and 2.9 ± 2.3 nights (range 0–21 nights) in those without NTE ($P = 0.807$).

In the 64 patients with NTE, there were a total of 69 sites of NTE, distributed between 6 different organs (Table 3). The gallbladder was the most frequently affected (49/69, 71.0%). Ten of the gallbladder NTE cases occurred after right hepatic artery lobar embolization (10/69, 14.5%). The stomach and right adrenal gland were the next most common sites; each affected six times (6/69, 8.7%). Other sites of NTE included the duodenum, right hemidiaphragm (from phrenic artery embolization), and pancreas. Representative images of NTE involving the gallbladder and stomach are shown in Figs. 1 and 2.

In the NTE group, there were three complications related to the embolization procedure (3/64, 4.7%) and seven (7/136, 5.1%) in those without NTE ($P = 0.889$) (Table 4). Complications in the NTE group included only one Grade 3 complication, a patient who developed acute ischemic cholecystitis following NTE that required cholecystostomy and ultimately cholecystectomy approximately 5 weeks later. The other two complications were Grade 2 and included one episode of contrast-induced nephropathy and one patient who developed pneumonia.

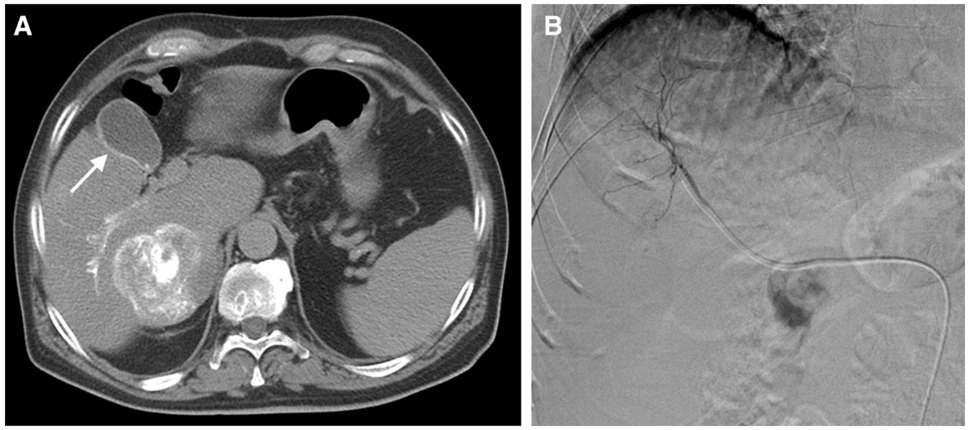

Fig. 1 **A** Nontarget embolization of the gallbladder and **B** pre-embolization DSA of the segment VIII branch right hepatic artery showing no extrahepatic perfusion

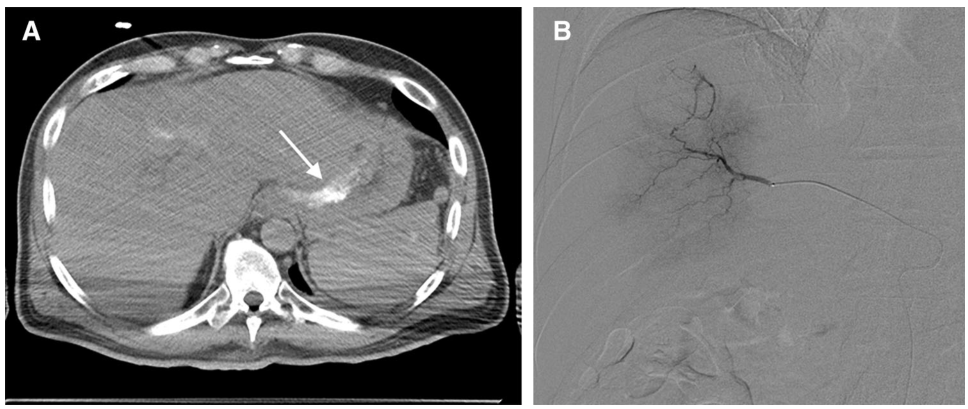

Fig. 2 **A** Nontarget embolization of the stomach and **B** pre-embolization angiogram of the accessory left hepatic artery showing no opacification of the right gastric artery

Table 4 Complications

	All patients $N = 200$	Nontarget embolization $N = 64$	No nontarget embolization $N = 136$	P
Total complications	10 (5.0%)	3 (4.7%)	7 (5.1%)	0.889
Complications requiring additional intervention	5 (2.5%)	1 (1.6%)	4 (2.9%)	0.560

