Original Article

Clinical impact and potential utility of non-enhanced computed tomography performed immediately after transarterial chemoembolization for hepatocellular carcinoma

Mi Young Kim[1], Subin Heo[2], Sejin Choi[2], Chong Hyun Suh[2]^, Eun Seoung Lee[1]^, Hyo Jung Park[2]^, Kyung Won Kim[2]^

[1]Department of Radiology, Asan Medical Institute of Convergence Science and Technology (AMIST), Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea

Contributions: (I) Conception and design: HJ Park, KW Kim; (II) Administrative support: HJ Park, KW Kim; (III) Provision of study materials or patients: HJ Park, KW Kim; (IV) Collection and assembly of data: MY Kim, HJ Park; (V) Data analysis and interpretation: MY Kim, S Heo, S Choi, KW Kim; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hyo Jung Park, MD, PhD; Kyung Won Kim, MD, PhD. Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-gu, 05505, Seoul, Republic of Korea. Email: hazelpark.radiology@amc.seoul.kr; medimash@gmail.com.

Background: Intratumoral lipiodol deposition following transarterial chemoembolization (TACE) is associated with the prognosis of hepatocellular carcinoma (HCC) patients. However, there is insufficient evidence regarding the actual clinical significance of the imaging tests conducted to evaluate the lipiodol uptake after TACE. This study evaluates the clinical impact and potential utility of performing immediate post-TACE non-enhanced computed tomography (NECT) on the treatment of HCC.

Methods: This retrospective study at a tertiary referral center included patients undergoing their first session of conventional TACE for initial treatment of HCC from November 2021 to December 2022 with available immediate post-TACE NECT. Patients were categorized based on lipiodol uptake into Cohorts A (incomplete uptake with additional treatment before the first follow-up 1 month after TACE), B incomplete uptake without additional treatment before first follow-up), and C (complete uptake). Survival curves for the time to progression (TTP) were estimated using the Kaplan-Meier method and were compared by using the log-rank test.

Results: Out of 189 patients, 58 (29.6%) showed incomplete lipiodol uptake; 2 in Cohort A and 56 in Cohort B. Cohort C included 131 patients (69.3%). Cohort B had the highest rate of residual viable tumor (48.2%) 1 month after TACE, compared to the other cohorts (0% in Cohort A and 32.1% in Cohort C). The median TTP of Cohort B was 7.9 months [95% confidence interval (CI): 4.6–15.7 months], significantly shorter than the 15.4 months (95% CI: 10.9–20.9 months) for Cohort C (P=0.03). During follow-up, no progression occurred in Cohort A.

Conclusions: Assessment of lipiodol uptake by performing immediate post-TACE NECT can stratify HCC patients and facilitate early prediction of therapeutic response. Identifying suboptimal lipiodol uptake immediately after TACE can aid future treatment adjustments and potentially improving oncologic outcomes.

Keywords: Hepatocellular carcinoma (HCC); chemoembolization; lipiodol; computed tomography; time to progression (TTP)

^ ORCID: Chong Hyun Suh, 0000-0002-4737-0530; Eun Seoung Lee, 0000-0001-9996-7083; Hyo Jung Park, 0000-0002-2364-9940; Kyung Won Kim, 0000-0002-1532-5970.

Submitted Feb 25, 2024. Accepted for publication May 24, 2024. Published online Jun 27, 2024.
doi: 10.21037/jgo-24-134
View this article at: https://dx.doi.org/10.21037/jgo-24-134

Introduction

Transarterial chemoembolization (TACE) is the standard treatment in patients with intermediate-stage hepatocellular carcinoma (HCC) (1-4). TACE can also be utilized for patients with early stage HCC, who are ineligible for surgery or ablation (5), and it also serves as a bridging treatment to liver transplantation or to downstage patients to become eligible for surgery (3). Given the wide variation in response to the initial TACE among patients, with a median overall survival (OS) ranging from 13 to 43 months (6-8), timely treatment adjustments are crucial for those showing refractoriness to initial TACE to prevent further disease progression and prolong survival (9). A reliable method to predict therapeutic response after TACE would aid clinical decision-making and adjustment of future treatment strategies (10).

Although not standard practice, immediate post-TACE non-enhanced CT (NECT) has occasionally been performed at our institution to promptly evaluate the procedure's success and potentially assess the need for early additional treatment. Using a non-enhanced scan with low radiation allows for assessment of intratumoral lipiodol retention more accurately than what can be seen under fluoroscopy guidance. The degree of intratumoral lipiodol deposition has been shown to correlate with prognosis after TACE (11-13). In previous studies, although CT images have been used to assess intratumoral lipiodol uptake, patients with hepatic malignancies other than HCC were included (11), had small sample sizes (<60 patients) (11-13), or utilized contrast-enhanced CT performed 4–6 weeks after TACE to evaluate lipiodol retention (12,13), thus not reflecting the immediate state of lipiodol retention after the procedure. Additionally, evidence regarding how immediate NECT should be interpreted and utilized, as well as its actual impact on management, is scarce. The objective of this study was to evaluate the actual clinical impact and potential utility of NECT performed immediately after TACE for the treatment of HCC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-134/rc).

Highlight box

Key findings

- Non-enhanced computed tomography (NECT)-based assessment of lipiodol uptake immediately after transarterial chemoembolization (TACE) for the treatment of hepatocellular carcinoma (HCC) can facilitate early prediction of therapeutic response. Identifying incomplete lipiodol uptake on immediate NECT can inform prompt adjustments to future treatment plans.

What is known and what is new?

- The response to the TACE varies greatly from patient to patient. A reliable method that predicts therapeutic response after the TACE would be beneficial in clinical decision-making.
- Patients with incomplete tumoral lipiodol uptake on immediate post-TACE NECT and without prompt additional treatment showed a higher rate of viable tumor 1 month after TACE and shorter time to progression compared to those with complete lipiodol uptake.

