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Comparison of Radiological Tumor Response Based on iRECIST and RECIST 1.1 in Metastatic Clear-Cell Renal Cell Carcinoma Patients Treated with Programmed Cell Death-1 Inhibitor Therapy

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Objective: To evaluate the radiological tumor response patterns and compare the response assessments based on immune-based therapeutics Response Evaluation Criteria in Solid Tumors (iRECIST) and RECIST 1.1 in metastatic clear-cell renal cell carcinoma (mccRCC) patients treated with programmed cell death-1 (PD-1) inhibitors.

Materials and Methods: All mccRCC patients treated with PD-1 inhibitors at Henan Cancer Hospital, China, between January 2018 and April 2019, were retrospectively studied. A total of 30 mccRCC patients (20 males and 10 females; mean age, 55.6 years; age range, 37–79 years) were analyzed. The target lesions were quantified on consecutive CT scans during therapy using iRECIST and RECIST 1.1. The tumor growth rate was calculated before and after therapy initiation. The response patterns were analyzed, and the differences in tumor response assessments of the two criteria were compared. The intra- and inter-observer variabilities of iRECIST and RECIST 1.1 were also analyzed.

Results: The objective response rate throughout therapy was 50% (95% confidence interval [CI]: 32.1–67.9) based on iRECIST and 30% (95% CI: 13.6–46.4) based on RECIST 1.1. The time-to-progression (TTP) based on iRECIST was longer than that based on RECIST 1.1 (median TTP: not reached vs. 170 days, $p = 0.04$). iRECIST and RECIST 1.1 were discordant in 8 cases, which were evaluated as immune-unconfirmed PD based on iRECIST and PD based on RECIST 1.1. Six patients (20%, 6/30) had pseudoprogression based on iRECIST, of which four demonstrated early pseudoprogression and two had delayed pseudoprogression. Significant differences in the tumor response assessments based on the two criteria were observed ($p < 0.001$). No patients demonstrated hyperprogression during the study period.

Conclusion: Our study confirmed that the iRECIST criteria are more capable of capturing immune-related atypical responses during immunotherapy, whereas conventional RECIST 1.1 may underestimate the benefit of PD-1 inhibitors. Pseudoprogression is not rare in mccRCC patients during PD-1 inhibitor therapy, and it may last for more than the recommended maximum of 8 weeks, indicating a limitation of the current strategy for immune response monitoring.

Keywords: *Clear cell renal cell carcinoma; Immune-checkpoint inhibitor; PD-1; Tumor response; iRECIST criteria*

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INTRODUCTION

Cancer immunotherapy using immune checkpoint inhibitors targeting programmed cell death-1 (PD-1) is a promising new strategy that has demonstrated unprecedented success against several types of advanced cancers (1). In the CheckMate-025 trial (2), nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, facilitated superior overall survival and fewer serious adverse events as compared to everolimus in patients with previously treated metastatic clear-cell renal cell carcinoma (mccRCC), leading to its approval by the Food and Drug Administration and European Medical Association.

Compared to targeted agents and conventional chemotherapy, immune-checkpoint inhibitors can demonstrate atypical patterns of response. A systematic review of 38 studies found a 6% rate of atypical responses (151 of 2400 patients with solid tumors treated with anti-PD-1 therapy) (3). Two conditions named "pseudoprogression" and "hyperprogression," as the most challenging scenarios, have been described in several reports, while a precise and standardized definition has not been established yet (4-8). The awareness and knowledge of clinicians for those atypical response patterns are imperative to guide beneficial treatment and support accurate clinical decision-making and patient management (9).

Conventional radiological response criteria, the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (10), have been widely used for tumor response assessment within the past two decades, and they have provided the basis for regulatory approvals for novel cancer therapy. However, RECIST 1.1 is insufficient for capturing atypical responses in patients treated with immune-checkpoint inhibitors (11-14). To overcome the limitations of the RECIST 1.1 criteria and accurately assess and categorize tumor response to immunotherapy, several novel radiological criteria, such as two-dimensional immune-related response criteria and a modification immune-related RECIST (irRECIST) have been developed (15-17). However, these criteria still have pitfalls, which led to complexities in patient management in different clinical trials and later during the final analysis (5, 18-20).

