Peer Review File

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Reviewer A

General:

A-1) Why were patients stratified to less than or greater than 50% lipidol coverage, this is well below typical goals of care.

Reply) We appreciate the reviewer's constructive criticism. The same concern was raised by another reviewer, and based on this common concern, ***we have revised the threshold of lipiodol uptake from 50% to a dichotomy of complete vs. incomplete***. We have re-performed all imaging and statistical analyses, and have revised the manuscript accordingly. There was significant difference in time to progression (TTP) between patients with incomplete lipiodol uptake (but no prompt management performed, i.e. Cohort B) and those with complete lipiodol uptake (i.e., Cohort C). Therefore, although the threshold has changed, the key message remains the same. Because too many sections were revised regarding this, it was difficult to display all the changes here. Several the key modifications are shown below. Please refer to our annotated revised manuscript, where all tracked changes are visible.

Changes in the text)

Location	Before revision	After revision
Method	"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."	(Deleted)
Method	"… 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)"	"…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), and Cohort C (complete lipiodol uptake).
Results	"Twenty-eight patients (4.5%) had less than 50% lipiodol uptake in the tumor on NECT… Twenty-six	"Among the 189 patients, 58 patients (30.7%) had incomplete lipiodol uptake in the tumor on

	patients, despite having less than 50% lipiodol uptake, … There were 161 patients who demonstrated 50% or greater lipiodol uptake in their tumors."	NECT… Fifty-six patients, despite having incomplete lipiodol uptake, … There were 131 patients who demonstrated complete lipiodol uptake in their tumors.
Results	"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) …"	"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 5). 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 = 0.026)."

A-2) This subject has been well documented and evaluated, what do the authors bring to the table in terms of new information.

Reply) We appreciate the reviewer's comment. In this paper, ***we propose that evaluating lipiodol uptake by performing NECT immediately after TACE may facilitate early interventions when necessary and has the potential to improve patient outcomes***. To clarify this further, we have revised the manuscript accordingly (see Page 1, line 30-31 in the annotated revised manuscript).

Changes in the text)

Location	Before revision	After revision
Abstract	"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	"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

	adjustments and potentially improving oncologic outcomes.”	future treatment adjustments and potentially improving oncologic outcomes.”

A-3) The method of reviewers just giving there opinion of how much of the tumor was covered by lipidol rather than quantifying in some objective manner is a significant risk and throws all results into question.

Reply) We appreciate the reviewer’s comment. Regarding this concern, we have revised the threshold of lipiodol uptake from 50% to a dichotomy of complete vs. incomplete. We have also re-performed all imaging and statistical analyses, and have revised the manuscript accordingly. Please refer to our detailed response to **Comment A-1**.

A-4) Well written.

Reply) We appreciate the reviewer’s comment.

A-5) Stratifying patients by more or less than 50% is an unusual choice.

Reply) We appreciate the reviewer’s comment. Regarding this concern, we have revised the threshold of lipiodol uptake from 50% to a dichotomy of complete vs. incomplete. We have also re-performed all imaging and statistical analyses, and have revised the manuscript accordingly. Please refer to our detailed response to **Comment A-1**.

Introduction:

A-6) Authors should be careful, while TACE is a mainstay of treatment in some parts of the world it has largely been set aside in favor of TARE in others.

Reply) According to the reviewer’s comment, we have rephrased our text as below (see Page 3, line 40 in the annotated revised manuscript).

Changes in the text)

Location	Before revision	After revision
Introduction	“Transarterial chemoembolization (TACE) is the mainstay treatment in patients with intermediate-stage hepatocellular carcinoma (HCC)…”	“Transarterial chemoembolization (TACE) is the standard treatment in patients with intermediate-stage hepatocellular carcinoma (HCC)…”

A-7) Well written

Reply) We appreciate the reviewer’s comment.

Materials and Methods:

A-8) The use of 1:1 chemo to lipidol mixture is interesting as 1:2 has been shown to be superior. This technical aspect may cloud the results.