What is the implication, and what should change now?

- Identifying incomplete lipiodol uptake immediately after TACE suggests that acting swiftly with additional treatment could be more beneficial than awaiting the routinely scheduled tumor assessment 1-month post-procedure.

Methods

Patient selection

This single-center retrospective study was approved by the institutional review board of the Asan Medical Center (No. 2023-0204) and informed consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). From November 2021 to December 2022, consecutive patients who had their first session of conventional TACE as the initial treatment for HCC were identified from the medical database of Radiology and Gastroenterology departments of Asan Medical Center. Inclusion criteria were (I) at least one measurable lesion 1 cm or larger, (II) no extrahepatic metastasis, and (III) available immediate post-TACE NECT performed on the same day or within one day after TACE. Patients must have had at least one index lesion measuring 1 cm or larger in diameter. This lesion should exhibit the typical HCC features of arterial

phase hyperenhancement followed by washout in the portal venous phase, as observed in a dynamic scan. In these patients, the lesions were confirmed as HCC according to the American Association for the Study of Liver Diseases or EASL guidelines (1,3). Target lesions were characterized as distinctly nodular (not infiltrative), allowing for accurate measurement (14). Patients with more than five HCCs were excluded because the multiplicity of lesions could impede the precise identification of local progression in individual tumors (13,15-17). Patients who were lost to follow-up after the first session of TACE were also excluded. Among the eligible patients, those who received NECT immediately after TACE constituted the final study population.

Data collection

Before their initial TACE, patients had laboratory tests, including a liver function test, serum alpha-fetoprotein (AFP), and hepatitis serologic tests. They also underwent dynamic liver CT or MRI and were evaluated for the presence of metastatic lesion. A subset of the patients underwent NECT immediately after TACE to assess whether lipiodol had been deposited in the index lesion(s), at the discretion of each treating physician. For patients who underwent immediate post-TACE NECT, whether there was prompt action regarding the results of the NECT scans was reviewed.

Routinely, the first follow-up dynamic liver CT or MRI was conducted 1 month after the TACE to assess the response to treatment. The assessment of the treatment response was performed in accordance with mRECIST criteria (14). Residual viable HCC is considered present if any residual tumor portion demonstrates unequivocal arterial hyperenhancement and washout on dynamic imaging, irrespective of size.

TACE procedure

The TACE procedure performed in our institution has been described previously (18,19). All TACE procedures were performed by eight interventional radiologists with 10–35 years of clinical experience. Both superior mesenteric and common hepatic arteriography were conducted to evaluate the overall arterial anatomy, tumor burden, and portal vein patency. Cisplatin (Cisplan; Dong-A Pharmaceutical, Seosan, Korea) was then administered into the lobar hepatic artery for 15 minutes without adding embolic particles. The dosage of cisplatin was 2 mg/kg of body weight. After selectively catheterizing the feeding artery with a microcatheter, an emulsion of 2–20 mL of iodized oil (Lipiodol Ultra-Fluide; Laboratoires Guerbet, Aulnay-sous-Bois, France) and cisplatin in a 1:1 ratio was injected into the feeding arteries. The feeder arteries were then embolized with 1-mm absorbable gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, Mich) until arterial flow stasis was achieved. Repeated chemoembolization was indicated every 6–8 weeks if sequential dynamic CT scans showed residual viable tumor without evidence of extrahepatic metastases, major portal vein invasion, or liver function deterioration. Each patient provided informed consent for chemoembolization before the procedure.

Assessment of lipiodol uptake on immediate NECT

Lipiodol uptake was evaluated using NECT performed immediately after the TACE session. To ensure comprehensive examination of the tumor, these images were meticulously compared with dynamic CT or MRI scans obtained before TACE. Lipiodol uptake was assessed by identifying the hyperattenuation of the tumor compared to the surrounding liver parenchyma. The pattern of lipiodol retention could manifest as either homogeneous or heterogeneous. Complete uptake was defined when the entire tumor nodule appeared hyperattenuating compared to the surrounding liver parenchyma. In contrast, uptake was deemed incomplete if only partial hyperattenuation was observed. All immediate NECT scans were retrospectively reviewed by two reviewers (M.Y.K., with 3 years of experience in imaging analysis and H.J.P., with 10 years of clinical experience in abdominal imaging interpretation) independently. They were blinded to the clinical characteristics and follow-up imaging results after TACE. In case of disagreement, a third reviewer (K.W.K., with more than 15 years of clinical experience in abdominal imaging) was involved to reach a final consensus. *Figure 1* illustrates schematic examples of the lipiodol retention patterns.

Patients were divided according to the degree of lipiodol uptake on NECT and whether prompt management had occurred prior to the next follow-up dynamic CT or MRI; patients were categorized as Cohort A (incomplete lipiodol uptake and any additional treatment was performed prior to the next follow-up), Cohort B (incomplete lipiodol uptake but there was no management prior to the next follow-up),

