공학석사 학위논문

# 간세포암에 대한 간동맥 화학색전술 직후 수행된 비조영증강 전산화 단층촬영의 임상적 영향

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

울 산 대 학 교 대 학 원

의 과 학 과

김 미 영

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이 논문을 공학석사학위 논문으로 제출함

2024 년  8 월

울 산 대 학 교  대 학 원

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## Abstract

**Background:** Intratumoral lipiodol deposition following transcatheter 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. Patients were divided into two groups based on whether they received immediate post-TACE NECT: immediate-NECT group and no-immediate-NECT group. The immediate-NECT group was further categorized based on lipiodol uptake into Cohorts A (<50% uptake with additional treatment before the first follow-up one month after TACE), B (<50% uptake without additional treatment before first follow-up), and C (≥50% 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 626 patients, 189 (30.2%) were in the immediate-NECT group. Twenty-eight patients (4.5%) showed less than 50% lipiodol uptake; two in Cohort A and 26 in Cohort B.

Cohort C included 161 patients (25.7%). Cohort B had the highest rate of residual viable tumor (73.1%) one month after TACE, compared to the other cohorts (0% in Cohort A and 31.1% in Cohort C). During follow-up, no progression occurred in Cohort A. The median TTP of Cohort B was 4.6 months (95% confidence interval [CI], 2.9–15.7 months), significantly shorter than the 15.2 months (95% CI, 10.9–20.9 months) for Cohort C ($p = 0.002$). In the no-immediate-NECT group of 437 patients, 163 (37.3%) showed residual viable HCC one month after TACE with a median TTP of 14.5 months (95% CI, 11.3–17.2 months).

**Conclusions:** Immediate post-TACE NECT assessment of lipiodol uptake 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, Chemoembolization, Lipiodol, Computed tomography, Time to progression

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## Introduction

Transarterial chemoembolization (TACE) is the mainstay treatment in patients with intermediate-stage hepatocellular carcinoma (HCC) not candidates for curative treatment, such as ablation, surgery, or liver transplantation (1-4). TACE can also be utilized for patients with early stage HCC, who are ineligible for surgery due to poor residual liver function and/or co-morbidities, and for ablation due to tumor location (5). TACE also serves as a bridging treatment to liver transplantation or to downstage patients to become eligible for surgery (3).

The response to the initial TACE varies greatly from patient to patient, with a variable median overall survival (OS) of 13–43 months (6-8). For HCC patients who show refractoriness to initial TACE, timely treatment adjustment, for example, conversion to radiation therapy or systemic treatment, is essential to prevent further disease progression and prolong survival (9). Therefore, a reliable method that predicts therapeutic response after the TACE would be beneficial in clinical decision-making and modification of future treatment strategies (10).

The degree of intratumoral lipiodol deposition has been shown to correlate with prognosis after TACE (11-13). In previous studies, CT images have been used to assess intratumoral lipiodol uptake; however, either included patients with hepatic malignancies other than HCC, had small sample sizes (<60 patients), or utilized contrast-enhanced CT performed 4–6 weeks

after TACE to evaluate lipiodol retention, thus not reflecting the immediate state of lipiodol retention after the procedure. Additionally, evidence regarding which threshold should be applied to classify lipiodol uptake and predict treatment response, 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 non-enhanced CT (NECT) performed immediately after TACE for the treatment of HCC. This article in accordance with the STROBE reporting checklist.

## Methods

### *Patient selection*

This single-center retrospective study was approved by the institutional review board of our institution, and informed consent was waived. From November 2021 to December 2022, patients who underwent a first session of conventional TACE for the initial treatment of HCC were retrieved from the medical database of our institution. Inclusion criteria were (i) the presence of at least measurable lesion 1 cm or larger, (ii) no extrahepatic metastasis, and (iii) dynamic contrast-enhanced CT or MRI within 7 days before TACE procedure. Patients should have had at least one index lesion (i.e., target lesion) measuring 1 cm or larger in diameter, wherein the typical features of HCC of arterial enhancement followed by washout during the portal venous phase could be observed on a dynamic scan, and in these patients, the lesions were confirmed as HCC based on American Association for the Study of Liver Diseases or EASL guidelines (1, 3). Target lesions were characterized as distinctly nodular and not infiltrative, thus permitting 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. Patients who were lost to follow-up after the first session of TACE were also excluded.

***Data collection***

Prior to the initial TACE, patients underwent laboratory tests, including a liver function panel, serum a-fetoprotein (AFP), and hepatitis serologic tests, as well as dynamic liver CT or MRI and a metastatic work-up. 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 were reviewed.

Routinely, the first follow-up dynamic liver CT or MRI was conducted one 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***

All TACE procedures were performed by highly experienced interventional radiologists. Both superior mesenteric and common hepatic arteriography were performed to assess overall anatomy, tumor burden, and portal vein patency. Cisplatin (Cisplan; Dong-A Pharmaceutical, Seosan, Korea) was then infused into the lobar hepatic artery for 15 minutes without embolic

particle administration. The infused dose of cisplatin was 2 mg per kilogram of body weight. After selective catheterization of 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 infused into the feeding arteries. The feeder arteries were subsequently embolized by using 1-mm-diameter absorbable gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, Mich) until arterial flow stasis was achieved. Informed consent for chemoembolization was obtained from each patient prior to the commencement of any procedure. Repeated chemoembolization was indicated every 6–8 weeks if residual viable tumor tissue was evident on sequential dynamic CT without the appearance of extrahepatic metastases, major portal vein invasion, or deterioration in liver function. Informed consent for chemoembolization was obtained from each patient prior to the commencement of any procedure.