Reply) The mixture ratio of lipiodol and chemoagent may vary slightly by institution (*Radiology 2012 Oct; 265(1):115-123, Korean J Radiol 2023 Jul; 24(7):606-625*). A 1:1 ratio has been widely used globally and has been implemented in recent randomized clinical trials (*Br J Cancer 2014 Jul 15; 111(2):255-64, J Gastroenterol 2018 Feb; 53(2):281-290*). As the reviewer mentioned, a 1:2 ratio has been shown to be superior in producing water-in-oil emulsion, which has been associated with higher embolic effect, higher drug carriage capacity, and a longer drug releasing time (*J Vasc Interv Radiol 2017 Oct;28(10):1461-1466*). However, ***we believe the mixture ratio will not significantly affect the conclusions of our study, which focuses on the relationship between the completeness or incompleteness of lipiodol uptake and patient outcomes***. In response to a reviewer's comment, we have added the following content to the discussion (see Page 10, line 312-316 in the annotated revised manuscript).

Changes in the text)

Location	Before revision	After revision
Discussion	"Our study has several limitations..."	"Our study has several limitations... Third, during TACE, we utilized a 1:1 mixture ratio of cisplatin and lipiodol. However, the mixing technique may vary by institution and could have influenced the embolic effect or drug carriage capacity in our subjects (reference). 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."

A-9) Why was 50% uptake used as a threshold, this is much less than typical goals of most Irs

Reply) We appreciate the reviewer's comment. Regarding this concern, we have revised the threshold of lipiodol uptake from 50% to 100%. We have also re-performed all imaging and statistical analyses, and have revised the manuscript accordingly. Please refer to our

detailed response to **Comment A-1**.

A-10) The method of reviewers just giving there opinion of how much of the tumor was covered by lipidol rather than quantifying in some objective manner is a significant risk and throws all results into question.

Reply) We appreciate the reviewer's comment. Regarding this concern, please refer to our detailed response to **Comment A-1**.

A-11) How were disagreements between interpreters solved.

Reply) Initially, we used consensus reading data as the primary image evaluation, without assessing interobserver agreement. However, during the revision process, we adjusted the threshold for lipiodol uptake from 50% to 100%. Subsequently, and in response to this comment, images were evaluated independently; in cases of disagreement, a third reviewer (with more experience in the liver imaging than the two primary reviewers) was consulted. The assessment was then determined by reaching a final consensus. We have revised the manuscript accordingly (see Page 6, line 126-131 and Page 12, line 311-312).

Changes in the text)

Location	Before revision	After revision
Methods	"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, …"	"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, who 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 conesnsus."
Discussion	"…Third, we used consensus reading data as the primary image evaluation data, …"	(Deleted)

Results:

A-12) Cohort A is so small it's likely that any interpretation of this cohort is faulty.

Reply) We agree the reviewer, and have deleted the statistical analysis comparing Cohort A and other groups in the revised manuscript, as follows (see Page 9, line 204-212; Page 10, line 243-245; Page 10, 253-255).

Changes in the text)

Location	Before revision	After revision
Results	"When comparing the TTP between Cohorts A and B … 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)."	"~~When comparing the TTP between Cohorts A and B~~ 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 5). ~~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).~~
Discussion	"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."	(Deleted)
Discussion	"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	"In our study, Cohort B demonstrated a significantly shorter TTP compared to Cohort C (lipiodol uptake ≥50%). In addition, patients in Cohort B exhibited a higher rate of residual viable tumor (73.1%) one month after TACE than those in Cohort C (31.1%). In contrast, the two patients in Cohort A who underwent immediate additional treatment showed no progression during follow-up period of more than 12 months."

	month after TACE, compared to the other cohorts (0% in Cohort A and 31.1% in Cohort C).”	

A-13) The unusual threshold and method of determination of lipidol retention makes it difficult to accept the results and unlikely that the results could be replicated. It is a fatal flaw for this manuscript.