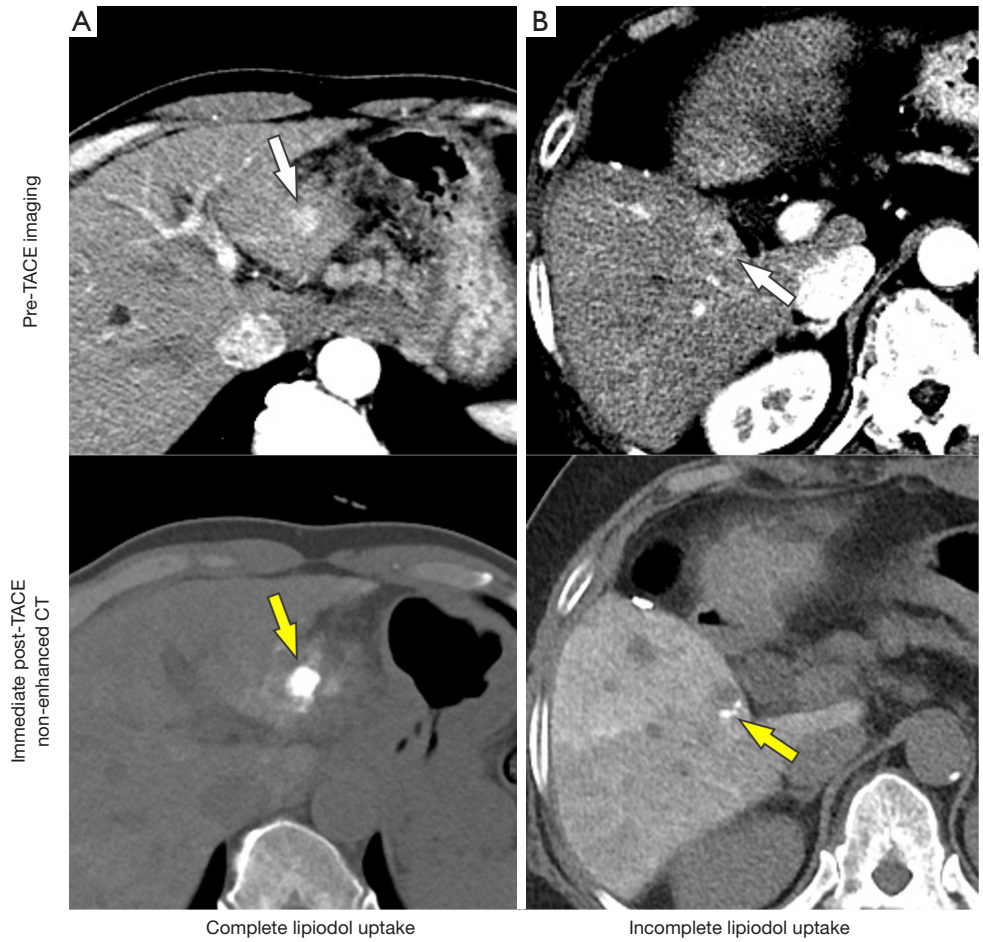

Figure 1 Schematic representation of lipiodol uptake on NECT after TACE. White arrows indicate HCC demonstrating arterial hyperenhancement on arterial phase imaging before TACE, while yellow arrows highlight lipiodol retention on immediate post-TACE NECT. (A) The tumor exhibits complete and homogeneous lipiodol retention on post-TACE NECT. (B) Only dot-like lipiodol uptake is observed at the tumor's periphery, suggesting incomplete lipiodol uptake. TACE, transarterial chemoembolization; CT, computed tomography; NECT, non-enhanced CT; HCC, hepatocellular carcinoma.

and Cohort C (complete lipiodol uptake) (*Figure 2*).

Statistical analysis

Data were expressed as means with standard deviations and ranges, or number of cases with frequencies, as appropriate. A Fisher exact test or a Chi-square test was used to compare frequencies while the Student's *t*-test or Mann-Whitney test was used to compare continuous variables based on data distribution.

Survival curves were estimated with the Kaplan-Meier method and were compared by using the log-rank test. OS was calculated from the day of initial TACE to the day of death, regardless of the cause (20). There were no procedure-related deaths within 1 month of the initial TACE. Time to progression (TTP) was calculated using radiologic progression based on mRECIST, with deaths during follow-up without evidence of radiologic progression being censored (20). Patients who underwent 2nd line treatment(s) like ablation was censored at the point of treatment. Data was analyzed by using SPSS software version 20.0 (SPSS Inc., USA). Two-sided P values <0.05

