Superselective vs. lobar transarterial ethiodized oil-chemoembolization - occurrence and clinical significance of non-target embolization

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ABSTRACT

Purpose: To determine occurrence and clinical significance of non-target embolization (NTE) after superselective and lobar transarterial chemoembolization (TACE) with ethiodized oil.

Material and Methods: Consecutive patients who underwent ethiodized oil-based TACE from 2000 to 2013 were evaluated. NTE was defined as the presence of ethiodized oil in organs other than the liver, as seen on non-contrast CT performed day after TACE. Medical records were retrospectively reviewed for NTE symptoms.

Results: 583 TACEs were performed in 360 patients. Superselective TACE had lower overall rate of NTE than non-selective TACE: 21% (34/164) vs. 38% (160/419), p<0.001, as well as lower rates of gallbladder NTE 4% (7/164) vs. 16% (67/419), p<0.001 and stomach NTE 1% (2/164) vs. 6% (25/419). The overall incidence of NTE was 33% (194/583): 20% (114/583) lung; 13% (74/583) gallbladder; 5% (27/583) stomach; 1% (8/583) pancreas; 1% (6/583) spleen; 0.5% (3/583) duodenum; and 0.3% (2/583) adrenal. The incidence of pulmonary symptoms was 7% (32/448) and higher in patients with lung oil deposition (17/88; 19%) than those without (15/360; 4%; p<0.001). Oil deposition in pancreas was associated with clinical pancreatitis in 38% (3/8); all patients with pancreatitis were treated with a lobar approach. The length of hospital stay was longer for patients with non-target embolization: 2.6 ± 1.5 days vs. 1.9 ± 1.0 days in patients without non-target embolization, p=0.01.

Conclusion: Transarterial chemoembolization with a superselective approach results in decreased incidence of non-target embolization.

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1. Introduction

Transarterial chemoembolization (TACE) has been performed for primary and secondary hepatic malignancies for several decades, conventionally using a mixture of one or more chemotherapeutic agents emulsified in ethiodized oil (lipiodol and ethiodol) and, increasingly, drug-eluting bead preparations [1, 2]. In early studies, TACE was used to treat an entire hepatic lobe (right or left) with injection of the chemoembolization mixture into either the right or left hepatic artery, respectively (also called lobar TACE). In some institutions, lobar embolization with ethiodized oil is performed without chemotherapy with varying degree of success, purely relying on embolization of the tumor without targeted chemotherapy. More recently in the last decade, clinical practice has evolved towards increasing use of selective catheterization of segmental and sub-segmental hepatic arterial branches to deliver chemoembolic material directly into arteries feeding tumor while minimizing delivery to non-tumor liver (also called superselective TACE) [3]. Advantages of superselective TACE include greater tumor necrosis, reduced overall arterial injury, and decreased post-TACE symptoms that improve tolerability [3]. Although TACE is usually well tolerated, a number of side effects can occur, including post-TACE syndrome, which is associated with fever, abdominal pain, elevated liver function tests and nausea. One under-recognized complication of TACE is non-target embolization (NTE) in which chemoembolic material is inadvertently delivered to extrahepatic tissues. NTE is thought to occur when extrahepatic arteries arising from the intrahepatic arterial bed (e.g., right gastric or supraduodenal arteries) are unintentionally included in the chemoembolization zone or due to vascular shunting within normal hepatic or dysmorphic intratumoral vessels. The presence of non-target embolization after ethiodized oil-TACE can be easily identified on post-treatment non-contrast CT imaging given the radiopaque nature of ethiodized oil [4]. While often asymptomatic, significant complications from non-target embolization following lobar TACE have also been described [5-14]. NTE after lobar TACE has been described with incidence varying from 2 to 25% of cases [4]. However, there are few studies on the overall incidence of NTE, and in particular, examining potential differences in incidence between lobar and superselective. The purpose of this study was to determine the incidence and clinical significance of non-target chemoembolization after lobar or superselective TACE.

Material and methods

2.1 IRB

This study was HIPAA-compliant and approved by the Institutional Review Board, with waiver of informed consent due to retrospective nature of the study. Standard of care informed consent for each procedure was obtained per hospital policy.