In early 2017, a consensus modification of RECIST 1.1 for immune-based therapeutics (iRECIST) was issued to guide the use of RECIST 1.1 in immunotherapy trials to standardize study design and data collection (21). To our knowledge, there are very limited data about the utilization of iRECIST in tumor response assessment in real-world clinical experience, and no study specifically focusing on atypical patterns of response in mccRCC patients have been published despite an abundance of published data from prospective trials.

The purpose of the current study was to describe radiological tumor response patterns using iRECIST and compare the response assessments using iRECIST and RECIST 1.1 in mccRCC patients treated with PD-1 inhibitors.

MATERIALS AND METHODS

Patients and Treatment

The Institutional Review Board of the Affiliated Cancer Hospital of Zhengzhou University approved this retrospective study, and written informed consent was waived. Patients with mccRCC who received PD-1 inhibitors after the failure of first-line tyrosine kinase inhibitors (TKI)-based therapy were retrospectively studied at the Affiliated Cancer Hospital of Zhengzhou University, China between June 2016 and October 2019.

The records of 30 eligible patients (20 males and 10 females) were centrally analyzed. More than half of the patients were male (67%), and the mean age was 55.6 years (range, 37–79 years).

Image Acquisition

All CT studies were performed with contrast agents, and they followed a standardized protocol on one of the three CT systems: Brilliance iCT scanner (Philips Healthcare), uCT 760 (United Imaging), and SOMATOM Perspective (Siemens Healthineers). The main scanning parameters were as follows: tube voltage = 120 kV, automatic tube current modulation (30–70 mAs), pitch = 1.0–1.5. mm, matrix = 512 x 512, slice thickness = 5 mm, field of view 350 x 350 mm. All images were reconstructed to 0.625–1.25-mm thickness. Other findings of imaging studies, such as brain MRI or 18F-fluorodeoxyglucose PET/CT, were also reviewed to identify new lesions and assess non-target lesions.

Tumor Measurements and TGR Calculation

Two experienced radiologists reviewed all consecutive eligible CT scans before and during PD-1 checkpoint inhibitor therapy independently, and they were blinded to each other's results and the clinical information of the patients. Reader A repeated the assessment procedure with at least a six-week interval. The tumor measurements were

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performed to generate response assessments. In brief, target lesions (≥ 10 mm in the longest diameter for non-nodal lesions and ≥ 15 mm in the short axis for nodal lesions) were selected on baseline scans, allowing up to 2 lesions per organ and up to 5 lesions in total, as in RECIST 1.1 (10).

The number of target lesions, the sum of the longest diameters of the target lesions, the percentage change in the sum of diameters of the target lesion from baseline, the descriptions of non-target lesions, presence or absence of new lesions, timepoint response, and time-to-progression (TTP) were recorded for each patient, according to RECIST 1.1 and iRECIST guidelines.

The tumor growth rate (TGR) is used to estimate the increase in tumor volume over time using 2 CT measurements based on an exponential growth model (22, 23). It is the percentage increase in tumor volume per month, computed from the sum of the largest diameters of the target lesions per RECIST and the time interval between the 2 CT scans. TGR can be used to identify a subset of patients experiencing hyperprogression (24). The TGR before and after initiating immune-checkpoint inhibitors of each patient was calculated according to the definition by Ferté et al. (22).

Patterns of Response according to RECIST 1.1 and iRECIST

Stable disease (SD), partial response (PR), and complete response (CR) were identified for both guidelines. Pseudoprogression was defined as progressive disease constituted by RECIST 1.1 at any assessment, followed by stabilization or response on follow-up imaging. Early and delayed pseudoprogression were differentiated. Early pseudoprogression was defined as pseudoprogression that occurred within 12 weeks, while delayed pseudoprogression was constituted after the week-12 assessment (25). Hyperprogression was defined as at least a twofold increase in TGR on treatment compared to TGR before treatment (26). The atypical response was defined as pseudoprogression and hyperprogression. The objective response rate (ORR) was defined as the proportion of patients with immune CR (iCR) and immune PR (iPR).

The two guidelines had identical definitions of CR, PR, and SD, but they differed in cases of progression disease (PD). There are two major innovations in the iRECIST guidelines. First, new lesions were separately documented and added to the assessment of progression. Second, a novel concept known as immune-unconfirmed PD (iUPD) was proposed. iUPD refers to an initial PD per RECIST 1.1, which needs to be confirmed. iUPD could be reassigned a couple of times as long as immune-confirmed PD (iCPD) has not been reached. iCPD should be evaluated on follow-up imaging 4–8 weeks after iUPD and defined as an additional increase in the size of the target or non-target lesions, increase in the sum of diameters of the new target lesions of > 5 mm, the progression of new non-target lesions, or the appearance of another new lesion. If progression was not confirmed, the response status was evaluated compared with baseline or nadir as iCR, iPR, immune SD (iSD), or iUPD (21).