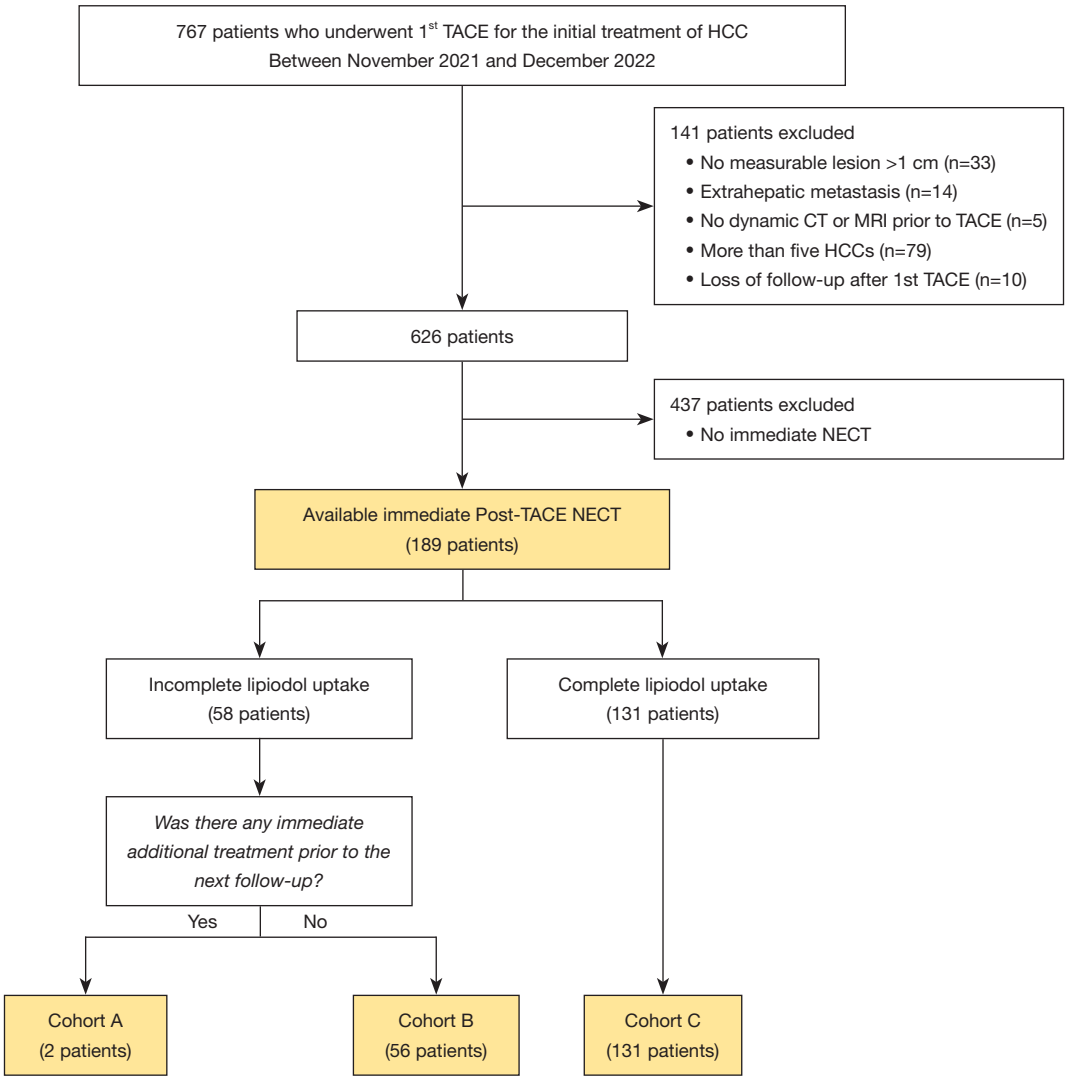

Figure 2 Patient recruitment and classification process. Cohort A, patients with incomplete lipiodol uptake on NECT immediately after TACE who underwent additional treatment before the follow-up; Cohort B, patients with incomplete lipiodol uptake on NECT immediately after TACE without additional treatment before follow-up; Cohort C, patients with complete lipiodol uptake on NECT performed immediately after TACE. TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; NECT, non-enhanced CT.

were considered significant.

Results

Patients characteristics

Patient recruitment process was shown in *Figure 2*. Among the 767 patients who underwent 1st TACE for the initial treatment of HCC, 141 patients were excluded (no measurable lesion >1 cm in 33 patients, extrahepatic metastasis in 14 patients, no dynamic CT or MRI prior to TACE in 5 patients, more than five HCCs in 79 patients, and early follow-up loss after 1st TACE in 10 patients). Among the 626 patients, 437 patients who had no immediate NECT were excluded. The baseline characteristics of 189 enrolled patients are summarized in *Table 1*. Hepatitis B was present in 108 patients (57.1%), hepatitis C in 19 (10.1%), alcohol-induced liver disease in 34 (18.0%), non-alcoholic steatohepatitis in 9 patients

Table 1 Characteristics of the patients

Characteristics	All patients (N=189)	Cohort B (N=56)	Cohort C (N=131)	P value
Age (years)	65 [58–73]	63 [58–70]	67 [58–73]	0.78
Sex				0.16
Men	143 (75.7)	46 (82.1)	95 (72.5)	
Women	46 (24.3)	10 (17.9)	36 (27.5)	
Underlying liver disease				0.98
Hepatitis B	108 (57.1)	32 (57.1)	75 (57.3)	
Alcohol-induced	34 (18.0)	11 (19.6)	23 (17.6)	
Hepatitis C	19 (10.1)	6 (10.7)	13 (9.9)	
Nonalcoholic steatohepatitis	9 (4.8)	2 (3.6)	7 (5.3)	
Others*	19 (10.1)	5 (8.9)	13 (9.9)	
Liver cirrhosis				0.76
Present	160 (84.7)	48 (85.7)	110 (84.0)	
Absent	29 (15.3)	8 (14.3)	21 (16.0)	
Child-Pugh class				0.43
A	156 (82.5)	48 (85.7)	106 (80.9)	
B	33 (17.5)	8 (14.3)	25 (19.1)	
Laboratory findings				
Aspartate aminotransferase (IU/mL)	32 [23–47]	33 [24–50]	32 [23–44]	0.98
Alanine aminotransferase (IU/mL)	24 [17–35]	23 [17–37]	24 [16–34]	0.99
Platelet count (10^9/L)	125 [79–174]	138 [81–180]	124 [79–173]	0.43
Total bilirubin (mg/dL)	0.6 [0.5–0.8]	0.6 [0.4–0.8]	0.6 [0.5–0.8]	0.35
Prothrombin time (INR)	1.1 [1.0–1.2]	1.1 [0.9–1.2]	1.1 [1.0–1.2]	0.74
Albumin (g/dL)	3.6 [3.2–3.9]	3.6 [3.2–3.9]	3.6 [3.2–3.9]	0.39
Alpha-fetoprotein (ng/mL)	7.4 [3.2–41.7]	8.6 [2.8–54.6]	6.0 [3.2–24.4]	0.66
Tumor size (cm)†	3.1 [1.0–20.0]	3.6 [1.0–20.0]	2.2 [1.7–3.3]	0.12
Number of tumors†	1.5 [1–2]	1.7 [1–5]	1.4 [1–5]	0.09
1	125 (66.1)	30 (53.6)	93 (71.0)	
2	47 (24.9)	17 (30.4)	30 (22.9)	
3–5	17 (9.0)	9 (16.1)	8 (6.1)	

Data are reported as number, n (%), or median [interquartile range]. *, included primary biliary cirrhosis, autoimmune hepatitis, and cryptogenic; †, mean (range). P values result from comparisons between Cohort B (patients with incomplete lipiodol uptake on non-enhanced computed tomography immediately after transarterial chemoembolization without additional treatment before follow-up) and Cohort C (patients with complete lipiodol uptake on non-enhanced computed tomography performed immediately after transarterial chemoembolization).