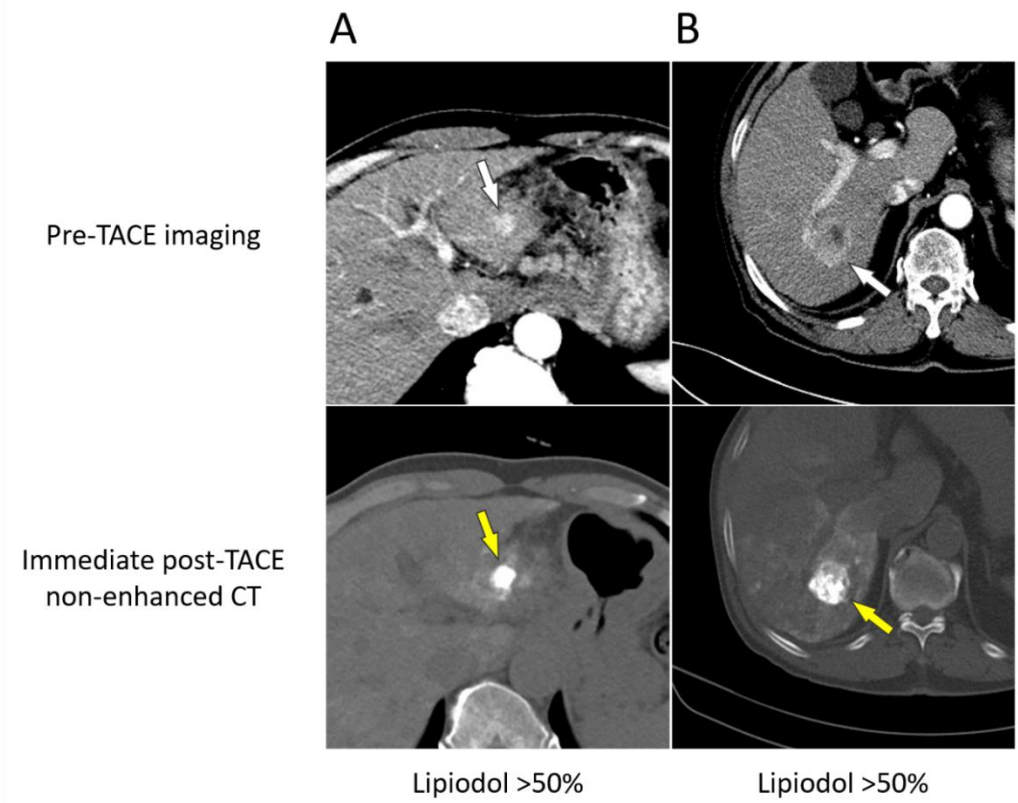
***Assessment of lipiodol uptake on immediate NECT***

In a subset of patients, lipiodol uptake was evaluated using NECT performed immediately after the TACE session (immediate-NECT group). To ensure comprehensive examination of the tumor, these images were meticulously compared with dynamic CT or MRI scans obtained before TACE. The presence of lipiodol uptake was determined by observing hyperattenuation

of the tumor relative 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. Lipiodol uptake was categorized in a binary manner as equal to or greater than 50% of the total tumor volume or less than 50% of the total tumor volume. 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) in consensus, who were blinded to the clinical characteristics and follow-up imaging results after TACE. **Figure 1** illustrates schematic examples of the lipiodol retention patterns.

According to the presence of NECT taken immediately after TACE, patients were divided into “immediate-NECT group” and “no-immediate-NECT group”. In addition, patients included in the immediate-NECT group was further divided according to the degree of lipiodol uptake on NECT and the presence of prompt management prior to the next follow-up dynamic CT or MRI; patients were categorized as Cohort A (lipiodol uptake < 50% of the total tumor volume and any additional treatment was performed prior to the next follow-up), Cohort B (lipiodol uptake < 50% of the total tumor volume but there was no management prior to the

next follow-up), and Cohort C (lipiodol uptake equal or more than 50% of the total tumor volume) (**Figure 2**).



