Original Article | Gastrointestinal Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2025.1849
Korean J Radiol 2026;27(5):428-439

Korean Journal of Radiology
KJR

Radiologic Response Assessment With RECIST 1.1 and mRECIST in Patients With Hepatocellular Carcinoma Treated With Atezolizumab Plus Bevacizumab

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Objective: Evidence remains limited regarding whether Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) or modified RECIST (mRECIST) more reliably assesses treatment response in patients with hepatocellular carcinoma (HCC) receiving atezolizumab plus bevacizumab (Atezo/Bev). This study aimed to evaluate response patterns based on RECIST 1.1 and mRECIST, analyze inter-reader agreement, and assess their prognostic value for overall survival (OS) in patients with HCC receiving first-line Atezo/Bev.

Materials and Methods: This retrospective study included patients with HCC treated with first-line Atezo/Bev between June 2020 and December 2022 at a tertiary center. Patients with at least one hypervascular hepatic target lesion were eligible. Two radiologists independently assessed treatment responses using RECIST 1.1 and mRECIST. Inter-reader agreement was evaluated using Cohen's kappa coefficient. Time-dependent Cox regression analysis was performed, with radiologic response and progression treated as time-varying covariates. Prognostic discrimination was evaluated using Harrell's concordance index (C-index).

Results: A total of 207 patients were included (171 men; median age, 63 years; median follow-up, 10.7 months [range, 0.8–46.4 months]; median OS, 10.7 months [95% confidence interval, 9.2–12.8 months]). mRECIST identified more responders than RECIST 1.1 (54.6% vs. 16.9%). RECIST 1.1 demonstrated excellent inter-reader agreement, whereas mRECIST showed substantial agreement (weighted kappa, 0.89 vs. 0.79). A significantly higher rate of dissociated responses was observed with mRECIST than with RECIST 1.1 (14.0% vs. 4.3%, $P < 0.001$). Both RECIST 1.1- and mRECIST-based responses and progression were independently associated with OS. Models incorporating RECIST 1.1 demonstrated slightly higher C-index values than those incorporating mRECIST (RECIST 1.1: 0.68 for response and 0.75 for progression; mRECIST: 0.65 and 0.70, respectively).

Conclusion: RECIST 1.1 is more reproducible and prognostically valuable for guiding treatment decisions in patients with HCC receiving first-line Atezo/Bev. However, this does not invalidate the use of mRECIST as a biological tumor response marker.

Keywords: Response evaluation criteria in solid tumors; Carcinoma, Hepatocellular; Atezolizumab; Bevacizumab; Survival

INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, and many patients are diagnosed at an advanced stage, with median overall survival (OS) ranging from 8 months to 2 years [1-3]. Atezolizumab plus bevacizumab (Atezo/Bev), which exert synergistic effects by activating T cells and inhibiting angiogenesis and tumor growth, have demonstrated superior survival benefits over sorafenib in patients with

Received: December 4, 2025 **Revised:** February 10, 2026 **Accepted:** February 28, 2026
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unresectable HCC [2,4,5], and have been approved as a first-line systemic therapy for these patients [4].

The Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [6] and modified RECIST (mRECIST) [7] are commonly used to evaluate treatment responses in patients with HCC. The primary distinction between these criteria lies in their assessment of hepatic lesions: RECIST 1.1 measures changes in tumor size, whereas mRECIST evaluates the arterial-enhancing portions of intrahepatic tumors. Previous guidelines from the European Association for the Study of the Liver (EASL) recommended using both RECIST 1.1 and mRECIST for response assessment in HCC during systemic treatment [8]. However, because evidence supporting the incremental prognostic benefit of mRECIST over RECIST 1.1 remains limited, the updated EASL guidelines designate RECIST 1.1 as the primary response assessment method in clinical trials of systemic therapies, while mRECIST may be used as a secondary or complementary criterion when appropriate [9].

Existing data directly comparing RECIST 1.1 and mRECIST are limited [10], and studies evaluating these criteria as surrogates for OS after various systemic therapies have reported conflicting findings [11-18]. Some studies have demonstrated that RECIST-based response categories are more strongly associated with OS in patients treated with immunotherapy, including Atezo/Bev [19], whereas others have suggested that mRECIST better reflects survival outcomes, particularly in sorafenib-treated patients [11-15]. Several studies indicate that both RECIST 1.1 and mRECIST may correlate with survival outcomes [16,17]. However, to date, evidence from head-to-head comparisons of RECIST 1.1 and mRECIST regarding treatment response assessment and reliability of the two criteria remains limited. This study aimed to compare treatment response patterns according to RECIST 1.1 and mRECIST in patients with HCC receiving first-line Atezo/Bev. Inter-reader and inter-criteria agreements were evaluated, and the prognostic value of RECIST 1.1 and mRECIST responses for predicting OS was assessed.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2023-0204), a tertiary hospital, which waived the requirement for informed consent. The study complied with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines [20].

Study Population

This study retrospectively enrolled consecutive patients with HCC treated with first-line Atezo/Bev between June 2020 and December 2022 at Asan Medical Center, a tertiary academic hospital. Patients were included if they 1) were aged ≥18 years and had a diagnosis of HCC according to the Liver Imaging Reporting and Data System v2018 [21], 2) received Atezo/Bev as first-line systemic therapy, and 3) underwent baseline imaging (liver dynamic CT or MRI) within 1 month before the initiation of Atezo/Bev. Patients were excluded if they 1) had other malignancies, 2) did not undergo follow-up imaging for response evaluation, 3) received concurrent locoregional therapy during Atezo/Bev treatment, or 4) did not have a hypervascular target lesion in the liver as defined by both RECIST 1.1 and mRECIST guidelines.

Data Collection

Patients were treated with atezolizumab 1,200 mg and bevacizumab 15 mg/kg every 3 weeks until unacceptable toxicity or radiological/symptomatic disease progression occurred. Baseline characteristics that were recorded within 1 month before treatment initiation included age, sex, etiology of liver disease, prior treatments, Eastern Cooperative Oncology Group (ECOG) performance status, Child–Pugh class, Barcelona Clinic Liver Cancer (BCLC) stage, and laboratory data. Information regarding subsequent management after progression on Atezo/Bev, including initiation of second-line systemic therapy or treatment discontinuation, was collected.