Reply) We appreciate the reviewer’s comment. Regarding this concern, please refer to our detailed response to **Comment A-1**.

Discussion:

A-14) Given cohort sizes (which were very small) the conclusions the authors draw cannot be made.

Reply) As the size of Cohort A was so small, we have deleted the statistical analysis comparing that Cohort and other groups, and have removed the conclusive description regarding the outcome of Cohort A. Please refer to our response to **Comment A-12.**

A-15) The authors do not even mention the significant design flaws described above in the limitations paragraph.

Reply) We appreciate the reviewer’s comment. Regarding this concern, please refer to our detailed response to **Comment A-1**.

End of Reviewer A’s comments.

Reviewer B

This is a single center retrospective study, evaluating the use of immediate CT after TACE. Authors noted that those tumors with lower lipoidal staining were associated with worse PFS, and **therefore recommend immediate CT after TACE**. Authors are commended for collecting and analyze a sample size of several hundreds. However, there are several major aspects that need to be addressed.

B-1. Patients with versus without immediate CT demonstrated similar PFS, suggesting that there is minimal use of obtaining immediate CT. However, such lack of statistical significance is likely because authors rarely intervene based on results of immediate CT. I suggest removing patients without immediate CT to avoid confusion.

Reply) We appreciate the reviewer's insightful comment. ***Follwing the comment, we have removed no-immediate-NECT group, and conducted the analyses with the 189 patients with immeidate CT***. We have revised the manuscript accordingly. Because too many sections were revised, it was difficult to display all the changes here. Several the key modifications are shown. Please refer to our annotated manuscript, where all tracked changes are visible.

Changes in the text)

Location	Before revision	After revision
Methods		(Added) "… and (iii) available immediate post-TACE NECT performed on the same day or within one day after TACE."
Results	"Among the 767 eligible patients, 141 patients were excluded … The baseline characteristics of 189626 enrolled patients are summarized …"	"Among the 767 patients … 141 patients were excluded ... Among the 626 patients, 437 patients who had no immediate NECT was excluded. The baseline characteristics of 189 enrolled patients are summarized ..."

B-2. Group A only has two patients. I recommend authors removing this subgroup as well. The author can focus on comparing Group B and C, which should lead to the conclusion that lipoidal retention affects the PFS.

Reply) We appreciate the reviewer's comment. The same concern was raised by another reviewer, and based on this common concern, ***we have deleted the statistical analysis comparing Cohort A and other groups, have removed the conclusive description regarding the outcome of Cohort A***, and have focused on comparing Cohorts B and C. We have revised the manuscript accordingly (see Page 9, line 204-212; Page 10, line 243-245;

Page 10, 253-255).

Changes in the text)

Location	Before revision	After revision
Results	"When comparing the TTP between Cohorts A and B … 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)."	"~~When comparing the TTP between Cohorts A and B~~ 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 5). ~~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).~~
Discussion	"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."	Deleted
Discussion	"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	"In our study, Cohort B demonstrated a significantly shorter TTP compared to Cohort C (lipiodol uptake ≥50%). In addition, patients in Cohort B exhibited a higher rate of residual viable tumor (73.1%) one month after TACE than those in Cohort C (31.1%). In contrast, the two patients in Cohort A who underwent immediate additional treatment showed no progression during follow-up period of more than 12 months."

	the other cohorts (0% in Cohort A and 31.1% in Cohort C).”	

B-3. The definition of immediate CT is vague. How soon is that? same day? 1 day afterwards?

Reply) It was the same day or at least one day afterwards. This information was ommitted, and has been added to the revised manuscript (see Page 4, line 73-75).

Changes in the text)

Location	Before revision	After revision
Methods		(Added) “…and (iii) available immediate post-TACE NECT performed on the same day or within one day after TACE.”

B-4. Please also explain why authors use 50% as the cutoff.

Prior literature used complete versus incomplete:

Dioguardi Burgio, Marco, et al. "Lipiodol retention pattern after TACE for HCC is a predictor for local progression in lesions with complete response." Cancer Imaging 19 (2019): 1-9.