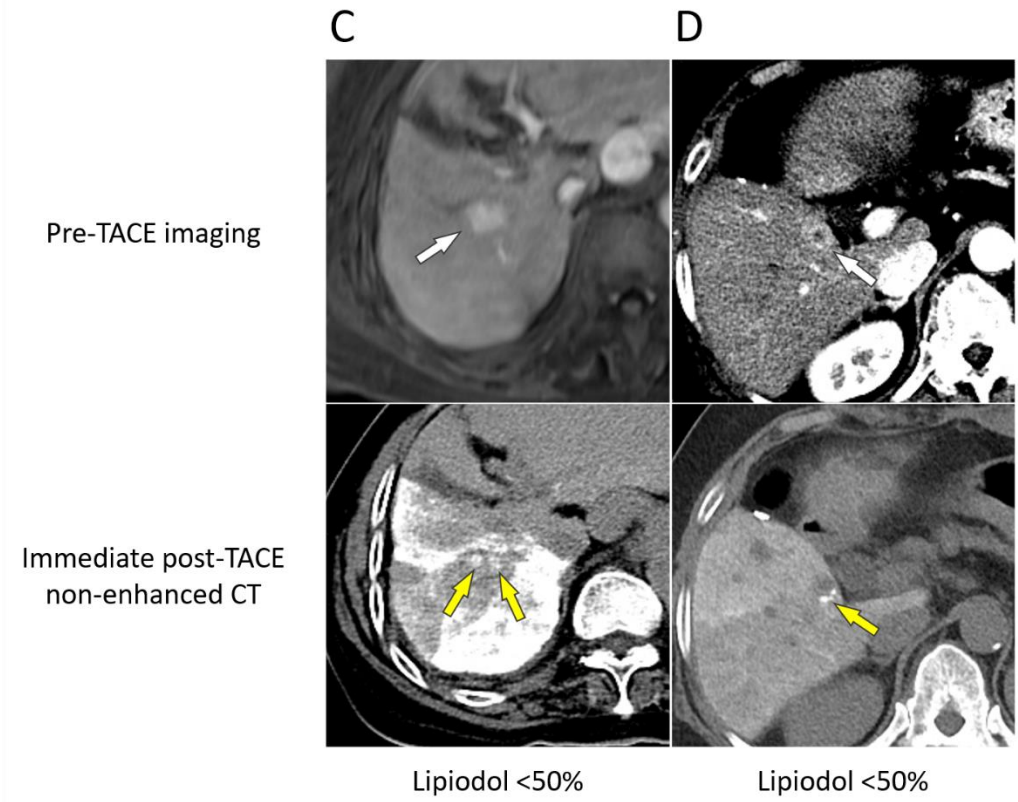



**Figure 1. Schematic representation of lipiodol uptake on non-enhanced CT (NECT) after transarterial chemoembolization (TACE).**

White arrows indicate hepatocellular carcinoma (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 homogeneous lipiodol retention on post-TACE NECT, covering more than 50% of the entire tumor area. (B) There is heterogeneous retention of lipiodol on post-TACE NECT, yet all tumor areas display higher attenuation compared to the liver parenchyma, indicating lipiodol uptake of more than 50% of the tumor. (C) Several nodular areas of lipiodol uptake are present within the tumor on post-TACE NECT, constituting less than 50% of the total tumor area. (D) Only dot-like lipiodol uptake is observed at the tumor's periphery, comprising less than 50% of the tumor area.

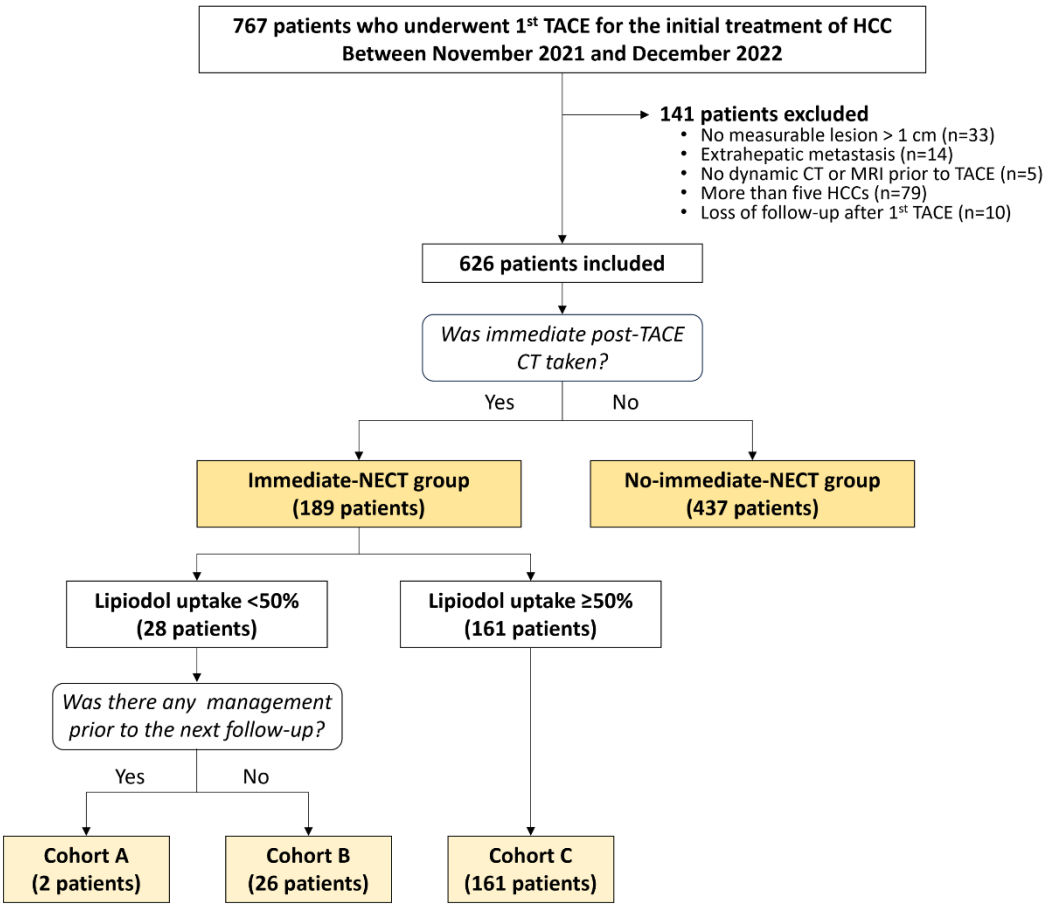



**Figure 2. Patient recruitment and classification process**

***Statistical analysis***

Data were expressed as means, standard deviations and ranges, or number of cases and frequencies, as appropriate. A Fisher exact test or a Chi square test was used to compare frequencies. The Student t test or Mann-Whitney test was used to compare continuous variables according to data distribution.

Survival curves were estimated with the Kaplan-Meier method and were compared by using the log-rank test. Overall survival (OS) was evaluated from the day of initial TACE session to the day of death, regardless of the cause of death (15); there were no procedure-related deaths within one month of the initial therapy. For calculation of the time to progression (TTP), radiologic progression was used according to mRECIST, and deaths during follow-up without evidence of radiologic progression were censored (15). A p value $< 0.05$ was considered to be significant. All analyses were performed with the Statistical Package for the Social Sciences software, version 20.0 (SPSS Inc.).