Imaging Analysis: RECIST 1.1 and mRECIST Guidelines

For both baseline and follow-up imaging, patients underwent chest CT and dynamic liver CT (including precontrast, arterial, portal venous, and delayed phases) or chest CT and dynamic contrast-enhanced liver MRI using a hepatobiliary-specific contrast agent (Primovist® [gadoxetate disodium]; Bayer AG, Leverkusen, Germany) at each timepoint. Most patients underwent follow-up imaging at regular intervals of 1–2 weeks: 80 (38.6%) patients every 6 weeks, 82 (39.6%) every 8 weeks, and 45 (21.7%) every 12 weeks. The mean inter-scan interval was 8.8 ± 2.7 weeks. Radiologic responses were independently evaluated by two board-certified radiologists (with 7 and 11 years of experience in liver imaging, respectively) who were blinded to clinical data. For the main analysis, disagreements between the two readers were resolved by consensus, with

 https://doi.org/10.3348/kjr.2025.1849

a third radiologist (20 years of experience) serving as an adjudicator when necessary. Tumor in vein was considered present when definite enhancing soft tissue was identified in a vein [21] and was considered as a non-measurable lesion [7]. Responses were categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). According to RECIST 1.1, PR or CR was required to be confirmed on the subsequent assessment performed 6–12 weeks later, with the response timepoint defined as the date of first documentation. If disease progression occurred without confirmation, patients were classified as having PD. The best overall response (BOR) was defined as the best response recorded from treatment initiation to discontinuation, considering both target and non-target lesions, as well as the presence of new lesions. The objective response rate (ORR) was defined as the proportion of patients who achieved CR or PR [6].

The primary distinction between RECIST 1.1 and mRECIST lies in the evaluation of intrahepatic lesions and the criteria for defining new lesions. RECIST 1.1 measures target lesions by their longest diameter and qualitatively evaluates non-target lesions based on size. Conversely, mRECIST measures only the arterial-enhancing portion of intrahepatic target lesions and evaluates non-target intrahepatic lesions based on changes in enhancement rather than size. In mRECIST, new hepatic lesions are defined as progression only if they demonstrate a typical HCC enhancement pattern (arterial enhancement followed by washout in the portal/delayed phase), while RECIST 1.1 considers any new lesion as progression. Patients were categorized as responders (i.e., BOR of CR or PR) or non-responders (i.e., BOR of SD or PD). Additionally, patients were classified as progressors (i.e., those who developed PD at any time) or non-progressors. Follow-up images were analyzed until the termination of Atezo/Bev treatment.

Statistical Analysis

Inter-reader agreement was assessed at each follow-up timepoint using each criterion, whereas inter-criterion agreement between RECIST 1.1 and mRECIST was assessed by comparing the BOR. The weighted Cohen's kappa coefficient was used for both analyses [22]. For inter-reader agreement, patient-level bootstrapping (1,000 iterations) was applied to account for within-patient clustering, and 95% confidence intervals (CIs) were estimated using bias-corrected and accelerated methods. Percent agreement and category-specific agreement (i.e., 2 x [number of cases with agreement] divided by the total number of cases assigned to that category by both readers) were calculated to account for potential effects of class imbalance.

OS was defined as the time from Atezo/Bev initiation to death from any cause [23,24]. OS was estimated using Simon–Makuch plots to account for the time-dependent nature of treatment response, and group comparisons (responders vs. non-responders and progressors vs. non-progressors according to RECIST 1.1 and mRECIST) were performed using the Mantel–Byar test or, when appropriate, the Kaplan–Meier method with log-rank tests. The association between radiologic treatment response assessment (according to RECIST 1.1 and mRECIST) and OS was evaluated using multivariable analyses. To address the potential time-varying effect and minimize immortal time bias, time-dependent Cox proportional hazards regression was used, with radiologic response (responder vs. non-responder) and progression status (progressor vs. non-progressor) treated as time-varying covariates in separate models. Harrell's concordance index (C-index) was calculated to assess the prognostic discrimination of the regression models [25]. The C-index values of models incorporating RECIST 1.1 were compared with those of models incorporating mRECIST using bootstrap resampling (1,000 samples).

To further investigate the prognostic implications of the discordance between RECIST 1.1 and mRECIST, we compared the hazard of death between concordant and discordant classifications using hazard ratio (HR). Specifically, we examined mRECIST-defined progressors vs. non-progressors among RECIST 1.1–defined progressors, and RECIST 1.1–defined progressors vs. non-progressors among mRECIST-defined non-progressors.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org). A *P*-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Of 537 eligible patients with HCC, 330 were excluded: 190 lacked targetable intrahepatic lesions according to mRECIST (59 had liver lesions <1 cm, 52 had infiltrative non-measurable lesions, 48 had only hypovascular lesions, and 31 had no detectable liver lesions), 92 received concurrent locoregional therapy during Atezo/Bev treatment,

https://doi.org/10.3348/kjr.2025.1849

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43 did not undergo follow-up imaging for response assessment, and 5 had other malignancies. The 59 patients with liver lesions <1 cm had intermediate- or advanced-stage HCC, characterized by multiple intrahepatic lesions, portal vein tumor thrombosis, or extrahepatic metastasis. The final study population comprised 207 patients (171 men and 36 women). The data cutoff date for OS was March 21, 2025, and the median follow-up duration was 10.7 months (range, 0.8–46.4 months). Table 1 summarizes the characteristics of the study population. Treatment response was assessed using chest and liver CT (n = 193) or chest CT combined with liver MRI (n = 14).