Table 2 Rate of residual viable HCC on the first follow-up imaging

Residual viable HCC one-month after TACE	All patients (N=189)	Cohort A (N=2)	Cohort B (N=56)	Cohort C (N=131)
Yes	69 (36.5)	0 (0.0)	27 (48.2)	42 (32.1)
No	120 (63.5)	2 (100.0)	29 (51.8)	89 (67.9)

Data are reported as n (%). Cohort A, patients with incomplete lipiodol uptake on non-enhanced computed tomography immediately after TACE who underwent additional treatment before the follow-up; Cohort B, patients with incomplete lipiodol uptake on non-enhanced computed tomography immediately after TACE without additional treatment before follow-up; Cohort C, patients with complete lipiodol uptake on non-enhanced computed tomography performed immediately after TACE. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

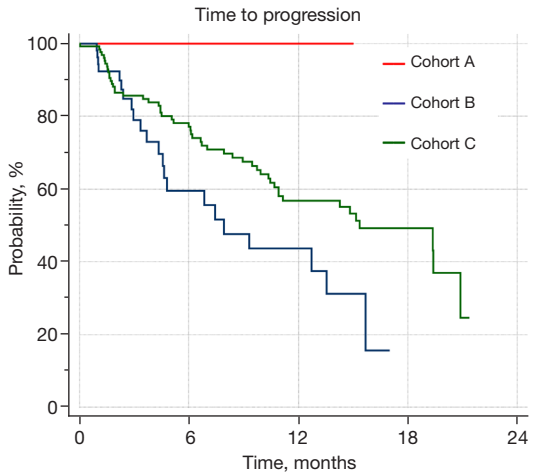

Figure 3 Kaplan-Meier curves of TTP of each group. TTP in Cohort A (red, patients with incomplete lipiodol uptake on non-enhanced computed tomography immediately after transarterial chemoembolization who underwent additional treatment before the follow-up), Cohort B (blue, patients with incomplete lipiodol uptake on non-enhanced computed tomography immediately after transarterial chemoembolization without additional treatment before follow-up), and Cohort C (green, patients with complete lipiodol uptake on non-enhanced computed tomography immediately after transarterial chemoembolization). The median TTP of Cohort B was 7.9 months (95% confidence interval: 4.6–15.7 months), significantly shorter than that of Cohort C (median, 15.4 months; 95% confidence interval: 10.9–20.9 months; P=0.03). TTP, time to progression.

(4.8%), and others (n=19, 10.1%). Among them, 160 (84.7%) had cirrhosis. Most patients were Child-Pugh class A (156 patients, 82.5%), and the remaining 33 patients were Child-Pugh class B (17.5%). Patients had 1.5 HCCs in average [range, 1–5] and the mean size of HCCs was 3.1± 2.6 cm (range, 1.0–20.0 cm). HCC was solitary in 75 patients (39.7%). All patients had dynamic imaging within 7 days of TACE.

Lipiodol uptake after TACE

Among the 189 patients, 58 patients (30.7%) had incomplete lipiodol uptake in the tumor on NECT. Two patients with incomplete lipiodol uptake received immediate additional treatment for the tumor within 7 days (Cohort A, 1.1%); one was treated with radiofrequency ablation, and the other was treated with radiation therapy. Fifty-six patients, despite having incomplete lipiodol uptake, did not receive any additional treatment before the next follow-up (Cohort B, 29.6%). There were 131 patients who demonstrated complete lipiodol uptake in their tumors (Cohort C, 69.3%).

Outcome on follow-up

The median follow-up was 17.2 months (IQR, 14.4–19.7 months; full range, 2.3–23.8 months). The median TTP was 14.8 months [95% confidence interval (CI): 11.5–16.4 months]. A total of 74 patients (39.2%) experienced progression. Twelve patients (6.3%) died, and the median OS was not reached. Sixty-nine (36.5%) showed evidence of residual viable HCC 1-month after TACE (*Table 2*).

Of the 56 patients in Cohort B, 27 (48.2%) had a residual viable tumor 1-month after TACE, while in Cohort C, 42 out of 131 patients (32.1%) showed residual viability 1-month after TACE. The rate of residual viable HCC in Cohort B was significantly higher than in Cohort C (P=0.04). In Cohort A (n=2), both patients had no evidence of residual viable HCC 1-month after TACE.

The TTPs of each cohort are shown in *Figure 3* and *Table 3*. Patients from Cohort B experienced tumor progression in 22 out of 56 patients (39.3%), with a median

TTP of 7.9 months (95% CI: 4.6–15.7 months) after TACE (*Figure 4*). In Cohort C, 52 out of 131 patients (39.7%) experienced tumor progression, with a median TTP of 15.4 months (95% CI: 10.9–20.9 months) significantly longer than that observed in Cohort B (P=0.03). No progression was observed in the two patients from Cohort A, with follow-ups of 18.8 and 15.0 months, respectively (*Figure 5*).