## Results

### *Patients characteristics*

Patient recruitment process was shown in **Figure 2**. Among the 767 eligible patients, 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). The baseline characteristics of 626 enrolled patients are summarized in **Table 1**. Hepatitis B was present in 403 patients (64.4%), hepatitis C in 46 (7.3%), alcohol-induced liver disease in 88 (14.1%), non-alcoholic steatohepatitis in 17 patients (2.7%), and others (n=72, 11.5%). Among them, 485 (77.5%) had cirrhosis. Most patients were Child-Pugh class A (536 patients, 85.6%), and the remaining 90 patients were Child Pugh class B (14.4%). Patients had 1.4 HCCs in average (IQR, 1–2; range, 1–5) and the mean size of HCCs were 3.1 ± 2.3 cm (range, 1.0–20.0 cm). HCC was solitary in 446 patients (71.2%).

**Table 1. Characteristics of the patients**

| Characteristics | Value |
|---|---|
| Number of patients | 626 |
| Age (years) | 65 (58–71) |
| Sex | |
| Men | 493 (78.8%) |
| Women | 133 (21.2%) |
| Underlying liver disease | |
| Hepatitis B | 403 (64.4%) |
| Alcohol-induced | 88 (4.1%) |
| Hepatitis C | 46 (7.3%) |
| NASH | 17 (2.7%$) |
| Others* | 72 (11.5%) |
| Liver cirrhosis | |
| Present | 485 (77.5%) |
| Absent | 141 (22.5%) |
| Child-Pugh class | |
| A | 536 (85.6%) |
| B | 90 (14.4%) |

| | |
|---|---|
| Laboratory findings | |
| Aspartate aminotransferase (IU/mL) | 29 (23–40) |
| Alanine aminotransferase (IU/mL) | 23 (16–34) |
| Platelet count ($10^9$/L) | 139 (93–179) |
| Total bilirubin (mg/dL) | 0.6 (0.4–0.8) |
| Prothrombin time (INR) | 1.0 (0.9–1.2) |
| Albumin (g/dL) | 3.7 (3.3–4.0) |
| Alpha-fetoprotein (ng/mL) | 7.2 (3.1–66.2) |
| Tumor size (cm)† | 3.1 (1.0–20.0) |
| Number of tumors | 1.4 (1–2) |
| 1 | 446 (71.2%) |
| 2 | 123 (19.6%) |
| 3–5 | 57 (9.1%) |

Data are reported as number, number (%), or median (interquartile range).

* Included primary biliary cirrhosis, autoimmune hepatitis, and cryptogenic.

† Mean (range).

***Lipiodol uptake after TACE***

Immediate-NECT group included 189 patients (30.2%), who underwent NECT immediately after their TACE. Twenty-eight patients (4.5%) had less than 50% lipiodol uptake in the tumor on NECT. Two patients, with less than half of their HCCs showing lipiodol uptake, received additional treatment for the tumor (Cohort A, 0.3%); one were treated with radiofrequency ablation, and the other was treated with radiation therapy. Twenty-six patients, despite having less than 50% lipiodol uptake, did not receive any additional treatment before the next follow-up (Cohort B, 4.2%). There were 161 patients who demonstrated 50% or greater lipiodol uptake in their tumors (Cohort C, 25.7%). In 437 patients, immediate post-TACE non-enhanced CT scans were not performed (no-immediate-NECT group, 69.8%).

***Outcome on follow-up***

For all 626 patients, the median follow-up was 17.0 months (interquartile range [IQR], 14.0–19.6 months; full range, 2.3–23.9 months). The median TTP was 14.5 months (95% confidence interval [CI], 11.5–16.4 months). A total of 245 patients (39.1%) experienced progression. Forty-two patients (6.7%) died, and the median OS was not reached.

Among the 189 patients in the immediate-NECT group, 69 (36.5%) showed evidence of residual viable HCC 1-month after TACE. Similarly, in the no-immediate-NECT group of 437

patients, 163 (37.3%) exhibited residual viable HCC 1-month after TACE. The rates of residual viable HCC 1-month after TACE between the two groups were not significantly different (p = 0.928) **(Table 2)**.

During follow-up, in immediate-NECT group, 74/189 patients (39.2%) experienced progression, with a median TTP of 14.8 months (95% CI, 10.4–19.4 months). In no-immediate-NECT group, 171/437 patients (39.1%) experienced progression, with a median TTP of 14.5 months (95% CI, 11.3–17.2 months). The median TTP was slightly longer in immediate-NECT group than that in no-immediate-NECT group, however the difference was not significant (p = 0.977) **(Figure 3A)**. The median OS was not reached in either group, and there was no significant difference in OS between them (p = 0.738).

In Cohort A (n=2), both patients had no evidence of residual viable HCC 1-month after TACE. Of the 26 patients in Cohort B, 19 (73.1%) had a residual viable tumor 1-month after TACE, while in Cohort C, 50 out of 161 patients (31.1%) showed residual viability 1-month after TACE. The rate of residual viable HCC in Cohort B was significantly higher than in Cohort C (p < 0.001).