Table 1. Clinical characteristics of the study population

Characteristic	Total (n = 207)
Age, yr	63 (55–71)
Sex, female:male	36 (17.4):171 (82.6)
ECOG performance status	
0	43 (20.8)
1	164 (79.2)
Child-Pugh class	
A	169 (81.6)
B	38 (18.4)
BCLC stage	
A or B*	57 (27.5)
C	150 (72.5)
Laboratory results	
ALT, IU/L†	26 (18–39)
AST, IU/L†	29 (23–38)
Total bilirubin, mg/dL	0.6 (0.4–0.7)
Albumin, g/dL	3.8 (3.6–4.1)
PT-INR	1.1 (1.0–1.1)
AFP	
≤200 ng/mL	93 (44.9)
>200 ng/mL	95 (45.9)
Missing	19 (9.2)
PIVKA-II, mAU/L‡	356 (49–35,575)
Tumor location	
Intrahepatic only	69 (33.3)
Both intrahepatic and extrahepatic	138 (66.7)
Treatment before Atezo/Bev§	144 (69.6)
Chemoembolization	136 (65.7)
Radiation	54 (26.1)
Resection	51 (24.6)
Ablation	41 (19.8)

Data are presented as medians with interquartile range in parentheses or numbers with percentages in parentheses.
*Twelve patients were classified as BCLC stage A, of whom 3 were enrolled in the neoadjuvant chemotherapy clinical trial, and 9 were refractory to local treatment, †Data were missing for 25 patients, ‡Data were missing for 21 patients, §The total percentage may exceed 100% because a single patient may have received multiple treatments.
BCLC = Barcelona Clinic Liver Cancer, ECOG = Eastern Cooperative Oncology Group, ALT = alanine aminotransferase, AST = aspartate transaminase, PT-INR = prothrombin time-international normalized ratio, AFP = alpha-fetoprotein, PIVKA = protein induced by vitamin K absence or antagonist, Atezo/Bev = atezolizumab plus bevacizumab

Response Evaluation According to RECIST 1.1 and mRECIST Criteria

RECIST 1.1 identified 35 responders (ORR, 16.9%), whereas mRECIST identified 113 responders (ORR, 54.6%) (Fig. 1). Among 172 non-responders according to RECIST 1.1, 78 patients (45.3%) were classified as responders by mRECIST. None of the mRECIST-defined non-responders were classified as responders according to RECIST 1.1. Among patients with Child–Pugh class A, the ORR was 19.5% (33/169) according to RECIST 1.1 and 58.6% (99/169) according to mRECIST. Among patients with Child–Pugh class B, the ORRs were 5.3% (2/38) and 36.8% (14/38), respectively.

Inter-Reader and Inter-Criteria Agreement and Dissociated Responses

Inter-reader agreement was assessed using 450 response assessments per criterion. RECIST 1.1 demonstrated excellent agreement (weighted kappa, 0.89; 95% CI, 0.83–0.93), whereas mRECIST showed substantial agreement

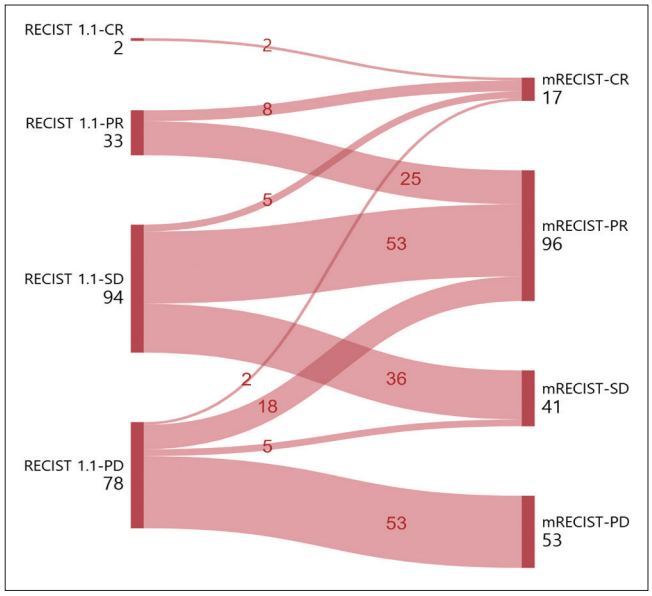

Fig. 1. Best overall response categories according to RECIST 1.1 and mRECIST criteria. RECIST = Response Evaluation Criteria in Solid Tumors, mRECIST = modified RECIST, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease

https://doi.org/10.3348/kjr.2025.1849

(weighted kappa, 0.79; 95% CI, 0.70–0.84). RECIST 1.1 consistently demonstrated higher agreement than mRECIST in both overall and category-specific agreements. Accordingly, mRECIST showed higher inter-reader discordance than RECIST 1.1 for both overall response classification (63 [14.0%] vs. 36 [8.0%], $P = 0.006$) and for classification of responders versus non-responders (32 [7.1%] vs. 5 [1.1%], $P < 0.001$) (Table 2).

Dissociated responses—defined as the coexistence of responding and non-responding lesions within the same patient [26]—occurred more frequently with mRECIST (29 of 207 patients [14.0%]) than with RECIST 1.1 (9 of 207 patients [4.3%]; $P < 0.001$). In these cases, patients demonstrated a response (CR or PR) in target lesions accompanied by simultaneous progression of non-target lesions or the emergence of new lesions. Agreement of BOR between RECIST 1.1 and mRECIST was moderate (weighted kappa, 0.46; 95% CI, 0.38–0.54).

Discordant Classification Between RECIST 1.1 and mRECIST

All 35 RECIST 1.1-defined responders also met the mRECIST criteria for response, with decreased extent or absent arterial enhancement. In contrast, among the 113 mRECIST-defined responders, lesion size remained stable or increased in 78 patients (69.0%), resulting in discordant classifications between the two criteria. Among the 143 RECIST 1.1–defined progressors (eventual progression regardless of BOR), 102 (71.3%) were also classified as progressors according to mRECIST at the time of RECIST 1.1–defined PD, whereas 41 (28.7%) were classified as non-progressors according to mRECIST because arterial enhancement remained stable, decreased, or disappeared. Figures 2 and 3 illustrate the representative cases of discordant responses between the two criteria.