Statistical Analysis

Comparisons across groups were performed using Fisher's exact test for categorical variables. TTP by RECIST 1.1 and iRECIST were estimated using the Kaplan-Meier method. All *p* values are based on a two-sided hypothesis. Kappa analysis was performed to evaluate intra- and inter-observer agreements for iRECIST and RECIST 1.1. The agreement was categorized as poor ($\kappa < 0$), slight ($\kappa = 0$–0.20), fair ($\kappa = 0.21$–0.40), moderate ($\kappa = 0.41$–0.60), substantial ($\kappa = 0.61$–0.80), and almost perfect ($\kappa > 0.80$). A *p* value of less than 0.05 was considered significant. Data were analyzed using the statistical software IBM SPSS 23.0 software (IBM Corp.).

RESULTS

Patient Characteristics

The patient characteristics are summarized in Table 1. Of the patients, 25 received nivolumab, and 5 were treated with pembrolizumab. Both PD-1 inhibitor agents were administered as monotherapy. The risk group breakdown based on the International Metastatic Renal Cell Carcinoma Database Consortium was as follows: 13% favorable, 77% intermediate, and 10% poor (27). Most patients (93%) had prior nephrectomy. Twenty-eight patients had 1–2 prior systemic therapies (93%), and 2 patients (10%) had 3 prior systemic treatments. The median follow-up duration was 373 days (range: 87–1073 days).

Response Assessment by iRECIST and RECIST 1.1

The ORRs throughout therapy for RECIST 1.1 and iRECIST were 30% (95% confidence interval [CI]: 13.6–46.4) and 50% (95% CI: 32.1–67.9), respectively; The median TTP for iRECIST was not reached, whereas the median

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TTP for RECIST 1.1 was 170 days (p = 0.04) (Fig. 1). The treatment outcomes are shown in Table 2 and Figure 2. Discordance in the assessments based on iRECIST and RECIST 1.1 were noted in 8 patients, of which 6 experienced pseudoprogression and 2 were assessed as iUPD during the last evaluation without the subsequent confirmation of PD. Compared with assessments based on RECIST 1.1, 5 more patients were assessed as having PRs whereas one more patient had a CR following iRECIST. Significant differences in tumor response were observed between iRECIST and RECIST 1.1 assessments (p < 0.001).

Intra-observer agreements in the response assessments using iRECIST (Table 3) and RECIST 1.1 were both substantial (κ = 0.697, 95% CI: 0.511–0.883; κ = 0.746, 95% CI: 0.548–0.944, respectively). Inter-observer agreements for iRECIST were almost perfect (κ = 0.869, 95% CI: 0.730–1).

Table 1. Demographics and Characteristics of the Included 30 Patients

	Value
Sex	
Male	20 (66.7)
Female	10 (33.3)
Age (years)	
Mean (range)	55.6 (37–79)
Treatment	
Nivolumab	25 (83.3)
Pembrolizumab	5 (16.7)
IMDC	
Favorable risk	4 (13.3)
Intermediate risk	23 (76.7)
Poor risk	3 (10.0)
Prior nephrectomy	
Yes	28 (93.3)
No	2 (6.7)
Anti-PD-1 therapy	
2nd line	12 (40.0)
3rd line	16 (53.3)
4th line	2 (6.7)

Except for age, data are number (%) of patients. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, PD-1 = programmed cell death-1

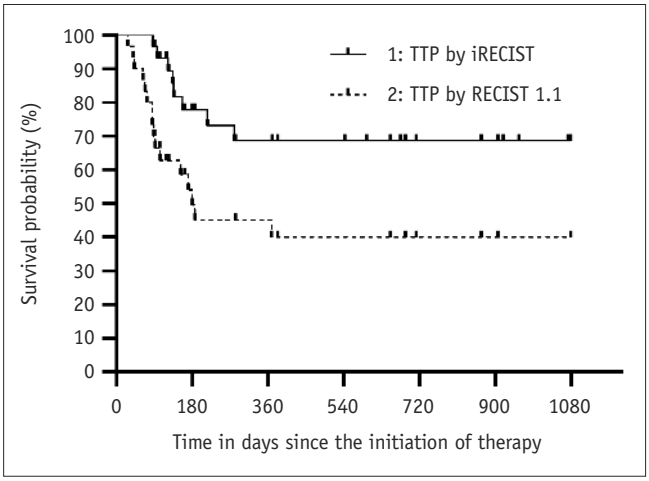

Fig. 1. TTP by iRECIST and RECIST 1.1. iRECIST = immune-based therapeutics Response Evaluation Criteria in Solid Tumors, RECIST = Response Evaluation Criteria in Solid Tumors, TTP = time-to-progression