The TTPs of each Cohort are shown in **Figure 3B** and **Table 3**. When comparing the TTP between Cohorts A and B—representing the presence (Cohort A) or absence (Cohort B) of additional tumor treatment before the next assessment— no progression was observed in the

two patients from Cohort A who underwent ablation or radiation therapy immediately after non-enhanced CT was performed, with follow-ups of 18.8 months and 15.0 months, respectively (**Figure 4**). In contrast, patients from Cohort B experienced tumor progression in 12 out of 26 patients (46.2%), with a median TTP of 4.6 months (95% CI, 2.9–15.7 months) after TACE. The difference in TTP between the two Cohorts were significant ($p = 0.025$). The median OS was not reached in either Cohort, and there was no significant difference in OS between them ($p = 0.705$).

In Cohort C, 62 out of 161 patients (38.5%) experienced tumor progression, with a median TTP of 15.2 months (95% CI, 10.9–20.9 months). The TTP of Cohort C was significantly longer than that observed in Cohort B ($p = 0.002$), 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 (**Figure 5**).

When comparing the TTP of the no-immediate-NECT group with that of Cohort B, the former exhibited a significantly longer TTP (median TTP, 14.5 months vs 4.6 months; $p = 0.003$). There was no significant difference in TTP between Cohort C and no-immediate-NECT group ($p = 0.5$).

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

| | No-immediate-NECT group | Immediate-NECT group | | |
|---|---|---|---|---|
| | | Cohort A | Cohort B | Cohort C |
| Number of patients | 437 | 2 | 26 | 161 |
| Residual viable HCC one-month after TACE | | | | |
| Yes | 163 (37.3%) | 0 (0%) | 19 (73.1%) | 50 (31.1%) |
| No | 274 (62.7%) | 2 (100%) | 7 (26.9%) | 111 (68.9%) |

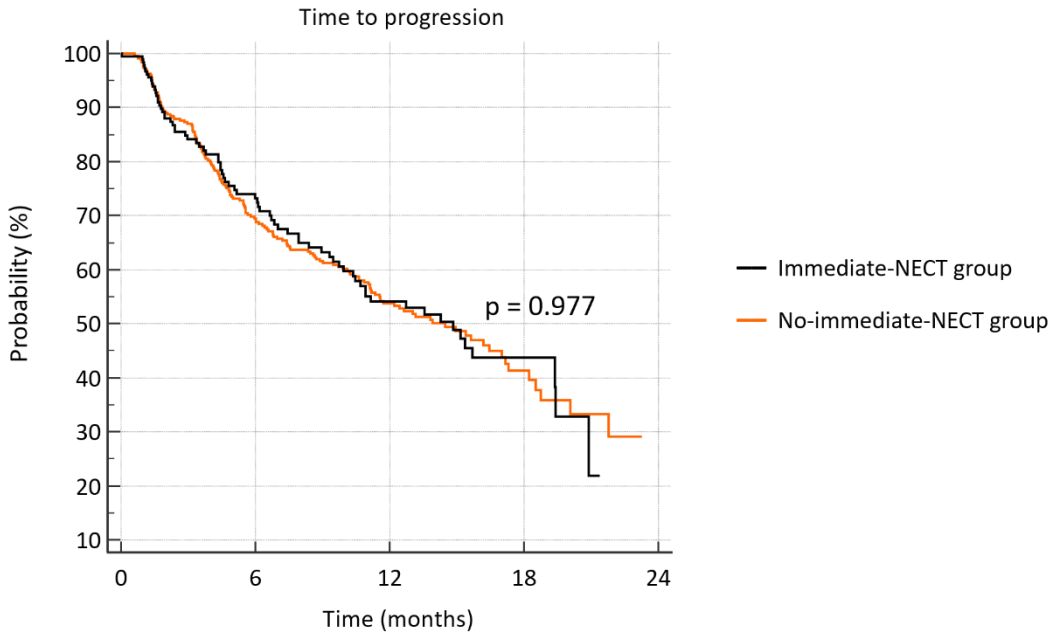
Data are reported as number (%).

**Table 3. Time to progression of each Cohort**

| | Median TTP (months) | p values (vs. Cohort B) |
|---|---|---|
| No-immediate-NECT group | 14.5 (11.3–17.2) | 0.003 |
| Immediate NECT group | 14.8 (10.4–19.4) | |
| Cohort A | Not reached | 0.025 |
| Cohort B | 4.6 (2.9–15.7) | – |
| Cohort C | 15.2 (10.9–20.9) | 0.002 |

Data are number (95% confidence interval).