Among the 143 RECIST 1.1–defined progressors, the HR for OS in mRECIST-defined progressors compared with non-progressors was 1.21 (95% CI, 0.83–1.76), indicating no significant difference in hazard ($P = 0.32$). In contrast, among the 105 patients classified as non-progressors by mRECIST, the HR for OS in the 41 RECIST 1.1–defined progressors compared with the 64 RECIST 1.1–defined non-progressors was 2.39 (95% CI, 1.52–3.77), demonstrating a significant difference ($P < 0.001$).

Survival Analysis According to RECIST 1.1 and mRECIST

The median OS was 10.7 months (95% CI, 9.2–12.8 months), with 173 deaths (83.6%) occurring during follow-up. The survival curves for mRECIST-defined responders and non-responders crossed during follow-up, with responders showing worse survival early after treatment initiation (Fig. 4). Figure 5 shows the OS across response categories according to RECIST 1.1 and mRECIST. Median OS differed significantly according to liver function, with 12.4 months for patients with Child–Pugh class A and 4.9 months for those with Child–Pugh class B ($P < 0.001$). The crossing of survival curves between mRECIST-defined responders and non-responders persisted among patients with Child–Pugh class A (Supplementary Fig. 1).

In multivariable time-dependent Cox regression analyses, responder versus non-responder status according to RECIST 1.1 and mRECIST remained independently associated with OS after adjustment for clinical covariates (HR, 0.31 and 0.56, respectively; both $P < 0.001$; Table 3). Similarly, progressor versus non-progressor status according to

Table 2. Percent agreement and discordance between readers according to RECIST 1.1 and mRECIST

	RECIST 1.1	mRECIST	*P*
Overall agreement	90.0 (414/450)	86.0 (387/450)	0.006
Category-based agreement*			
CR or PR	96.4 (160/166)	89.9 (320/356)	
SD	90.8 (314/346)	84.7 (150/177)	
PD	91.8 (356/388)	86.4 (304/352)	
Discordant assessment	8.0 (36/450)	14.0 (63/450)	0.006
Target lesion	1.8 (8/450)	7.8 (35/450)	
Non-target lesion	5.1 (23/450)	5.8 (26/450)	
New lesion	1.1 (5/450)	0.4 (2/450)	
Discordance in response status (responders vs. non-responders)	1.1 (5/450)	7.1 (32/450)	<0.001

Data are presented as percentages.
*Calculated as 2 x (number of cases with agreement)/(total number of times the category was assigned by both readers).
RECIST = Response Evaluation Criteria in Solid Tumors, mRECIST = modified RECIST, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease

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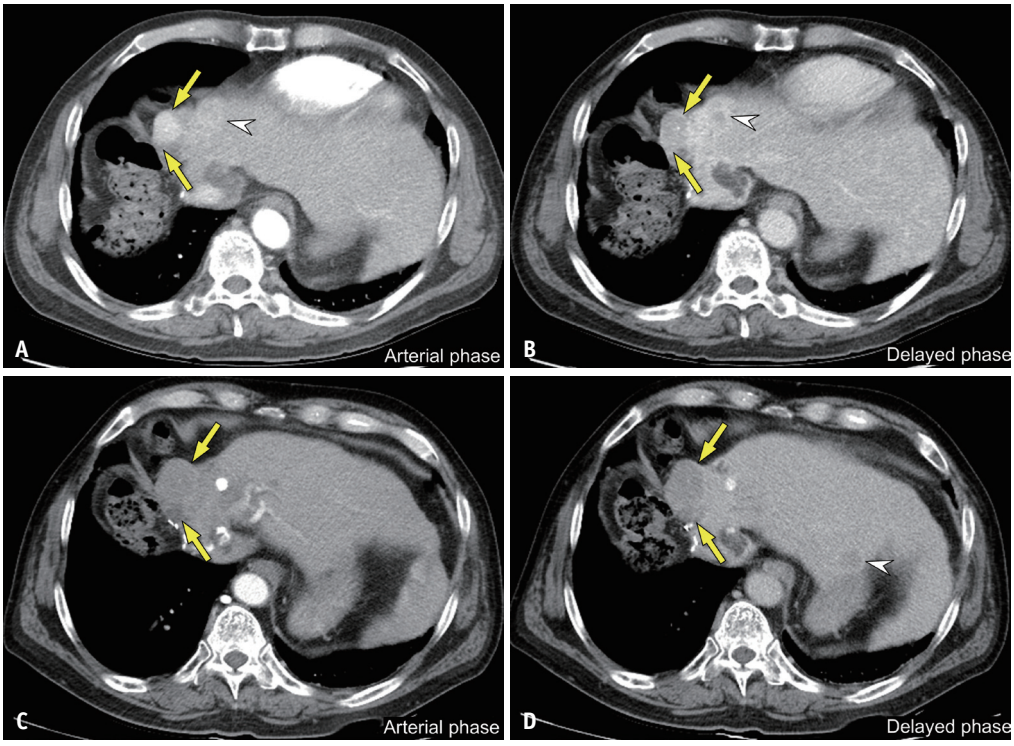

Fig. 2. A case example of discordant response classification by RECIST 1.1 and mRECIST with poor outcome. **A, B:** A 66-year-old man with HCC was treated with Atezo/Bev. Baseline CT images obtained before treatment initiation show a 2.6-cm mass in segment IV of the liver, demonstrating arterial phase enhancement (arrows, **A**) and washout on the delayed phase (arrows, **B**), consistent with HCC. An additional lesion is also observed medially, exhibiting similar enhancement and washout characteristics (arrowheads). **C, D:** Follow-up CT performed 42 weeks later reveals that arterial enhancement of the lesion has resolved, although the lesion has increased in size to 4.1 cm (arrows). A new hypodense lesion (arrowhead) is also present in the left lateral section. According to RECIST 1.1, the patient met the criteria for progressive disease; however, based on mRECIST, the patient was classified as a responder. The patient died 5 months after the follow-up scan. RECIST = Response Evaluation Criteria in Solid Tumors, mRECIST = modified RECIST, HCC = hepatocellular carcinoma, Atezo/Bev = atezolizumab plus bevacizumab

RECIST 1.1 and mRECIST was independently associated with OS (HR, 4.90 and 2.66, respectively; both $P < 0.001$; Table 4).