Dioguardi Burgio, Marco, et al. "Correlation of tumor response on computed tomography with pathological necrosis in hepatocellular carcinoma treated by chemoembolization before liver transplantation." Liver Transplantation 22.11 (2016): 1491-1500.

Reply) We appreciate the reviewer’s constructive criticism. The concern regarding the threshold of 50% uptake was also raised by another reviewer. Based on this shared concern, we have revised the lipiodol uptake threshold from 50% to a dichotomy of complete vs. incomplete, in alignment with prior literature suggested by the reviewer. We have re-performed all imaging and statistical analyses, and have revised the manuscript accordingly. Because too many sections were revised, it was difficult to display all the changes here. Several the key modifications are shown. Please refer to our annotated manuscript, where all tracked changes are visible.

Changes in the text)

Location	Before revision	After revision
Method	“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.”	Deleted

Method	"… 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)"	"…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), and Cohort C (complete lipiodol uptake).
Results	"Twenty-eight patients (4.5%) had less than 50% lipiodol uptake in the tumor on NECT… Twenty-six patients, despite having less than 50% lipiodol uptake, … There were 161 patients who demonstrated 50% or greater lipiodol uptake in their tumors."	"Among the 189 patients, 58 patients (30.7%) had incomplete lipiodol uptake in the tumor on NECT… Fifty-six patients, despite having incomplete lipiodol uptake, … There were 131 patients who demonstrated complete lipiodol uptake in their tumors.
Results	"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) …"	"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 5). 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 = 0.026)."

Introduction:

B-5. Line 43-54: First two paragraphs are too tedious. Readers of a gastrointestinal oncology journal are typically familiar with TACE. Please consider shortening.

Reply) We have revised the manuscript in accordance with the reviewer's suggestion (see Page 3, line 41-51).

Changes in the text)

Location	Before revision	After revision
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 content has been further condensed) "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 4HCC, 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). As 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 those who show refractoriness to initial TACE, timely treatment adjustment, is essential to prevent further disease progression and prolong survival (9). Aa reliable method that predicts therapeutic response after the TACE would be beneficial in clinical decision-making and modification of future treatment strategies (10)."

B-6. Line 63: sentence regarding strobe checklist should be moved to Method section.

Reply) We have revised the manuscript accordingly (see Page 5, line 84).

Changes in the text)

Before revision	After revision
(In Introduction) "…This article in accordance with the STROBE reporting checklist."	(In Methods, first paragraph) "…This article in accordance with the STROBE reporting checklist."

Methods:

B-7. Line 72: why contrast enhanced CT or MRI has to be available 7 days prior to TACE? In my practice, we often treat patients with pre-interventional CT/MRI dating more than 7 days.

Reply) We appreciate the reviewer's comment. In practice at our institution, almost all patients scheduled for TACE are admitted and undergo dynamic imaging just before the procedure. Consequently, dynamic imaging within 7 days of the procedure naturally occurs, which led to the inclusion of this criterion. However, we agree that not having imaging within 7 days should not be a reason for exclusion. Therefore, we have removed this inclusion criterion, and specified in the Results that "all patients had dynamic imaging within 7 days of TACE" (see Page 4, line 73-74; Page 7-8, line 169-170).

Changes in the text)

Location	Before revision	After revision
Methods	"… and (iii) dynamic contrast-enhanced CT or MRI within 7 days before TACE procedure"	(Removed)
Results		(Added) "... All patients had dynamic imaging within 7 days of TACE."

B-8. Line 79: please provide reference for such exclusion criteria.

Reply) We have provided reference studies that applied similar exclusion criteria, as detailed below. It has been regarded that the greater the number of lesions, the more complex the evaluation becomes and it becomes difficult to accurately determine the location, size, and boundaries of the lesions, which can affect the accuracy of the image interpretation. Therefore, we applied such exclusion criteria. We have added the following references in the revised manuscript (see Page 4, line 80-82).