A




B

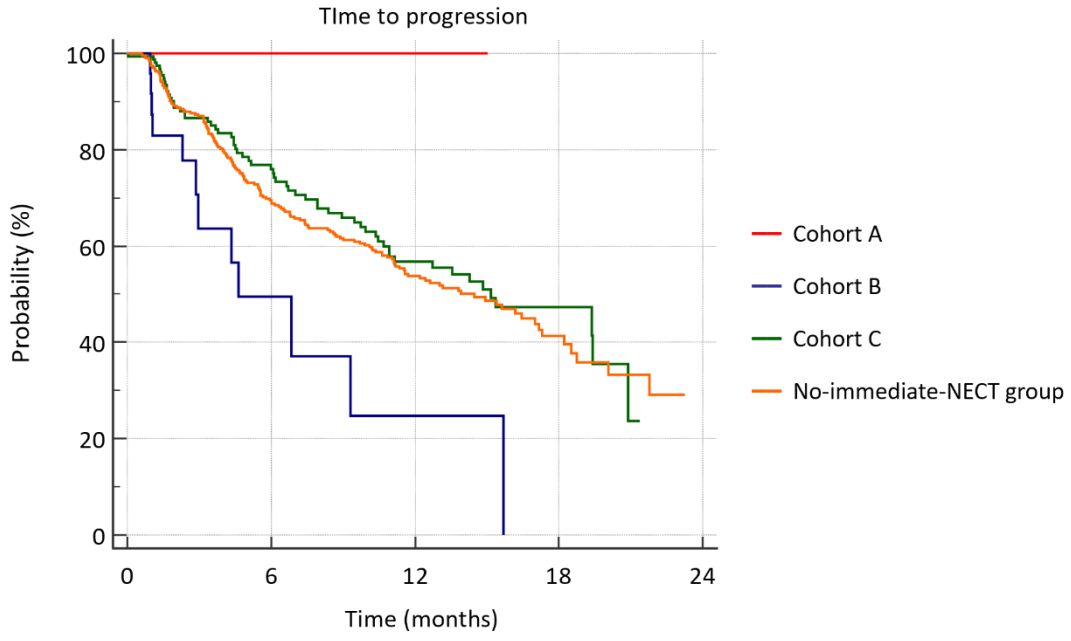


**Figure 3. Kaplan-Meier curves of time to progression (TTP) of each group.**

(A) TTP stratified by the presence of non-enhanced CT (NECT) immediately performed after transarterial chemoembolization. There was no significant difference in TTP between immediate-NECT group (black) and no-immediate-NECT group (orange).

(B) TTP in Cohort A (red), Cohort B (blue), Cohort C (green), and the no-immediate-NECT group (orange). The median TTP of Cohort A was not reached. A significant difference was noted between Cohort A and Cohort B ($p = 0.025$), as well as between Cohort B and Cohort C ($p = 0.002$).

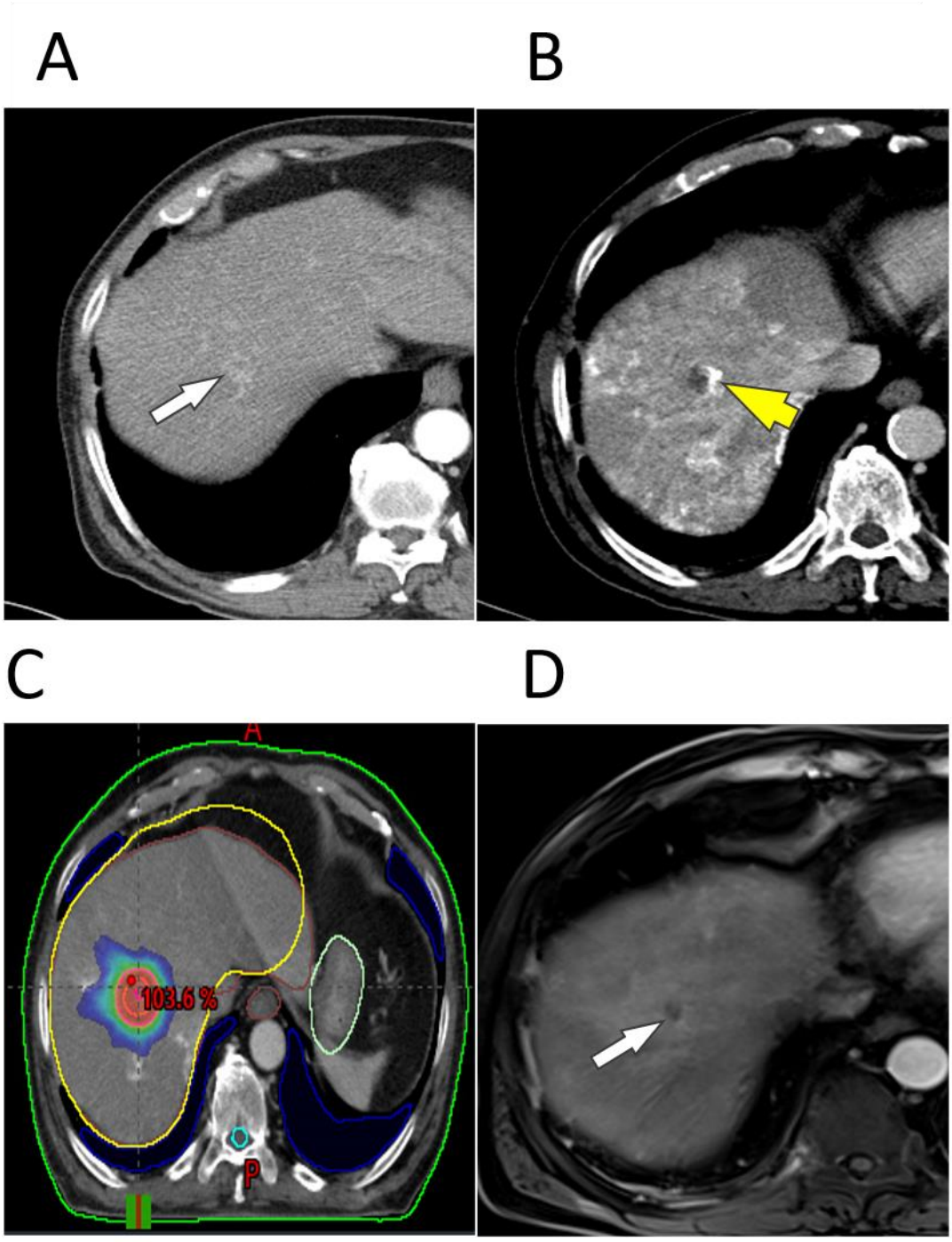


**Figure 4. A representative example of Cohort A.**

(A) On CT arterial phase imaging before transarterial chemoembolization (TACE), there is a 1.3 cm nodular arterial hyperenhancing hepatocellular carcinoma (HCC) in liver segment VIII (white arrow). (B) Non-enhanced CT (NECT) immediately after TACE shows less than 50% 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 stereotactic body radiation therapy (SBRT) with a total dose of 45 Gy in three fractions for 3 days. (D) One month after TACE, and two 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.