Regression models incorporating RECIST 1.1–based assessment and clinical variables (age, sex, Child–Pugh class, alpha-fetoprotein level, and BCLC stage) yielded C-indices of 0.68 (95% CI, 0.67–0.69) for responder versus non-responder and 0.75 (95% CI, 0.73–0.77) for progressor versus non-progressor. Models incorporating mRECIST assessment yielded C-indices of 0.65 (95% CI, 0.63–0.67) and 0.70 (95% CI, 0.68–0.72), respectively. The C-index values were significantly higher for RECIST 1.1 than for mRECIST (Supplementary Table 1).

Subsequent Treatment

Among the 143 patients who experienced radiologic progression according to RECIST 1.1, 129 (90.2%) discontinued Atezo/Bev therapy at the time of progression. Of these, 45 discontinued treatment due to poor performance status, refusal of further treatment, or death. The remaining 84 patients initiated second-line systemic therapy: 65 received sorafenib, 11 received lenvatinib, 6 received regorafenib, and 2 received cabozantinib. The remaining 14 patients (9.8%) continued Atezo/Bev treatment beyond RECIST 1.1–defined progression. Among these patients, the median duration of treatment beyond progression was 3.0 months (range, 1.1–9.9 months).

DISCUSSION

In this study, we assessed the reliability and clinical implications of RECIST 1.1 and mRECIST in patients with HCC receiving first-line Atezo/Bev treatment. Higher inter-reader agreement was observed with RECIST 1.1 than with mRECIST. Discrepancies in response assessment occurred more frequently with mRECIST, particularly when evaluating target lesions, often resulting in discordant classifications

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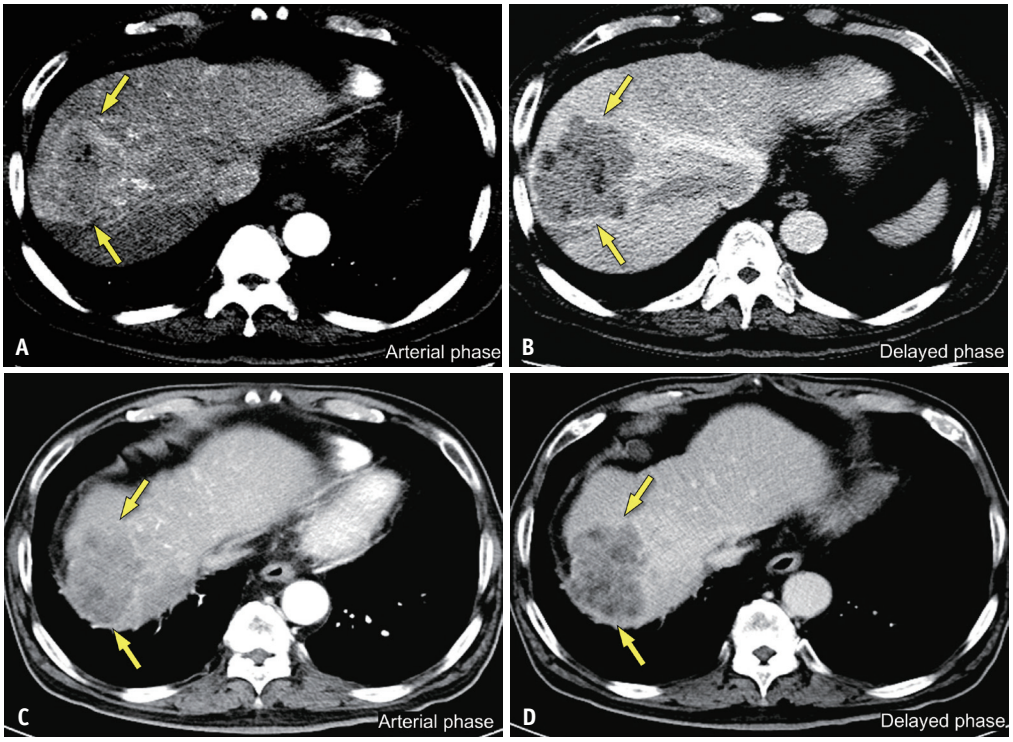

Fig. 3. A case example of discordant response classification by RECIST 1.1 and mRECIST with prolonged survival. **A, B:** A 67-year-old man with HCC treated with Atezo/Bev. Baseline CT images demonstrate a 6.8-cm mass in the right hemiliver showing arterial phase enhancement (arrows, **A**) and washout on the delayed phase image (arrows, **B**). **C, D:** Follow-up CT performed 36 weeks later revealed that the lesion size remained stable at 6.5 cm, whereas arterial enhancement of the lesion had resolved (arrows). Although the patient was classified as a non-responder (stable disease) according to RECIST 1.1, he was classified as a responder according to mRECIST, illustrating discordant response classification between the two criteria. The patient survived for more than 2 years after initiation of Atezo/Bev treatment. RECIST = Response Evaluation Criteria in Solid Tumors, mRECIST = modified RECIST, HCC = hepatocellular carcinoma, Atezo/Bev = atezolizumab plus bevacizumab

between responders and non-responders. Models incorporating RECIST 1.1 demonstrated C-indices of ≥0.68 for predicting OS.

The higher inter-reader variability observed with mRECIST, particularly in target lesion assessment, may reflect the greater measurement variability associated with evaluating the arterial-enhancing portion. One potential source of measurement variability is the relatively small size of the arterial-enhancing portion compared with the overall tumor size, as well as heterogeneous decreases in enhancement and ill-defined boundaries between enhancing and non-enhancing regions. Furthermore, among mRECIST-defined responders, tumor size did not always decrease in parallel with reductions in arterial enhancement. mRECIST also exhibited a higher rate of dissociated responses between target and non-target lesions than RECIST 1.1, suggesting that enhancement-based assessment of intrahepatic target lesions may not completely reflect the overall tumor burden, particularly in the presence of non-target lesion growth or new lesions.