2.2 Study population

All consecutive patients that underwent liver transarterial chemoembolization (TACE) with ethiodized oil for treatment of hepatocellular carcinoma or hepatic metastatic disease from January 2000 until September 2013 in our institution were included in the study. TACE procedures with drug-eluting beads were excluded from the study, as this procedure does not utilize ethiodized oil and a post-procedure non-enhanced CT scan is not routinely obtained.

2.3 TACE procedure

TACE procedure was performed using previously described technique [1, 15]. In summary, standard femoral arterial access was used, followed by contrast angiography of the celiac, SMA, and selective right or left hepatic arteries with 5Fr catheter. In the superselective cases, further superselective angiography was performed using a 3Fr microcatheter to delineate target vessel(s) that supply the tumor. The chemoembolic mixture (60 mg of doxorubicin mixed with 20 mL of ethiodized oil (Lipiodol 480 mgI/mL, Guerbet, Roissy CdG Cedex, France) and 10 mL of iodinated contrast (Optiray 320, Mallinckrodt, Dublin,
Ireland) was then injected until near stasis was achieved. Lobar chemoembolization was defined as administration of chemotherapy mix from the right or left hepatic artery (regardless of conventional or variant anatomic origin). Superselective chemoembolization was defined as administration of chemotherapy from a first-order or higher branch of the right or left hepatic artery treated as described in the written report.

All TACE procedures were performed by a fellowship-trained attending interventional radiologist with assistance of a vascular and interventional radiology fellow.

As per standard of care at our institution for TACE patients with ethiodized oil, all patients underwent non-contrast CT scan of the abdomen within 24 hours after the procedure for evaluation of ethiodized oil deposition in the target and non-target areas.

### 2.4 Image analysis

All CT studies and angiographic images relevant to the procedure were retrospectively re-reviewed on PACS using a standardized process by a fellowship-trained interventional and abdominal imaging radiologist (Olga R. Brook). Non-target embolization was defined as a presence of ethiodized oil (high density material not seen on the prior imaging) in the organs other than liver on the non-contrast CT scan performed within 24 hours after the TACE. Presence of vascular anatomical variants was determined based on the angiographic report and review of the angiographic images.

### 2.5 Clinical follow up

As per standard of care at our institution, patients are admitted for observation after TACE and the majority is discharged within 24 hours. Patients are observed and

### Table 1. Non-target embolization rates in patients treated with lobar vs. superselective TACE by tumor category

<table>
<thead>
<tr>
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<th>Lobar TACE</th>
<th>Superselective TACE</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>HCC</td>
<td>100/245</td>
<td>41%</td>
<td>31/149</td>
</tr>
<tr>
<td>Neuroendocrine metastases</td>
<td>38/99</td>
<td>38%</td>
<td>2/11</td>
</tr>
<tr>
<td>Other metastases</td>
<td>22/75</td>
<td>29%</td>
<td>1/4</td>
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### Table 2. Incidence of organ specific non-target embolization in lobar and superselective TACE procedures. Sites with less than 5 cases of non-target embolization (duodenum and adrenal) are not shown due to limited level of statistical evidence. In total of 194 studies there was evidence of some non-targeted embolization, however the total number of NTE episodes was higher as some patients had multiple sites of NTE

<table>
<thead>
<tr>
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<th>Lobar (n=419)</th>
<th>Superselective (n=164)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Lung</td>
<td>88</td>
<td>21%</td>
<td>26</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>67</td>
<td>16%</td>
<td>7</td>
</tr>
<tr>
<td>Stomach</td>
<td>25</td>
<td>6%</td>
<td>2</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8</td>
<td>2%</td>
<td>0</td>
</tr>
<tr>
<td>Spleen</td>
<td>6</td>
<td>1%</td>
<td>0</td>
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treated for a longer period of time if they exhibit poorly tolerated post-embolization syndrome (i.e., pain not controlled by oral medications, uncontrollable nausea, vomiting, high fever etc.) or complications such as encephalopathy, liver failure and significant vascular access complications.

Medical records for all patients included in the study were reviewed by a fellowship-trained interventional and abdominal imaging radiologist [ORB] to identify the length of post procedure hospitalization, the presence of clinical symptoms during the hospitalization, admission to intensive care unit and death.