References that applied the similar exclusion criteria:

Cancer Imaging 2019 Nov 15;19(1):75	iMRI 2021;25:172-182

Materials and methods **Patients selection** This single center retrospective study was performed in BLINDED and approved by the institutional review board. Informed consent was waived because of the retrospective design. From January 2014 to May 2016 treatment-naïve patients who underwent a first session of cTACE for the treatment of HCC were retrieved from the medical database of our institution. Inclusion criteria were (i) the presence of at least one HCC according to EASL clinical practice guidelines [1], (ii) contrast-enhanced computed tomography (CT) before the cTACE procedure, and during follow-up and (iii) the presence of up to three HCCs to better identify local progression of individual tumors. Tumors that could not be evaluated for response according to mRECIST criteria, (i.e. hypoenhanced on arterial phase and/or infiltrative tumors) were not included in the study.	MATERIALS AND METHODS **Patient Selection** The inclusion criteria for this study were 1) patients with previous histories of locoregional treatment of HCC, such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), radiation therapy, and hepatic resection, 2) patients who underwent liver transplantation or any type of hepatic resection for HCC under radiological or clinical diagnosis of new HCC, and 3) patients who underwent gadoxetic acid-enhanced liver MRI within one month before surgery. The exclusion criteria were 1) patients with more than five HCCs, to avoid the difficulty of lesion-by-lesion matching and 2) patients with infiltrative HCC only. A total of 216 patients who underwent liver surgery for HCC and also had gadoxetic acid-enhanced liver MRI taken within one month before surgery. Among them, 65 patients had previously treated HCC and 15 patients were excluded because they had more than five HCCs (n = 12) or infiltrative type HCCs only (n = 3). Finally, a total of 50 patients (M:F = 39:11; mean age, 56.8 ± 8.2 years old) were included in the final study sample (Fig. 1). Of these, 29 patients were treated by TACE for original HCCs, 16 patients by RFA, 3 patients by TACE+RFA, one patient by TACE+RFA+radiation therapy, and one patient by hepatic resection.
J Magn Reson Imaging 2010 Feb;31(2):365-72	Korean J Radiol 2014 Sep-Oct;15(5):605-12
Detection Rate of Hypervascular HCCs Two experienced radiologists, reader 1 and reader 2 (seven and nine years of experience in abdominal imaging, respectively), blinded to the injection rate and the patients' clinical information, reviewed the arterial phase images of the patients independently and in randomized orders. They were asked to record the location and number of intrahepatic hypervascular HCCs identified on the hepatic arterial phase images. The presence of hypervascular HCCs was determined according to the results of dense lipiodol uptake on follow-up diagnostic images including CT, MRI or conventional angiography, characteristic features of dynamic liver MRI or pathological results including biopsy and surgical excision. Patients with more than five HCCs ($N = 5$) were not included in this analysis. Thus, 43 hypervascular HCCs in 35 patients were included from a total of 45 HCCs in 36 patients.	**Sensitivity for HCC Detection** Patients with another intrahepatic tumor (n = 43) such as hemangioma, metastatic tumor, or angiosarcoma were excluded from the analysis, and patients with more than five HCCs (n = 6) were also excluded from the analysis.

Changes in the text)

Location	Before revision	After revision
Methods	…"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 with more than five HCCs were excluded because the multiplicity of lesions could impede the precise identification of local progression in individual tumors (reference added)."

B-9. Line 86: please define immediate NECT. 1 day? 1 week?

Reply) It was the same day or at least one day afterwards. This information has been added to the revised manuscript (see Page 4, line 73-75).

Changes in the text)

Location	Before revision	After revision
Methods		(Added) "…and (iii) available immediate post-TACE NECT performed on the same day or within one day after TACE."

B-10. Line 97: "highly experienced IR" is not a scientific term. Please specify number of years of practice of each IR. Consider using initials if they were authors.

Reply) We have revised the manuscript accordingly (see Page 5, line 101-102).