Table 3 TTP of each cohort

Patient groups	Median TTP (months)	P value (*vs.* Cohort B)
All patients	14.8 (10.4–19.4)	–
Cohort A	Not reached	–
Cohort B	7.9 (4.6–15.7)	–
Cohort C	15.4 (10.9–20.9)	0.03

Data in the parentheses are 95% confidence interval. Cohort A, patients with incomplete lipiodol uptake on non-enhanced computed tomography immediately after transarterial chemoembolization who underwent additional treatment before the follow-up; Cohort B, patients with incomplete lipiodol uptake on non-enhanced computed tomography immediately after transarterial chemoembolization without additional treatment before follow-up; Cohort C, patients with complete lipiodol uptake on non-enhanced computed tomography performed immediately after transarterial chemoembolization. TTP, time to progression.

Analyses of target tumor TTP and hepatic TTP are presented in Figure S1; similar to the overall TTP, the target TTP and hepatic TTP both showed significant differences between Cohort B and Cohort C.

Discrepancy between retrospective review & real-time interpretation of immediate post-TACE NECT

Among the 58 patients with incomplete tumoral lipiodol uptake on immediate post-TACE NECT, the degree of lipiodol uptake was not detailed in the NECT reports of 12 patients (20.7%; merely mentioned as 'lipiodol uptake present'), while in the reports of 46 patients, it was described variably (i.e., 'partial', 'incomplete', 'faint', or 'uncertain', 'mild, and 'with defect'). In Cohort C, comprising 131 patients, 34 NECT reports (26.0%) lacked a description of the degree of lipiodol uptake (merely mentioned as 'lipiodol uptake present'). The reports of 79 patients mentioned 'compact lipiodol uptake', while 18 patients were described using variable terms ('dense', 'well', 'good', 'diffuse', and 'successful', or others).

Discussion

Our study showed that assessing lipiodol uptake using

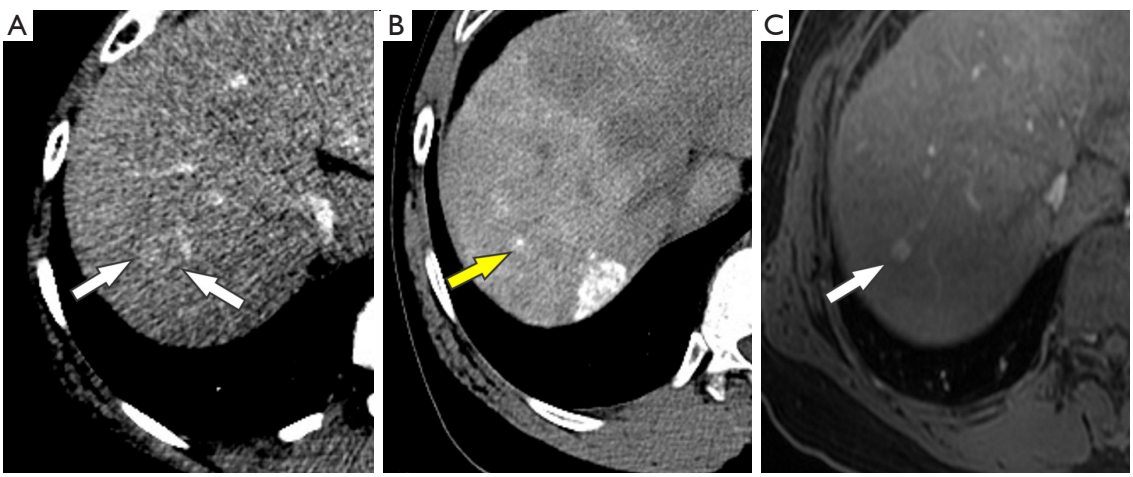

Figure 4 A case of Cohort B. Cohort B represents patients with incomplete lipiodol uptake on NECT immediately after TACE without additional treatment before follow-up). (A) CT arterial phase imaging taken before TACE displays a 2.0-cm nodular arterial hyperenhancing HCC in liver segment VII (white arrows). (B) Post-TACE NECT shows only dot-like retention of lipiodol in the tumor (yellow arrow), suggesting incomplete lipiodol uptake. The patient underwent follow-up imaging without additional treatment. (C) One month after TACE, the first follow-up MRI arterial phase imaging reveals a persistent arterial hyperenhancing nodule (white arrow) suggestive of residual viable HCC. This patient experienced tumor progression 4.6 months after the initial TACE. NECT, non-enhanced computed tomography; TACE, transarterial chemoembolization; CT, computed tomography; HCC, hepatocellular carcinoma.