2.6 Statistical analysis

The mean, standard deviation and range were determined for patients’ age and length of the hospital stay. Chi square test was used to assess differences between the proportions of procedures associated with non-target embolization for patients treated with lobar versus superselective approaches, as well as between tumor subgroups.

Fischer’s exact test was used to compare the rate of non-target embolization in different sites with lobar and superselective approach. Wilcoxon test was used to compare length of the hospital stay in patients with and without non-target embolization. Statistical significance was set at <0.05. Statistical analysis was carried out using Matlab (Mathworks, Natick, MA).

3. Results

360 patients were included in the study in whom 583 TACE procedures were performed during the study time-period: 419 (72%) lobar and 164 (28%) superselective TACE procedures. The average age of the patients was 61 ± 11 years (range 28-92 years) and the majority were men (n=253, 70%). TACE was performed to the right lobe of the liver (n=399, 68%) in the majority of the procedures, followed by the left lobe (n=167, 29%) and, in a small number of cases, both lobes were treated in a single session (n=17, 3%) procedures. The majority of procedures treated primary Hepatocellular Carcinoma (HCC) (n=394, 68%) and the remainder treated metastatic disease, primarily neuroendocrine tumors (n=97, 17%) and metastatic disease from a range of other primary sites (n=92, 16%). During the study time period, 14 different attendees performed the TACE procedure, with number of procedures contributed to the study by operator ranging from 11 to 121 (median=51 procedures per operator) and years of experience ranging from 4-19 years. Of note, the number of procedures contributed to the study do not fully reflect the experience of the operators as TACE procedures may have been performed prior to the study period or at another institutions.

The overall incidence of non-target embolization was 33% (n=194), with 20% (n=114) to lung, 13% (n=74) gallbladder, 5% (n=27) stomach, 1% (n=8) pancreas, 1% (n=6) spleen, 0.5% (n=3) duodenum and 0.2% (n=2) adrenal.
Superselective TACE (164 procedures) resulted in a lower proportion of non-target embolization than a lobar approach: 21% (34/164) vs. 38% (160/419), p<0.001. When the type of tumor was taken into account, patients with HCC had a significantly lower proportion of non-target embolization with the superselective approach, as compared to lobar approach (p<0.001), while similar proportion of non-target embolization were seen for metastatic disease with the lobar and superselective approaches (Table 1). However, metastatic disease was predominantly treated with the lobar approach with low number of patients in superselective group.

The proportion of procedures associated with organ-specific non-target embolization was also lower with the superselective compared to the lobar approach. However, the difference was only statistically significant only for the gallbladder (16%, 67/419 NTEs for the lobar approach vs. 4%, 7/164 NTEs for superselective approach, p<0.001) and the stomach (6%, 25/419 NTEs for the lobar approach versus 1%, 2/164 NTEs for superselective approach, p=0.01) (Table 2).

Over the last 5 years of the study, the use of superselective approach increased and the overall rate of non-target embolization decreased (Fig. 1). In a similar fashion, the rate of individual organ-specific non-target embolization has decreased over the years (Fig. 2).

The length of hospital stay was longer for patients with non-target embolization: 2.6 ± 1.5 days vs. 1.9 ± 1.0 days in patients without non-target embolization, p=0.01. Similarly, a greater proportion of patients stayed two or more days with non-target embolization than without, 50% vs. 40%, p=0.02. When we further evaluated the length of stay by organ site of non-target embolization, pancreas, lung and gallbladder were leading with 2.9, 2.8 and 2.3 days respectively, while stomach and spleen had lower stays of 2.1 and 1.5 days. This finding may reflect the higher sensitivity of the pancreas, lung and gallbladder to non-target embolization.

The proportion of procedures associated with pulmonary symptoms such as new shortness of breath or cough, was 8% (47/583). Although pulmonary symptoms were more frequent in procedures associated with lung oil deposition 24/114 (21%), they were present in 23/469 (5%) cases without lung oil deposition, (p<0.001). One patient with oil deposition in the lung died from pulmonary failure. 3/8 (38%) patients with pancreas oil deposition had clinical pancreatitis, as seen by elevated enzymes, such as lipase and amylase and clinical symptoms. All underwent procedures with lobar approach.