Changes in the text)

Location	Before revision	After revision
Methods	"All TACE procedures were performed by highly experienced interventional radiologists."	"All TACE procedures were performed by eight interventional radiologists with 10–35 years of clinical experience."

B-11. Line 97-107: The downside of conventional TACE is demonstrated here. Institutions differ in terms of formula. Please provide reference for this formula.

Reply) We have provided the reference articles for the formula used in our study in the revised manuscript (see Page 5, line 100). Specifically, we have included the following references:

- Radiology 2012;262:708–718
- Liver Int 2018;38:1646–1654

Changes in the text)

Location	Before revision	After revision
Methods	***TACE procedure*** "All TACE procedures were performed by…"	***TACE procedure*** "The TACE procedure performed in our institution has been described previously (reference added). All TACE procedures were performed by…"

B-12. Line 123: determination of lipiodal uptake appears subjective.

Reply) As the reviewer mentioned, the assessment of the degree of lipiodol uptake was performed in a subjective manner, as is customary in our routine clinical practice. Previous studies, including the two reference articles suggested by the reviewer in **Comment B-4** (*Cancer Imaging 2019 Nov 15;19(1):75, Liver Transpl 2016 Nov;22(11):1491-1500),* have

also assessed lipiodol retention qualitatively and subjectively. During the revision, we changed the lipiodol retention threshold from to a dichotomy of complete vs. incomplete, as in line with previous studies. Please also refer to the detailed response to **Comment B-4**. The relevant changes are shown in the revised manuscript.

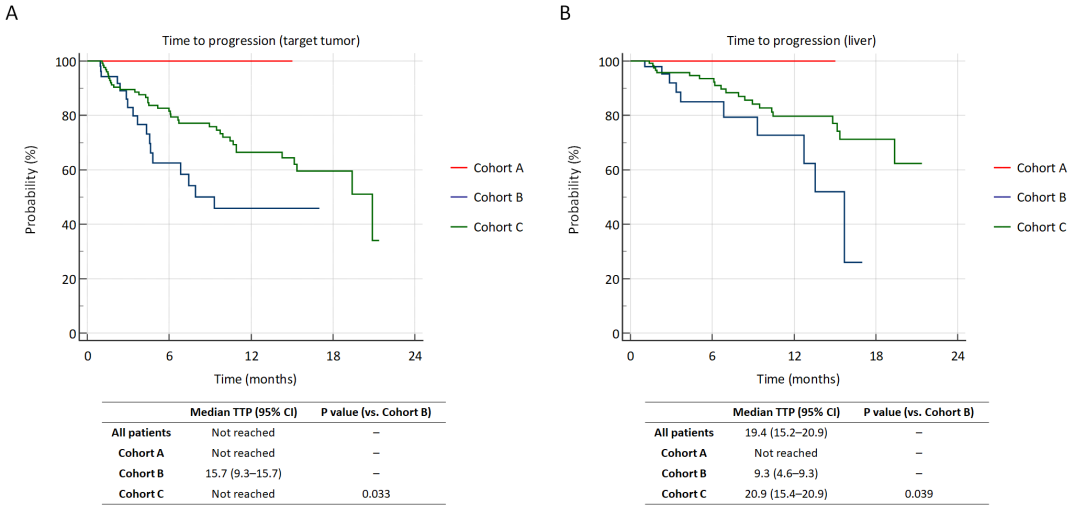
B-13. Line 144: Considering performing stratefied analysis based on target tumor pfs, hepatic pfs, and overall pfs.

Reply) We appreciate the reviewer's insightful comment. Following the reviewer's suggestion, we have conducted additional stratified analyses. As there were no patients with extra-hepatic involvement at the time of the first TACE, the target tumor response pertained to up to two intrahepatic HCCs, while the overall tumor response corresponded to the response of all hepatic tumors unless any new extra-hepatic lesions appeared (including tumor thrombus, lymph node metastasis or metastasis in other sites***). The results are as follows; similar to the overall TTP, the target TTP and hepatic TTP both showed significant differences between Cohort B and Cohort C***. We have included them in the revised manuscript (Page 9, line 222-224 and **Figure S1**).