The higher ORR observed in mRECIST compared with RECIST 1.1, consistent with previous studies [18,19,27], suggests greater sensitivity for detecting radiologic responses. However, in our study, OS did not differ significantly according to mRECIST classification. The survival curves for mRECIST-defined responders and non-responders crossed during follow-up, and responders exhibited an early survival disadvantage. This pattern may be attributable to the limited performance of enhancement-based assessment in the presence of dissociated responses, as well as to measurement variability that may reduce the reproducibility of quantifying the enhancing portion measurement. However, these findings do not preclude the potential clinical relevance of mRECIST. Because treatment decisions in our study population were primarily guided by RECIST 1.1, the prognostic value of mRECIST may not have been fully evaluated.

The ORR of 55% by mRECIST observed in this study was

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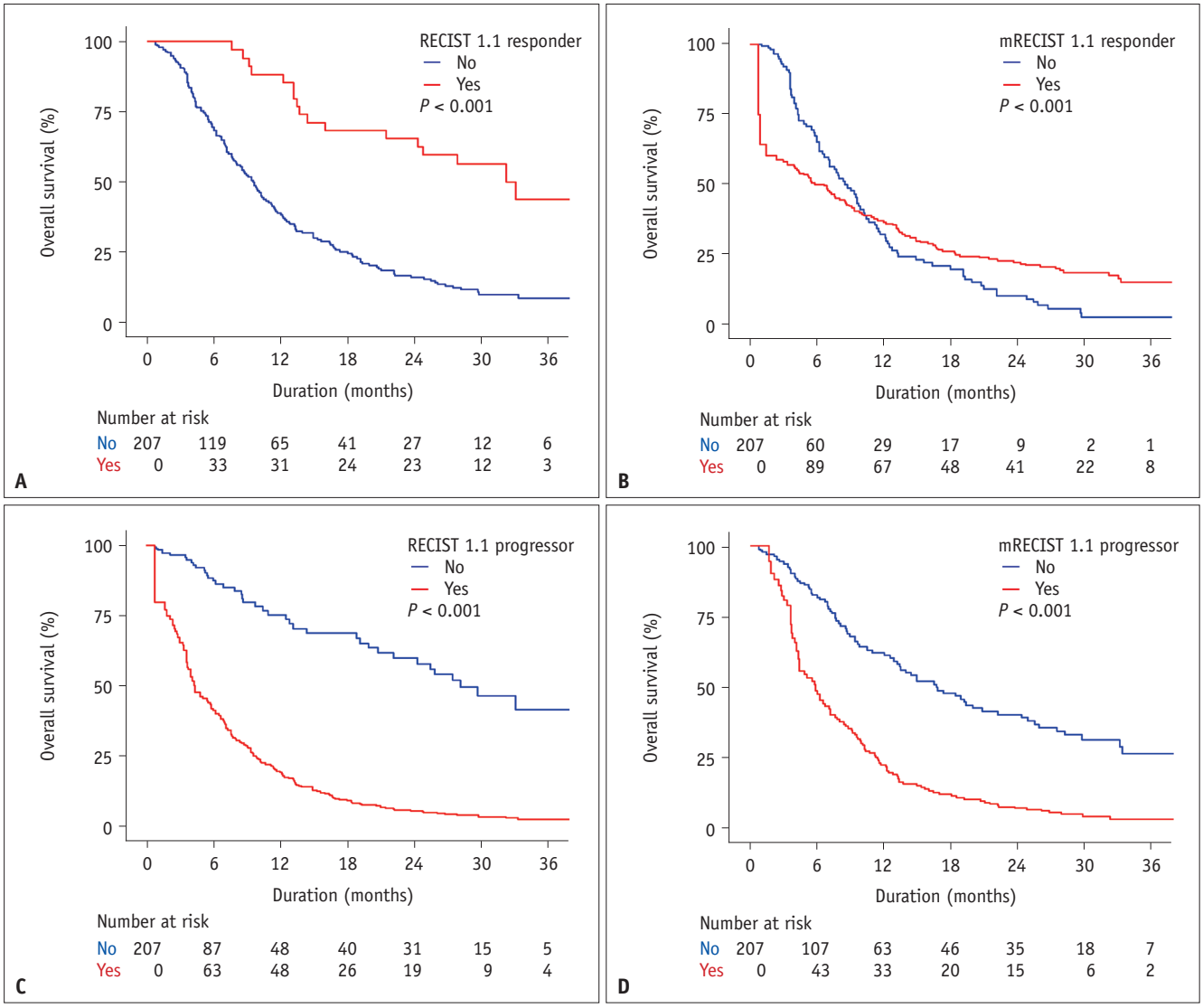

Fig. 4. Simon–Makuch plots showing overall survival comparing responders and non-responders. **A-D:** Simon–Makuch plots for overall survival stratified by **(A)** RECIST 1.1–defined responders vs. non-responders, **(B)** mRECIST-defined responders vs. non-responders, **(C)** RECIST 1.1–defined progressors vs. non-progressors, and **(D)** mRECIST-defined progressors vs. non-progressors. All comparisons using the Mantel–Byar test demonstrated statistically significant differences ($P < 0.001$). RECIST = Response Evaluation Criteria in Solid Tumors, mRECIST = modified RECIST

higher than that reported in previous clinical trials and real-world data [28-31]. Cheng et al. [28] reported an ORR of 33% using data from the IMbrave150 trial, and meta-analyses of real-world data have shown pooled ORRs of 35%–40.1% [29-31]. The difference in ORRs between RECIST 1.1 and mRECIST was substantial in our study (17% vs. 55%), and these discrepancies relative to prior studies may stem from our specific inclusion criteria, which enriched the cohort for hypervascular lesions prone to intratumoral devascularization after Atezo/Bev therapy, thereby facilitating detection of mRECIST-based response. Additionally, the observed discrepancies may reflect the lower reliability of mRECIST, potentially leading to overestimation of response. In our study, dissociated responses were more frequent, and inter-reader concordance was lower with mRECIST. Consistent with these findings, meta-analyses have shown that pooled ORRs assessed by RECIST 1.1 exhibit low heterogeneity (I^2 near zero), whereas pooled ORRs assessed by mRECIST are substantially more heterogeneous (I^2 up to 71%), underscoring that mRECIST may introduce greater variability [31].