Of the seven complications in those without NTE, six were Grade 3 or worse, including one death secondary to hepatic failure (Grade 6). This patient had rapid progression of tumor burden in the 4 weeks between pre-embolization imaging and the procedure, including portal venous involvement. A different treatment strategy may have been employed had this been recognized prior to the procedure. Two patients were re-admitted 8 and 9 days after discharge with gastrointestinal bleeds. Both are Grade 3 since both patients required admission. One patient underwent endoscopic treatment of a duodenal ulcer and then required gastroduodenal artery embolization for recurrent bleeding. The other had known gastric varices and was found to have gastritis on endoscopy that resolved following medical treatment. Two patients developed hepatic abscesses approximately 1 month after the embolization procedure. Both of these are Grade 3 since they required percutaneous drainage and one drain was ultimately converted to a biliary drain. Neither patient had any identifiable risk factors for post-embolization abscess. An additional Grade 3 complication occurred in a patient with atrial fibrillation who developed flash pulmonary edema and required transfer to the intensive care unit. The other complication was Grade 2: a patient who developed mild acute pancreatitis. Thus, Grade 3 or greater complications occurred in one patient in the NTE group (1/64, 1.6%) and six patients in those without NTE (6/136, 4.4%, $P = 0.306$). Five patients required an additional intervention, and one patient died.

Forty patients with evidence of their first incidence of gallbladder NTE on the immediate post-procedure CT who did not develop clinical cholecystitis had a routine follow-up CT available for review. Nineteen of these examinations showed changes in the gallbladder appearance compared to the pre-treatment CT (19/40, 47.5%), including a combination of shrunken appearance and thickened and occasionally enhancing gallbladder wall. Follow-up of all 19 patients was by review of the electronic medical record (EMR), including review of clinic notes for GI symptoms, as well as review of imaging. Median length of follow-up was 19.3 months (range 8.2–58.9 months) until last clinic visit (3 patients) or death (16 patients). During this time, none of the 19 patients developed gallbladder-related symptoms secondary to NTE following bland embolization. Four of the nineteen (21.1%) patients' gallbladders reverted to normal appearance after a median of 10.3 months (range 5.2–15.4 months).

Discussion

Nontarget embolization is a recognized complication of hepatic transarterial therapies thought to be uncommon [6]. Post-embolization cholecystitis or pancreatitis is presumably secondary to NTE, though careful review of images may reveal no angiographic evidence of NTE. Meticulous angiographic technique and a thorough understanding of hepatic arterial variants are important to reduce the incidence of NTE. Cone beam CT (CBCT), in more widespread use currently, is also likely to reduce NTE. This is of particular importance when treating extrahepatic vessels that may supply hepatic tumors [7]. Even CBCT or CTA with the catheter in the vessel to be embolized will not eliminate the risk of NTE since NTE may occur as a result of changes in flow dynamics that occur during embolization, particularly when the endpoint is stasis. These changes could result in reflux into nontarget territories and, as such, might be better prevented with the use of catheters intended to reduce reflux [8]. Evidence of NTE was seen on immediate post-procedure CT in 32% of our cases, CT being a more sensitive contrast discriminator than fluoroscopy. The fact that CT findings of NTE occur frequently in patients who do not develop clinical sequelae supports our hypothesis that NTE occurs much more frequently than suspected angiographically but is typically subclinical following HAE. While one of the 64 patients with gallbladder NTE in this series developed cholecystitis that required cholecystectomy, the overall cholecystectomy rate for the entire group was 1 in 200 (0.5%). This may not be the case when chemoembolization or radioembolization is performed. However, according to a report by Gates et al. from 1999, the day after conventional lipiodol-based TACE, CT demonstrates lipiodol in the stomach in 1% and in the gallbladder in 14% of cases. In most cases, the patients remained asymptomatic with only 1 patient of 251 (0.4%) requiring cholecystectomy [9]. They did acknowledge that gastric ulceration and gallbladder necrosis had been reported. Similarly, following 569 yttrium-90 treatments in 327 patients, a prospective evaluation of biliary complications by Atassi et al. [10] found a 0.6% rate of radiation-induced cholecystitis requiring cholecystectomy. In the entire cohort, 1.8% of the 327 patients required additional unplanned intervention related to biliary sequelae.

Patients in the NTE group were more likely to have an accessory or replaced hepatic or a non-hepatic artery treated. Patients in the group without NTE were significantly more likely to have undergone a concurrent percutaneous ablation. Ablation is added to embolization for solitary tumors < 7 cm in size, typically treated super-selectively, possibly decreasing the incidence of NTE. The gallbladder was the organ most frequently affected by NTE, accounting for 49 of the 69 sites (71.0%), not surprising as the cystic artery typically arises from one of the hepatic arteries, usually the right [11]. Despite a high incidence of NTE involving the gallbladder, only one patient developed clinical cholecystitis in the immediate post-embolization period, unfortunately requiring cholecystostomy and eventually cholecystectomy. Thus, the overall cholecystitis rate was 0.5%, 1.6% for patients in NTE group, and 2.0% for patients with gallbladder NTE.