Changes in the text)

Location	Before revision	After revision
Results		(Added) "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 difference between Cohort B and Cohort C."

The following figure was included as **Figure S1.**



	Median TTP (95% CI)	P value (vs. Cohort B)
All patients	Not reached	–
Cohort A	Not reached	–
Cohort B	15.7 (9.3–15.7)	–
Cohort C	Not reached	0.033

	Median TTP (95% CI)	P value (vs. Cohort B)
All patients	19.4 (15.2–20.9)	–
Cohort A	Not reached	–
Cohort B	9.3 (4.6–9.3)	–
Cohort C	20.9 (15.4–20.9)	0.039

Results:

B-14. Line 181-187: Similar outcomes between groups with or without immediate NECT argues against routinely obtaining immediate NECT.

Reply) It is true that the time to progression (TTP) was similar between the immediate-NECT group and the no-immediate NECT group. However, this does not imply that immediate NECT is unnecessary. The similarity in TTP between the two groups is likely because actions have rarely been taken based on the results of immediate NECT; the information regarding the extent of lipiodol retention in the tumor, which can be assessed through immediate NECT, has not been utilized in patient care, which aligns with the reviewer's **Comment B-1**. Therefore, following the reviewer's recommendation, we have removed the no-immediate-NECT group from the manuscript. Please refer to our detailed response to the **Comment B-1**.

B-15. Line 195: did authors censor patients who underwent 2nd line treatment such as

ablation in PFS analysis?

Reply) Yes. The patients who underwent 2nd line treatment was censored at that point in TTP analysis. We have added this information in the revised manuscript (see Page 7, line 152-153).

Changes in the text)

Location	Before revision	After revision
Methods		(Added) "Patients who underwent 2nd line treatment(s) like ablation was censored at the point of treatment."

B-16. Line 192: any statistical analysis including cohort A is meaning less as there are only 2 patients in this group.

Reply) Based on this common concerns expressed by the reviewers, we have removed the statistical analysis that compared Cohort A and other groups, and removed the conclusive description regarding the outcome of Cohort A. We have revised the manuscript accordingly. Please refer to our response in **Comment B-2.**

B-17. line 203-205: interpretation belongs discussion rather than results section.

Reply) We agree with the reviewer, and have made the relevant changes in the revised manuscript (see Page 10, line 258-260).

Changes in the text)

Before revision	After revision
(In Results) "… 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 Discussion) "… 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**."**

B-18. Line 206-207: i am not sure what is the purpose of comparing non-NECT group and cohort B.

Reply) Following the reviewers' suggestion, the no-immediate NECT group has now been removed in the revised manuscript. Please refer to our detailed response to the **Comment B-1**.

B-19. Please also provide information why immediately NECT was obtained, which is not the standard of care.

Reply) Although performing immediate CT after TACE is not the standard of care, a subset of gastroenterologists and interventional radiologists in our institution have been conducting immediate post-TACE NECT to promptly evaluate the procedure's technical 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. We have added this information in the revised manuscript (see Page 4, line 52-55).

Changes in the text)

Location	Before revision	After revision
Introduction		(Added) "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."

Discussion:

B-20. Please revise after major revision.