The median OS in our study was 10.7 months, which was shorter than the 19.2 months reported in the IMbrave150 trial. This discrepancy likely reflects differences in patient

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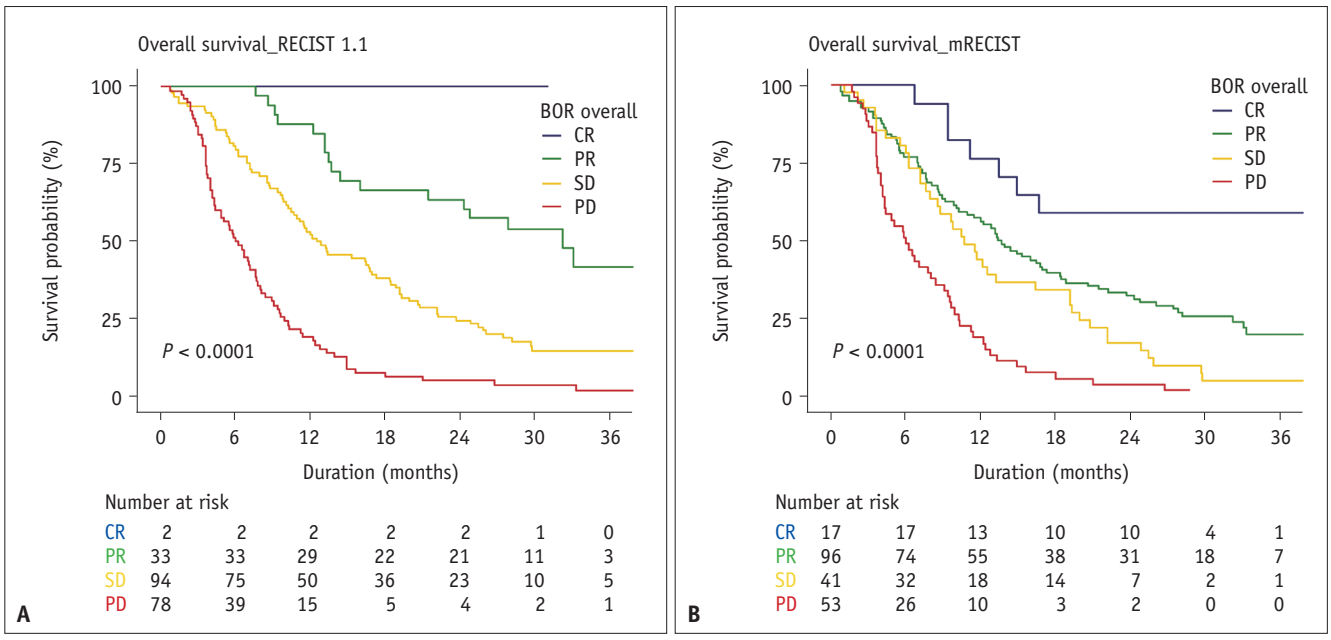

Fig. 5. Kaplan–Meier analyses of overall survival across response categories by **(A)** RECIST 1.1 and **(B)** mRECIST. Comparisons among groups using the log-rank test demonstrated statistically significant differences ($P < 0.001$). RECIST = Response Evaluation Criteria in Solid Tumors, mRECIST = modified RECIST, BOR = best overall response, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease

Table 3. Cox regression analysis of factors associated with overall survival including responders vs. non-responders

Variable	Univariable analysis		Multivariable analysis–RECIST 1.1		Multivaraiable analysis–mRECIST	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age	1.00 (0.98–1.01)	0.54	1.02 (1.00–1.03)	0.02	1.01 (1.00–1.02)	0.19
Sex, male	1.17 (0.79–1.74)	0.44	1.24 (0.84–1.85)	0.28	1.20 (0.81–1.78)	0.37
Child-Pugh class B*	2.47 (1.70–3.58)	<0.001	2.41 (1.64–3.53)	<0.001	2.55 (1.74–3.75)	<0.001
AFP >200 ng/mL	1.90 (1.39–2.61)	<0.001	1.52 (1.11–2.09)	0.01	1.53 (1.11–2.10)	0.01
BCLC stage C†	1.73 (1.21–2.46)	0.003	1.54 (1.07–2.21)	0.02	1.53 (1.06–2.19)	0.02
RECIST responders‡	0.29 (0.17–0.48)	<0.001	0.31 (0.19–0.53)	<0.001	–	–
mRECIST responders‡	0.49 (0.36–0.67)	<0.001	–	–	0.56 (0.40–0.77)	<0.001

Statistical test: time-dependent Cox regression with radiologic response statuses treated as time-varying covariates; level of significance: $P < 0.05$.
*Compared with Child-Pugh class A, †Compared with BCLC stage A or B, ‡Compared with non-responders.
BCLC = Barcelona Clinic Liver Cancer, RECIST = Response Evaluation Criteria in Solid Tumors, mRECIST = modified RECIST, CI = confidence interval, AFP = alpha-fetoprotein

characteristics and clinical settings. Our cohort included patients with more heterogeneous liver functions, including 18.4% with Child–Pugh class B, whereas only patients with Child–Pugh class A were enrolled in IMbrave150. Indeed, median OS differed significantly by Child-Pugh class in our study (12.4 months for Child–Pugh class A vs. 4.9 months for Child–Pugh class B; $P < 0.001$). Additional contributing factors may include a lower proportion of patients with ECOG performance status 0 (21% vs. 62% in IMbrave150) and more extensive prior locoregional treatments (70% vs. 52%). Other biological and clinical factors known to influence response and survival outcomes after Atezo/Bev therapy—such as immune-active or immune-suppressive molecular profiles, gene expression signatures, and underlying disease etiology—were not fully captured in this study. Although several real-world studies have reported similarly shorter OS [17,32-34], direct comparisons of our response rates or survival outcomes with those of other studies are limited and should be interpreted with caution.