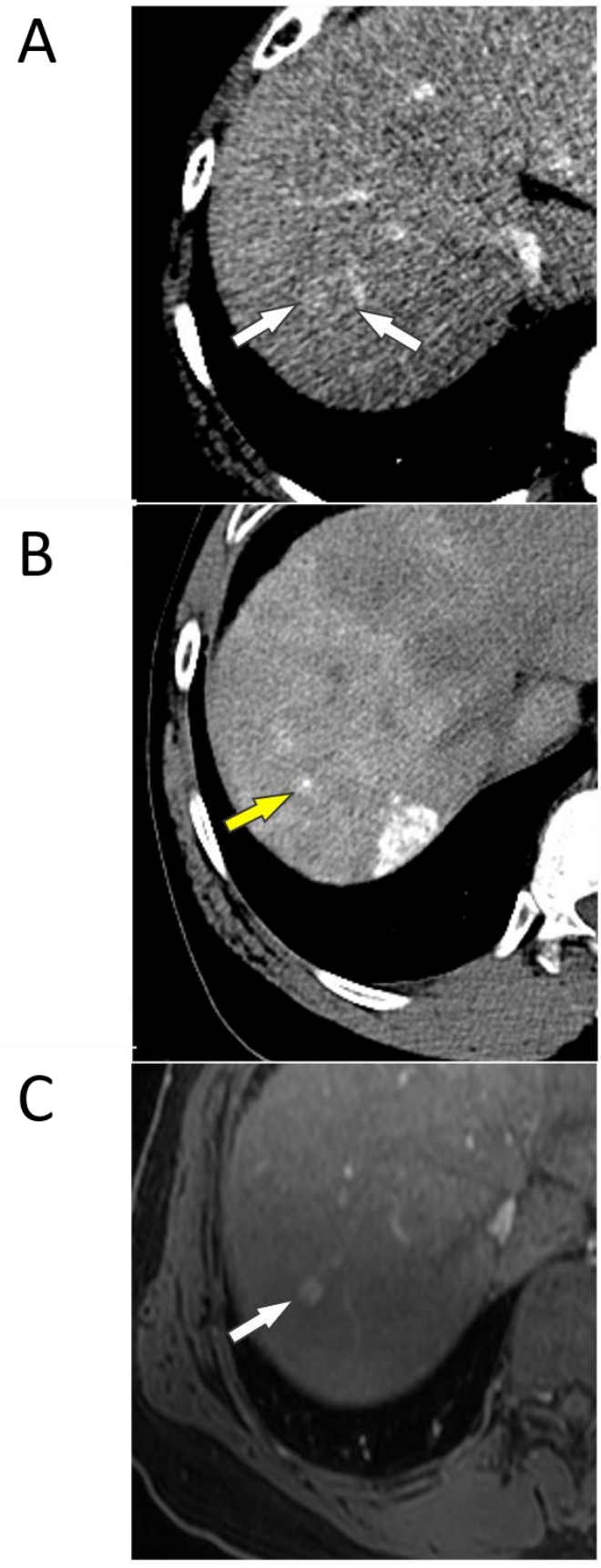


**Figure 5. A case of Cohort B.**

(A) CT arterial phase imaging taken before transarterial chemoembolization (TACE) displays a 2.0 cm nodular arterial hyperenhancing hepatocellular carcinoma (HCC) in liver segment VII (white arrows). (B) Post-TACE non-enhanced CT shows only dot-like retention of lipiodol in the tumor (yellow arrow), representing less than 50% of the whole tumor. 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.

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

Among the 28 patients in Cohorts A and B, who had tumoral lipiodol uptake of <50% on immediate post-TACE NECT, the degree of lipiodol uptake was not detailed in the NECT reports of 4 patients (14.3%; merely mentioned as 'lipiodol uptake present'), while in the reports of 24 patients (85.7%), it was described as 'partial', 'incomplete', 'faint', or 'uncertain'. In Cohort C, comprising 161 patients, 42 NECT reports (26.1%) 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 15 patients were described using terms like 'dense', 'well', 'good', 'diffuse', and 'successful'. For 25 patients, terms suggesting incomplete uptake were variedly used ('partial', 'uncertain', 'faint', 'mild', 'with defect').

## Discussion

Our study showed that assessing lipiodol uptake using NECT immediately after TACE could facilitate early prediction of therapeutic response. Patients with tumoral lipiodol uptake <50% and without prompt additional treatment displayed a higher rate of viable tumor one month after TACE, and shorter TTP compared to those with lipiodol uptake ≥50%. Conversely, those with tumoral lipiodol uptake <50% but with immediate treatment adjustments showed no evidence of tumor progression on follow-up, indicating that detecting suboptimal lipiodol uptake on immediate NECT may guide future treatment plans.

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. Among the 189 patients who underwent immediate post-TACE NECT, lipiodol uptake in the tumor was observed to be <50% in 28 patients (14.8%). This may be due to the challenges in detecting and accurately superselecting the feeding arteries of the HCC during TACE (16-18), and underscores the importance of evaluating the treatment effect and tumor state immediately after performing TACE.