There was no correlation between the presence of vascular anatomical variants and non-target embolization: 63/190, 33% vs. 131/393, 33% (p=0.97). Similarly, there was no correlation between the lobe of the liver embolized and presence of the non-target embolization:
angiography with vessel tracking system [16]. Ultimately, the angiography with conventional 2D digital subtraction showed a cyst artery detection rate of 48% during TACE hepatic artery-artery shunts. In particular, these smaller vessels can often be more difficult to identify on conventional selective approach (including hepatic artery-vein or artery-artery shunts) or 2) reduced vascular shunting in large volumes of non-tumor normal liver spared with a lobar approach.

4. Discussion
Superselective approach appears to reduce the rate of non-target embolization compared to lobar TACE in our patient population, despite similar high overall rates of radiographic non-target embolization compared to existing literature [4]. Therefore, in addition to evidence that superselective TACE may offer a better therapeutic response [3], this approach is even more appealing given the potential reduction in complications from non-target embolization. Indeed, we did identify an overall increase in the length of post-procedure hospital admission after NTE, suggesting that efforts to reduce overall NTE are warranted. The lower proportion of TACE procedures associated with NTE when using the superselective approach may be due to the a number of factors: 1) exclusion of extrahepatic arteries that are known to arise from proximal portions of the right and left hepatic arteries (i.e., right gastric, supraduodenal, and falciform arteries to name a few) or 2) reduced vascular shunting in large volumes of non-tumor normal liver spared with a selective approach (including hepatic artery-vein or artery-artery shunts). In particular, these smaller vessels can often be more difficult to identify on conventional digital subtraction angiography, though may be increasingly detected using advanced imaging techniques available in newer angiography suites (such as cone-beam CT with multiplanar/3D reconstructions and vessel tracking software). For example, Wang et al. demonstrated a cystic artery detection rate of 48% during TACE hepatic angiography with conventional 2D digital subtraction angiography as compared to 100% with three dimensional angiography with vessel tracking system [16]. Ultimately, we acknowledge that in many cases of multifocal intrahepatic tumor, lobar TACE will be required, and that it is possible that certain low-grade non-target embolization may be radiographically visible while still safely tolerated. However, in some instances there may be significant complications (particularly with pulmonary and pancreatic NTE) that warrant a superselective approach, or in the very least, careful positioning of the microcatheter in such a manner as to minimize the amount of non-target embolization.

Our results show the rate of non-target embolization to the lung to be similar to that previously reported: 20% to the lung in our study group vs. 25% [4]. However other studies showed varied rates of pulmonary non-target embolization: 2% (6/336 patients) by Chung et al. [15], 9% (20/219 patients) by Wu et al. [17]. The variable proportion of procedures with non-target embolization are likely due to patients, tumor and procedure characteristics [17], timing of the non-contrast CT scan and interpretation of CT scan. In our study only 24% of the non-target embolization cases were reported by attending abdominal diagnostic radiologists on the official report of the non-contrast, Post TACE imaging.

The clinical impact of the ethiodized oil deposition in the lungs is likely to be significant, although it is hard to accurately determine this in a retrospective study. However, we did find that patients with pulmonary ethiodized oil deposition had longer hospital stays and one patient expired from pulmonary failure. These findings are in agreement with prior literature [13, 15] that reports acute respiratory distress syndrome (ARDS) from pulmonary ethiodized oil deposition to be a rare, but life threatening condition.

Gallbladder non-target embolization had a relatively high proportion of 13%, however none of our patients had required surgery. This is in agreement with prior literature that shows up to 53% incidence of gallbladder non-target embolization but with no need for surgery [7,12,18].

Gastric non-target embolization was detected in 5% and duodenal non-target embolization was seen in 0.5% of our study population. Gastric and duodenal lesions after TACE has been reported previously with varying degree of severity, from 0.3% [8], 4% [19] to 45% [6]. Importantly, the gastric non-target embolization was significantly decreased with superselective compared to the lobar approach.
Fig. 5. Non-target embolization of the stomach. Depiction of the high density material of the dependent as well as non-dependent mucosal lining of the stomach (white arrows) on the CT performed without oral or intravenous contrast is seen in the non-target embolization of the stomach (1). When stomach is collapsed hyperdense gastric ruga (white arrows) are prominent (2), especially on the coronal reconstructions (3). At times non-target embolization is associated with wall edema (double arrow) (4).
Pancreatic non-target embolization had a very low incidence of 1% with 8 patients. This is lower than the previously reported rate of 15% [9]. However 38% of them had clinical pancreatitis. We have not encountered any pancreatic non-target embolization with a superselective approach. It is important to avoid non-target embolization to the pancreas and also evaluate pancreatic enzymes to differentiate from the pain of post-embolization syndrome in patients with pancreatic non-target embolization on CT, particularly given differences in clinical management - pancreatitis requires NPO, IV hydration, potentially antibiotics, etc.