This study has several limitations. First, treatment response was assessed retrospectively and did not influence real-time clinical decision-making. Treatment discontinuation was guided primarily by RECIST 1.1, which may have underestimated the prognostic utility of

https://doi.org/10.3348/kjr.2025.1849

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Table 4. Cox regression analysis of factors associated with overall survival including progressors vs. non-progressors

Variable	Univariable analysis		Multivariable analysis–RECIST 1.1		Multivariable analysis–mRECIST	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age	1.00 (0.98–1.01)	0.54	1.02 (1.01–1.03)	0.002	1.01 (1.00–1.03)	0.03
Sex, male	1.17 (0.79–1.74)	0.44	1.24 (0.84–1.84)	0.29	1.15 (0.77–1.71)	0.49
Child-Pugh class B*	2.47 (1.70–3.58)	<0.001	2.23 (1.52–3.27)	<0.001	2.34 (1.60–3.43)	<0.001
AFP >200 ng/mL	1.90 (1.38–2.61)	<0.001	1.76 (1.28–2.41)	0.001	1.72 (1.25–2.36)	0.001
BCLC stage C†	1.73 (1.21–2.46)	0.003	1.22 (0.85–1.75)	0.29	1.28 (0.88–1.85)	0.2
RECIST progressors‡	4.87 (3.38–7.02)	<0.001	4.90 (3.36–7.14)	<0.001	–	–
mRECIST progressors‡	2.82 (2.08–3.83)	<0.001	–	–	2.66 (1.93–3.67)	<0.001

Statistical test: time-dependent Cox regression with progression statuses treated as time-varying covariates; level of significance: P <0.05.
*Compared with Child-Pugh class A, †Compared with BCLC stage A or B, ‡Compared with non-progressors.
BCLC = Barcelona Clinic Liver Cancer, RECIST = Response Evaluation Criteria in Solid Tumors, mRECIST = modified RECIST, CI = confidence interval, AFP = alpha-fetoprotein

mRECIST, as the potential survival impact of continuing treatment beyond RECIST 1.1–defined progression could not be evaluated. Therefore, the findings of this study should be interpreted with caution. However, the impact of this structural limitation on the evaluation of mRECIST may be limited for several reasons. First, response status was analyzed based on BOR, and the poorer survival observed among mRECIST-defined responders emerged early after treatment initiation, when the effect of treatment discontinuation due to RECIST 1.1–defined progression was likely minimal. Moreover, 71.3% of RECIST 1.1–defined progressors were concurrently classified as progressors by mRECIST at the time of RECIST 1.1–defined PD, and 35% of patients who discontinued Atezo/Bev had additional reasons for discontinuation beyond RECIST 1.1–defined progression. Furthermore, RECIST 1.1 demonstrated higher interobserver agreement, fewer dissociated responses, and a significant correlation with OS, with acceptable C-indices, supporting its reproducibility and prognostic relevance in clinical practice. Second, 61.5% of screened patients were excluded, most commonly because of the absence of measurable intrahepatic target lesions according to mRECIST. This high exclusion rate may have limited the generalizability of our findings. In addition, the requirement for hypervascular intrahepatic target lesions may have introduced selection bias toward patients with greater tumor devascularization after Atezo/Bev therapy, potentially favoring mRECIST-based response rates. This may have led to overestimation of response rates and dissociated responses according to mRECIST. Nonetheless, because non-measurable intrahepatic and extrahepatic lesions are assessed similarly under both criteria, the study design remains valid for a meaningful comparison between RECIST 1.1 and mRECIST. Third, only patients who underwent at least one follow-up imaging study were included for the radiologic response assessment. Patients without follow-up imaging due to early clinical deterioration or rapid disease progression were excluded. Although this exclusion was applied equally to both RECIST 1.1 and mRECIST and is unlikely to have biased the comparison between the two criteria, it may have resulted in an overestimation of the ORR and potentially influenced the observed association between response and OS. Fourth, heterogeneity in imaging modalities and protocols, including differences between CT and MRI, contrast agents, and arterial-phase timing, may have affected response evaluation according to mRECIST. In particular, liver MRI performed using gadoxetic acid may hinder accurate assessment of intratumoral arterial enhancement due to suboptimal arterial-phase imaging [35]. Lastly, a direct head-to-head comparison of the prognostic performance of RECIST 1.1 and mRECIST was not feasible given the study design. The reported C-index values represent the overall performance of the multivariable models rather than the discriminative ability of RECIST 1.1 or mRECIST alone. Therefore, a higher C-index for the model including RECIST 1.1 compared with that including mRECIST should not be interpreted as evidence of the superiority of RECIST 1.1.

The purpose of the multivariable analyses was not to directly compare the prognostic performance of RECIST 1.1 and mRECIST. Given that treatment decisions in this retrospective cohort were predominantly guided by RECIST 1.1, adjustment for response-driven management differences was not feasible. Accordingly, these analyses should be interpreted as ancillary, assessing the independent association of each criterion with OS after accounting for known prognostic variables.

 https://doi.org/10.3348/kjr.2025.1849

In conclusion, RECIST 1.1 is more reproducible and provides greater prognostic value for guiding treatment decisions in patients with HCC receiving first-line Atezo/Bev. However, this does not invalidate the use of mRECIST as a biological response marker.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2025.1849.

Availability of Data and Material

The datasets generated or analysed during the study are available from the corresponding author upon reasonable request.

Conflicts of Interest

Seung Soo Lee, Section Editor, and So Yeon Kim, Editorial Board Member, of the *Korean Journal of Radiology*, were not involved in the editorial evaluation or decision to publish this article. The remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Hyo Jung Park. Data curation: Boryeong Jeong, Hyo Jung Park. Formal analysis: Boryeong Jeong, Hyo Jung Park. Investigation: Boryeong Jeong, Hyo Jung Park. Methodology: all authors. Supervision: Hyo Jung Park. Visualization: Boryeong Jeong. Writing—original draft: Boryeong Jeong, Hyo Jung Park. Writing—review & editing: all authors.

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Funding Statement

None

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