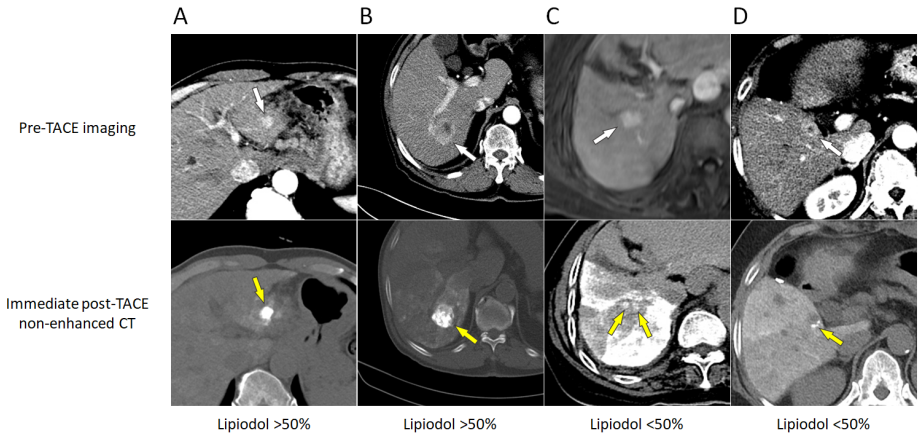
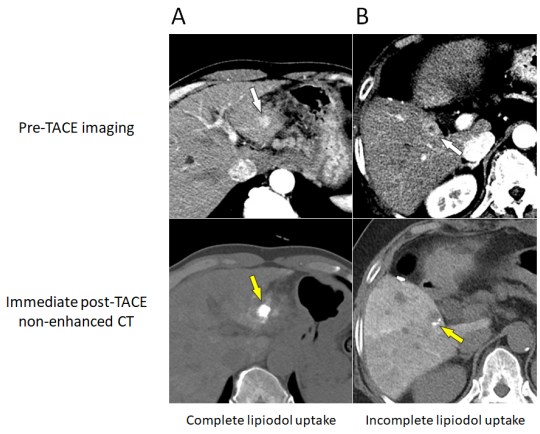
Reply) We have revised the Discussion section by incorporating all the comments provided by the reviewers. Please refer to our revised manuscript (see Page 10-12, line 239-316).

Figures:

B-21. Fig 1C quality is low.

Reply) During the revision process, we have removed Fig 1C. Please refer to the revised **Figure 1**.

Changes in the text)

Before revision	
After revision	

Tables:

B-22. Table 1: Comparison should be performed based on subgroups: i.e. Group B and C.

Reply) Following the reviewer's suggestion, we have incorporated the results of inter-group comparisons into **Table 1**.

Changes in the text)

Before revision

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%)

After revision

Table 1. Characteristics of the patients

Characteristics	All patients	Cohort B	Cohort C	p value
Number of patients	189	56	131	
Age (years)	65 (58–73)	63 (58–70)	67 (58–73)	0.780
Sex				0.163
Men	143 (75.7%)	46 (82.1%)	95 (72.5%)	
Women	46 (24.3%)	10 (17.9%)	36 (27.5%)	
Underlying liver disease				0.981
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%)	
NASH	9 (4.8%)	2 (3.6%)	7 (5.3%)	
Others*	19 (10.1%)	5 (8.9%)	13 (9.9%)	
Liver cirrhosis				0.763
Present	160 (84.7%)	48 (85.7%)	110 (84.0%)	
Absent	29 (15.3%)	8 (14.3%)	21 (16.0%)	
Child-Pugh class				0.432
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)	0.979
Alanine aminotransferase (IU/mL)	24 (17–35)	23 (17–37)	24 (16–34)	0.994
Platelet count (10^9/L)	125 (79–174)	138 (81–180)	124 (79–173)	0.434
Total bilirubin (mg/dL)	0.6 (0.5–0.8)	0.6 (0.4–0.8)	0.6 (0.5–0.8)	0.349
Prothrombin time (INR)	1.1 (1.0–1.2)	1.1 (0.9–1.2)	1.1 (1.0–1.2)	0.737
Albumin (g/dL)	3.6 (3.2–3.9)	3.6 (3.2–3.9)	3.6 (3.2–3.9)	0.394
Alpha-fetoprotein (ng/mL)	7.4 (3.2–41.7)	8.6 (2.8–54.6)	6.0 (3.2–24.4)	0.660
Tumor size (cm)†	3.1 (1.0–20.0)	3.6 (1.0–20.0)	2.2 (1.7–3.3)	0.120
Number of tumors†	1.5 (1–2)	1.7 (1–5)	1.4 (1–5)	0.089
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%)	