Our complication rate of 4.7% for the NTE group was not significantly different from 5.1% for those without NTE. The overall complication rate was 5.0%, concordant with the published threshold of 5% for major complications following HAE [12]. There was a 2.5% rate of complications requiring an additional procedure (1.6% in the NTE group and 2.9% in the group without NTE). Only one patient required surgery (cholecystectomy) and that was in the NTE group (1.6% in the NTE group and 0.5% overall). Though the rates of complications requiring additional intervention in the two study groups were not significantly different, the patient requiring cholecystostomy and then cholecystectomy secondary to gallbladder NTE confirms that NTE is not without inherent risks and should be avoided. Nonetheless, 98.5% of patients who had evidence of NTE required no intervention. Though the gallbladder may demonstrate imaging changes following NTE, these are typically subclinical, and in one-fifth of cases, the imaging findings resolve.

Thorough angiographic investigation prior to embolization is critical, requiring familiarity with classic and variant anatomy. As Lewandowski et al. [11] describe, the falciform artery, supra-duodenal artery supplying the proximal duodenum and pylorus, cystic artery, and dorsal pancreatic artery are extrahepatic vessels of particular interest when performing RAE and should also be looked for during other transarterial treatments. It is important to

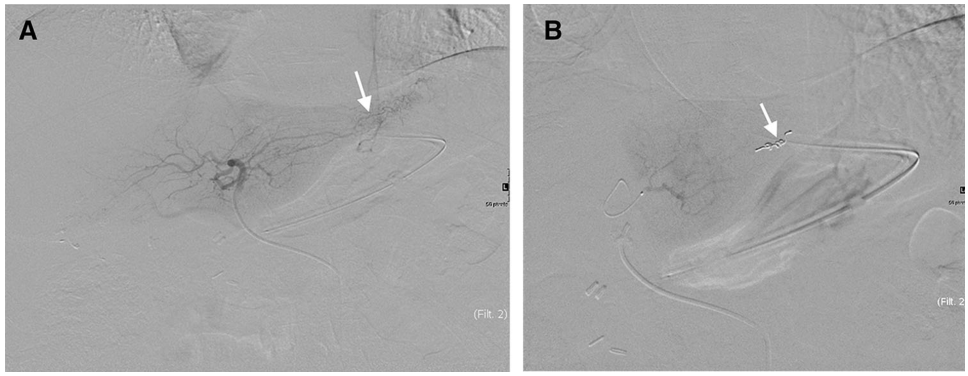

Fig. 3 **A** DSA of the left hepatic artery (LHA) showing gastric communicating branches originating from the segment II branch and **B** post-microcoil-embolization DSA of the segment II/III branch LHA demonstrates exclusion of gastric communications by microcoils

recognize the vulnerability of the cystic artery. Even adrenal arteries may originate from the celiac artery [13], although uncommon. Aberrant vasculature and unrecognized extrahepatic flow are most often encountered in the left hepatic territory, suggesting enhanced vigilance when treating left hepatic tumors [11]. Gastric branches may originate from the lateral segment left hepatic artery branches. These branches should be looked for and can be embolized with microcoils to prevent gastric NTE (Fig. 3).

Following HAE, patients may experience post-embolization syndrome (nausea, pain, and fever). In our study, the hospital stay of patients with NTE was not significantly different from those without, suggesting that the degree to which they experienced post-embolization symptoms was similar, in contrast to the findings of Leung et al. following TACE who reported a trend toward statistical significance for gallbladder NTE as a risk factor for prolonged hospital stay, reaching a *P* value of 0.05 [14]. This may be related to NTE following TACE having two components, one ischemic and the other related to cytotoxicity from the chemotherapeutic agent.

This study is limited by its retrospective nature and is intended as a cautionary report that NTE may occur more often than is appreciated angiographically. As is always the case at a tertiary referral center, it is possible that patients in either group may have presented to outside facilities with problems related to the embolization that would not have been detected by chart review. Future investigations might track patients prospectively and use pain assessment surveys in addition to monitoring for complications.

In conclusion, NTE following HAE is seen on immediate cross-sectional imaging in up to one-third of cases. NTE identified on the immediate post-procedure CT should not be a cause for immediate alarm. Rather, asymptomatic patients should be assessed on routine clinical follow-up within 1 month and encouraged to report new symptoms in the interim. Further investigation should be undertaken only if clinically warranted. This may not be the case following chemoembolization or radioembolization. NTE following bland embolization is associated with neither a prolonged hospital stay nor a higher early complication rate.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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