In our study, significantly shorter TTP was noted in Cohort B (lipiodol uptake <50%, with no additional treatment before the next assessment) than Cohort A (lipiodol uptake <50%, with

prompt additional treatment before the next assessment). Furthermore, Cohort B demonstrated a significantly shorter TTP compared to Cohort C (lipiodol uptake ≥50%). In addition, patients in Cohort B exhibited the highest rate of residual viable tumor (73.1%) one month after TACE, compared to the other cohorts (0% in Cohort A and 31.1% in Cohort C). Altogether, these findings suggest the importance of timely additional treatment when observing less than 50% lipiodol uptake immediately after TACE, rather than waiting for the routinely scheduled tumor assessment one month after the procedure.

When comparing the immediate-NECT group with the no-immediate-NECT group, the median TTP was slightly longer in the immediate-NECT group (14.8 months) than that in the no-immediate-NECT group (14.5 months), although the difference was not significant. We expect that, similar to the immediate-NECT group, the degree of immediate lipiodol uptake might have varied in the no-immediate-NECT group. Notably, no cases in the no-immediate-NECT group underwent additional treatment before the first assessment after TACE, and in the immediate-NECT group, prompt action was taken in only two patients included in Cohort A. Considering these points, the performance of immediate NECT alone may not carry intrinsic significance, but it emphasizes the importance of using it as a reference for promptly and appropriately adjusting treatment strategies.

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 dividing lipiodol uptake by 50% as a threshold. While this method is not quantitative and has not been previously validated, 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 (19, 20); 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 one 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 28 patients who showed lipiodol uptake of

<50% (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 Cohorts A and B, where lipiodol uptake was less than 50%, 14.3% of the patients had no mention of its uptake, and the rest (85.7%) were described using vague terms without quantitative information. Similarly, in Cohort C, with over 50% lipiodol uptake, 26.1% of the patients' immediate post-TACE NECT reports lacked any mention of the degree of uptake, and descriptions were subjectively interpreted without any standardized criteria. Our study, despite applying an arbitrary threshold of 50%, demonstrated that prognosis could be stratified by the degree of lipiodol uptake. 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, our work lacks pathologic confirmation of radiologic assessments. However, pathologic explants cannot reveal the effects of treatment on survival times before explantation. Although radiologic non-enhancement may not allow complete differentiation of viable from histopathologic necrotic tumors (21), the use of imaging-based assessment of

intratumoral enhancement is of great clinical value in the estimation of treatment response. Third, we used consensus reading data as the primary image evaluation data, in which the interobserver agreement is not assessed.

## 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.

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## 국문요약

**배경 및 목적:** 간동맥 화학색전술(transcatheter chemoembolization, TACE) 후 관찰된 종양 내 리피오돌 흡수율은 간세포암(hepatocellular carcinoma, HCC) 환자의 예후와 관련이 있는 것으로 나타나 있다. 그러나 TACE 후 리피오돌(Lipiodol) 흡수 정도를 평가하기 위해 수행된 영상 검사의 실제 임상적 중요성에 대한 증거는 아직 부족하다. 본 연구에서는 HCC 환자에서 TACE 직후 비조영증강 전산화 단층 촬영(non-enhanced computed tomography, NECT)을 수행하여 리피오돌 흡수율을 평가하는 것에 대한 임상적 영향을 평가하고자 하였다.

**방법:** 2021년 11월부터 2022년 12월의 기간 내에 HCC 진단을 받고 첫 번째 TACE를 시행한 환자들을 대상으로 연구를 진행하였다. 환자들은 TACE 직후 NECT를 수행하였는지 여부에 따라 두 그룹, 즉 immediate-NECT 그룹과 no-immediate-NECT 그룹으로 나뉘었다. 추가로 immediate-NECT 그룹은 리피오돌 흡수율 50%를 기준으로 코호트 A(<50% 흡수, TACE 한 달 후 첫 번째 추적 검사 전 추가 치료 시행), B(<50% 흡수, 첫 번째 추적 검사 전 추가 치료 안함), C(≥50% 흡수)로 세분화되었다. 각 그룹별 생존 데이터(overall survival) 및 HCC의 질병 무진행 생존 데이터(time to progression, TTP)를 분석하기 위해 Kaplan-Meier 방법을 사용하였고, Log-rank test로 비교하였다.

**결과:** 626명의 환자 중, 189명(30.2%)이 immediate-NECT 그룹으로 구성되었다. 코

호트 A에는 2명, 코호트 B에는 26명으로 50% 미만의 리피오돌 흡수율을 보인 28명의 환자(4.5%)가 포함되었고, 코호트 C에는 161명의 환자(25.7%)가 포함되었다. 코호트 B는 TACE 한 달 후 시행한 영상검사에서 HCC가 남아 있을 확률(73.1%)이 모든 코호트 중 가장 높았다(코호트 A = 0%, 코호트 C = 31.1%). 추적 관찰 기간 동안 코호트 A에서는 종양의 진행이 발생하지 않았다. 코호트 B의 중위수 TTP는 4.6개월(95% 신뢰 구간[confidence interval, CI], 2.9–15.7개월)로 코호트 C의 15.2개월(95% CI, 10.9–20.9개월) 보다 유의미하게 짧았다(p = 0.002). 437명의 환자로 구성된 no-immediate-NECT 그룹에서는 163명(37.3%)이 TACE 한 달 후 시행한 영상검사에서 잔여 HCC의 소견을 보였고 중위수 TTP는 14.5개월(95% CI, 11.3–17.2개월)이었다.

**결론:** TACE 직후 NECT를 수행하여 리피오돌 흡수율을 평가하는 것은 HCC 환자를 계층화 하고 치료 반응의 조기 예측을 용이하게 할 수 있다. 즉 TACE 직후 불충분한 리피오돌 흡수율을 보이는 HCC를 식별함으로 향후 효과적인 치료 계획 조정과 종양학적 결과를 개선하는데 도움이 될 수 있다.