Finally, we have identified significant underreporting (in over 75% of cases) of the presence of non-target embolization on non-contrast CT studies performed within 24 hours after TACE by diagnostic radiologists. Potential explanations for this include a lack of specific training on the appearance, potential sites, and clinical significance of extrahepatic ethiodized oil presence. Early identification and reporting of non-target embolization is crucial as it may guide early clinical management in symptomatic patients (e.g., conservative medical management for symptomatic acute ischemic cholecystitis from non-target gallbladder embolization) or for NTE in specific sites (e.g., steroid administration in patients with NTE to the lung or medical management with hydration and IV nutrition in patients with NTE-induced pancreatitis). This also underscores the need for post-procedure imaging review by the performing interventional radiologist, who can match imaging findings with intra-procedural imaging, procedure technical details, and follow-up clinical assessment of the patient. Finally, this may explain wide variations in reported incidence of non-target embolization in the literature (from 2-25%) if some studies relied on review of imaging reports.

Our study has a number of limitations. First, our study was performed in the retrospective manner, which may have introduced reporting bias. However, our hospital has a robust online medical records and PACS system that allow obtaining accurate data. Second, as the study was performed over a long period (14 years), various operators may have used slightly different techniques during embolization. In particular, a decision by the operator to perform TACE regardless of whether extrahepatic arterial supply (such as a right gastric, cystic, or supraduodenal arteries) was identified on angiography (and therefore favor treatment even with likely non-target embolization) is difficult to assess in this retrospec-

Fig. 6. Non-target embolization to the gallbladder. Axial non-contrast CT image obtained without oral or intravenous contrast showed high density material in the mucosa (white arrow) of the gallbladder (1). Care should be taken to exclude porcelain gallbladder by comparing with prior studies. In some cases non-target embolization to the gallbladder is accompanied by the wall edema (double arrow) (2)
Fig. 7. Axial non-contrast CT image obtained without oral or intravenous contrast shows non-target embolization of the head of the pancreas (blue arrow) and duodenum (white arrow), as well as appropriate deposition of the ethiodized oil in the right lobe of the liver after lobar TACE.

Fig. 8. Axial non-contrast CT image obtained without oral or intravenous contrast shows non-target embolization of the spleen with striated high density areas in the splenic parenchyma (white arrows).

tive study. Third, it is possible that the documented presence of non-target embolization may have prompted a longer hospital stay due to the concerns of potentially clinically important complications, while not actually representing presence of clinical symptoms. However, as non-target embolization was officially reported in a minority of cases, and as the interventional radiology service regularly reviews all such imaging but makes recommendations on extended hospital stay based upon clinical assessment, we feel that this is less likely to have contributed to this bias. We have not evaluated impact of lobar vs. superselective embolization on the procedural radiation exposure. It is safe to assume that getting into a specific small vessel that supplies only tumor may take longer and will require more radiation exposure than lobar approach. However, as these are cancer patients with overall poor long term prognosis, long term effects of radiation are likely negligible. None of our patients exceeded radiation exposure limits for a single procedure. Additional bias is in a single reviewer evaluating the images. However, the reviewer is fellowship-trained both in vascular and interventional radiology, as well as in abdominal imaging. Furthermore, even though the total number of patients is relatively large, the number of patients in subgroups is not as high. However, our study has the largest reported group of patients evaluated for NTE. Finally, this is a single institution study which may limit the applicability of these rates to broader practice, though our overall rates are consistent with existing literature.

In conclusion, in our study superselective transarterial chemoembolization results in a lower proportion of non-target embolization than the lobar approach. The presence of non-target embolization is associated with a longer hospital stay. Careful attention for non-target embolization on follow-up imaging, and awareness of specific clinical implications is required.

Conflict of interest:
This study was supported by educational Guerbet grant.
REFERENCES


READY-MADE CITATION