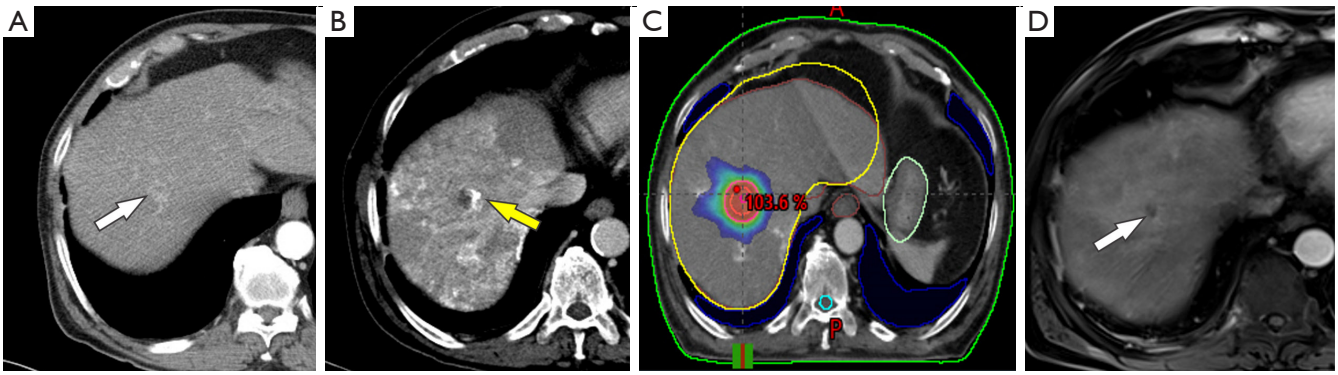

Figure 5 A representative example of Cohort A. Cohort A represents patients with incomplete lipiodol uptake on NECT immediately after TACE who underwent additional treatment before the follow-up (A) On CT arterial phase imaging before TACE, there is a 1.3-cm nodular arterial hyperenhancing HCC in liver segment VIII (white arrow). (B) NECT immediately after TACE shows incomplete uptake of lipiodol in the tumor (yellow arrow). (C) One week after NECT, a CT scan for planning radiation therapy was performed, and the patient underwent SBRT with a total dose of 45 Gy in 3 fractions for 3 days. (D) One month after TACE, and 2 weeks after SBRT, an arterial phase image of follow-up liver dynamic MRI reveals an enhancement defect at the previous HCC site (white arrow) with no evidence of residual viable HCC. This patient has remained alive without evidence of recurrence for 18.8 months. NECT, non-enhanced computed tomography; TACE, transarterial chemoembolization; CT, computed tomography; HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy.

NECT immediately after TACE could facilitate early prediction of therapeutic response. Patients with incomplete lipiodol uptake in the tumor and without prompt additional treatment displayed a higher rate of viable tumor 1 month after TACE, and shorter TTP compared to those with complete lipiodol uptake in the tumor.

Although we included patients with HCCs that displaying a distinctly nodular appearance and unequivocal arterial hyperenhancement on pre-TACE dynamic CT or MRI, not all patients exhibited satisfactory lipiodol uptake in the hypervascular portion of the tumors. Lipiodol uptake in the tumor was observed to be incomplete in 58 patients (30.7%). This may be due to the challenges in detecting and accurately superselecting the feeding arteries of the HCC during TACE (21-23), and underscores the importance of evaluating the treatment effect and tumor state immediately after performing TACE.

In our study, Cohort B demonstrated a significantly shorter TTP compared to Cohort C (complete lipiodol uptake). In addition, patients in Cohort B exhibited a higher rate of residual viable tumor (48.2%) 1 month after TACE than those in Cohort C (32.1%), indicating that tumor progression occurs more rapidly in patients who display less than 50% lipiodol uptake on immediate post-TACE CT scans and do not undergo prompt additional treatment, compared to those with 50% or more lipiodol uptake.

In contrast, two patients in Cohort A who underwent immediate additional treatment showed no progression during follow-up period of more than 12 months. Altogether, these findings suggest the importance of timely additional treatment when observing incomplete lipiodol uptake immediately after TACE, rather than waiting for the routinely scheduled tumor assessment 1 month after the procedure.

Another advantage of NECT is the avoidance of intravenous iodinated contrast media. Patients with HCC often require periodic contrast-enhanced CT scans for monitoring disease progression or assessing treatment efficacy. This necessitates repetitive exposure to iodinated contrast media, leading to patients' discomfort and potential toxicity of contrast agents. With a purpose of accurately assessing lipiodol uptake, there is no need to use iodinated contrast agent, and performing NECT immediately after TACE is considered to offer more benefits than harms.

When evaluating lipiodol retention on NECT, we employed a binary classification (i.e., complete *vs.* incomplete). While this method is not quantitative, it enabled rapid evaluation on the degree of lipiodol uptake. Previous studies have utilized computer-aided quantification or volumetric assessment to quantitatively analyze lipiodol uptake (24,25); however, these methods are time-consuming and challenging for radiologists to implement in the

clinical practice while facing a large volume of CT scans to interpret. Furthermore, our approach effectively stratified the proportion of patients with residual viable tumor 1 month after TACE and TTP among different groups. Our method may hold potential for reliably assessing and effectively distinguishing optimal and suboptimal lipiodol uptake in patients undergoing TACE. Further validation is warranted to confirm its efficacy.

It is surprising that only two patients among 58 patients who showed incomplete lipiodol uptake (Cohorts A and B) underwent prompt additional treatment. Upon reviewing actual NECT reports, we found that the descriptions of tumoral lipiodol uptake visible on NECT immediately after TACE were not structured and varied significantly among readers. In NECT reports of all cohorts, significant portion lacked any mention of the degree of lipiodol uptake, and descriptions were subjective without any standardized criteria. Our study demonstrated that prognosis could be stratified by evaluating the degree of lipiodol uptake, using a simple method of categorizing it into complete and incomplete. Therefore, it is advisable to carefully assess the extent of lipiodol uptake and clearly mention it in the reports. Both radiologists and treating physicians should be aware of the potential utility of immediate post-TACE NECT and incorporate its information into their interpretation and actual patient care.

Our study has several limitations. First, the retrospective design of study may have produced biases. Second, the radiologic assessment in our work was not confirmed pathologically. However, pathologic examinations cannot demonstrate the effects of treatment on survival times before surgery. Although radiologic non-enhancement may not fully distinguish viable from necrotic tumors histopathologically (26), imaging-based evaluation of intratumoral enhancement remains highly valuable for assessing treatment response. Third, during TACE, we utilized a 1:1 mixture ratio of cisplatin and iodized oil. The mixing technique may vary by institution and could have influenced the embolic effect or drug carriage capacity in our subjects (27). Nevertheless, we believe that the mixture ratio will not significantly affect the results of our study, which primarily focuses on the relationship between the completeness or incompleteness of lipiodol uptake and patient outcomes.

Conclusions

Assessing lipiodol uptake using NECT immediately after TACE for the treatment of HCC could stratify patients and facilitate early prediction of therapeutic response. Detecting suboptimal lipiodol uptake on NECT performed immediately after TACE may guide modifications of future treatment plans and ultimately improve the oncologic outcomes of patients with HCC.

Acknowledgments

Funding: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2021R1C1C1010138).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-134/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-134/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-134/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-134/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of the Asan Medical Center (No. 2023-0204) and individual consent for this retrospective analysis was waived.

References

1. Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 2023;78:1922-65.
2. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol 2022;28:583-705.
3. European Association for the Study of the Liver. Electronic address: easloffice@easloffice; . EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
4. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. J Hepatol 2015;62:1187-95.
5. Raoul JL, Forner A, Bolondi L, et al. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer Treat Rev 2019;72:28-36.
6. Sangro B, Salem R. Transarterial chemoembolization and radioembolization. Semin Liver Dis 2014;34:435-43.
7. Kotsifa E, Vergadis C, Vailas M, et al. Transarterial Chemoembolization for Hepatocellular Carcinoma: Why, When, How? J Pers Med 2022;12:436.
8. Ma Y, Duan L, Li L, et al. (131)Iodine-DEM TACE vs. conventional TACE in cirrhotic patients with hepatocellular carcinoma: a single center experiment. J Gastrointest Oncol 2021;12:762-9.
9. Arizumi T, Ueshima K, Minami T, et al. Effectiveness of Sorafenib in Patients with Transcatheter Arterial Chemoembolization (TACE) Refractory and Intermediate-Stage Hepatocellular Carcinoma. Liver Cancer 2015;4:253-62.
10. Cappelli A, Cucchetti A, Cabibbo G, et al. Refining prognosis after trans-arterial chemo-embolization for hepatocellular carcinoma. Liver Int 2016;36:729-36.
11. Monsky WL, Kim I, Loh S, et al. Semiautomated segmentation for volumetric analysis of intratumoral ethiodol uptake and subsequent tumor necrosis after chemoembolization. AJR Am J Roentgenol 2010;195:1220-30.
12. Takayasu K, Muramatsu Y, Maeda T, et al. Targeted transarterial oily chemoembolization for small foci of hepatocellular carcinoma using a unified helical CT and angiography system: analysis of factors affecting local recurrence and survival rates. AJR Am J Roentgenol 2001;176:681-8.
13. Dioguardi Burgio M, Sartoris R, Libotean C, et al. Lipiodol retention pattern after TACE for HCC is a predictor for local progression in lesions with complete response. Cancer Imaging 2019;19:75.
14. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52-60.
15. Kim H, Choi J-I, Kim BH, et al. LI-RADS version 2018 in Patients with Prior History of Hepatocellular Carcinoma: Are LR4 Observations Enough for the Diagnosis of Recurrent HCC? Investig Magn Reson Imaging 2021;25:172-82.
16. Chung SH, Kim MJ, Choi JY, et al. Comparison of two different injection rates of gadoxetic acid for arterial phase MRI of the liver. J Magn Reson Imaging 2010;31:365-72.
17. Kim SM, Heo SH, Kim JW, et al. Hepatic arterial phase on gadoxetic acid-enhanced liver MR imaging: a randomized comparison of 0.5 mL/s and 1 mL/s injection rates. Korean J Radiol 2014;15:605-12.
18. Shim JH, Lee HC, Kim SO, et al. Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology 2012;262:708-18.
19. Kim JH, Shim JH, Yoon HK, et al. Chemoembolization related to good survival for selected patients with hepatocellular carcinoma invading segmental portal vein. Liver Int 2018;38:1646-54.
20. Brody T. Clinical trials: study design, endpoints and biomarkers, drug safety, and FDA and ICH guidelines. Amsterdam: Academic Press; 2016.
21. Cho Y, Choi JW, Kwon H, et al. Transarterial Chemoembolization for Hepatocellular Carcinoma: 2023 Expert Consensus-Based Practical Recommendations of the Korean Liver Cancer Association. Korean J Radiol 2023;24:606-25.
22. Wallace MJ. C-arm computed tomography for guiding hepatic vascular interventions. Tech Vasc Interv Radiol 2007;10:79-86.
23. Kakeda S, Korogi Y, Hatakeyama Y, et al. The usefulness of three-dimensional angiography with a flat panel detector of direct conversion type in a transcatheter arterial chemoembolization procedure for hepatocellular carcinoma: initial experience. Cardiovasc Intervent Radiol 2008;31:281-8.
24. Matsui Y, Horikawa M, Jahangiri Noudeh Y, et al. Baseline Tumor Lipiodol Uptake after Transarterial

Chemoembolization for Hepatocellular Carcinoma: Identification of a Threshold Value Predicting Tumor Recurrence. Radiol Oncol 2017;51:393-400.
25. Stark S, Wang C, Savic LJ, et al. Automated feature quantification of Lipiodol as imaging biomarker to predict therapeutic efficacy of conventional transarterial chemoembolization of liver cancer. Sci Rep 2020;10:18026.
26. Maddala YK, Stadheim L, Andrews JC, et al. Drop-out rates of patients with hepatocellular cancer listed for liver transplantation: outcome with chemoembolization. Liver Transpl 2004;10:449-55.
27. Masada T, Tanaka T, Nishiofuku H, et al. Techniques to Form a Suitable Lipiodol-Epirubicin Emulsion by Using 3-Way Stopcock Methods in Transarterial Chemoembolization for Liver Tumor. J Vasc Interv Radiol 2017;28:1461-6.

Cite this article as: Kim MY, Heo S, Choi S, Suh CH, Lee ES, Park HJ, Kim KW. Clinical impact and potential utility of non-enhanced computed tomography performed immediately after transarterial chemoembolization for hepatocellular carcinoma. J Gastrointest Oncol 2024;15(3):1141-1152. doi: 10.21037/jgo-24-134