Atypical Response

The percentage change in the sum of the target lesion

Table 2. Treatment Outcomes

n = 30	RECIST 1.1	iRECIST
Best response-no. (%)		
CR/iCR	5 (16.7)	6 (20)
PR/iPR	4 (13.3)	9 (30)
SD/iSD	5 (16.7)	5 (16.7)
PD/iCPD	16 (53.3)	8 (26.7)
iUPD		2 (6.6)
CR or PR		
No. of patients (%)	9 (30)	15 (50)
95% CI	13.6–46.4	32.1–67.9

CI = confidence interval, CR = complete response, iCPD = confirmed progressive disease, iCR = immune CR, iPR = immune PR, iRECIST = immune-based therapeutics Response Evaluation Criteria in Solid Tumors, iSD = immune SD, iUPD = immune unconfirmed progressive disease, PD = progressive disease, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease

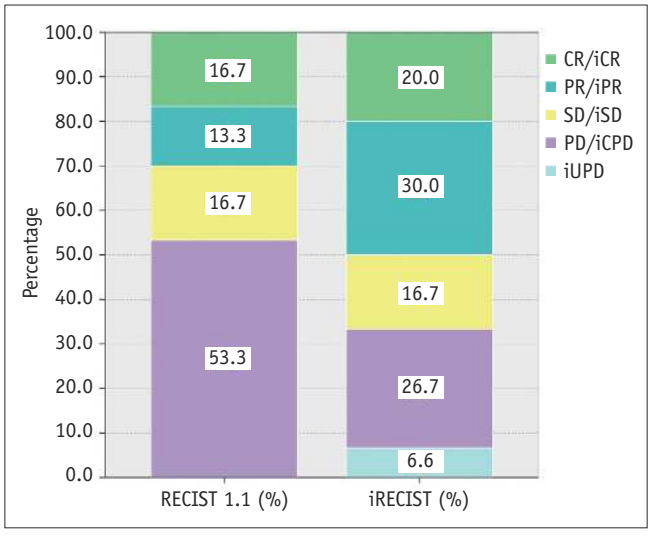

Fig. 2. Best tumor responses per RECIST 1.1 and iRECIST. CR = complete response, iCPD = confirmed progressive disease, iCR = immune CR, iPR = immune PR, iSD = immune SD, iUPD = immune unconfirmed progressive disease, PD = progressive disease, PR = partial response, SD = stable disease

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from baseline during PD-1 inhibitor therapy is demonstrated in the spider plot (Fig. 3). Atypical responses were observed in 6 (20%) of the 30 patients.

Pseudoprogression

Six (20%) out of 30 patients experienced pseudoprogression (Table 4). All the 6 pseudoprogression cases were initially classified as PD based on RECIST 1.1 and iUPD based on iRECIST. The median time to pseudoprogression since baseline was 57 days (range: 27–386), and 4 patients met the definition of early pseudoprogression whereas 2 had delayed pseudoprogression. Of the 6 patients, 3 demonstrated a pattern of the appearance of new lesions along with the enlargement of the target lesions, followed by tumor regression (Fig. 4). Three patients experienced transient enlargement of the initial target lesions and subsequent tumor shrinkage (Fig. 5). One patient underwent iUPD during week 13, and it lasted for 18 weeks, followed by tumor shrinkage during week 31. A CR was achieved in one patient during week 114, and it lasted until the data were collected. Five patients achieved PR after pseudoprogression during follow-up assessments.

Table 3. Joint Judgments of Two Readers Regarding Tumor Responses according to iRECIST

	Reader A 1st					
	iCR	iPR	iSD	iUPD	iCPD	Total
Reader B						
iCR	4					4
iPR	2	9				11
iSD			4	2		6
iUPD			1		2	3
iCPD					6	6
Total	6	9	5	2	8	30

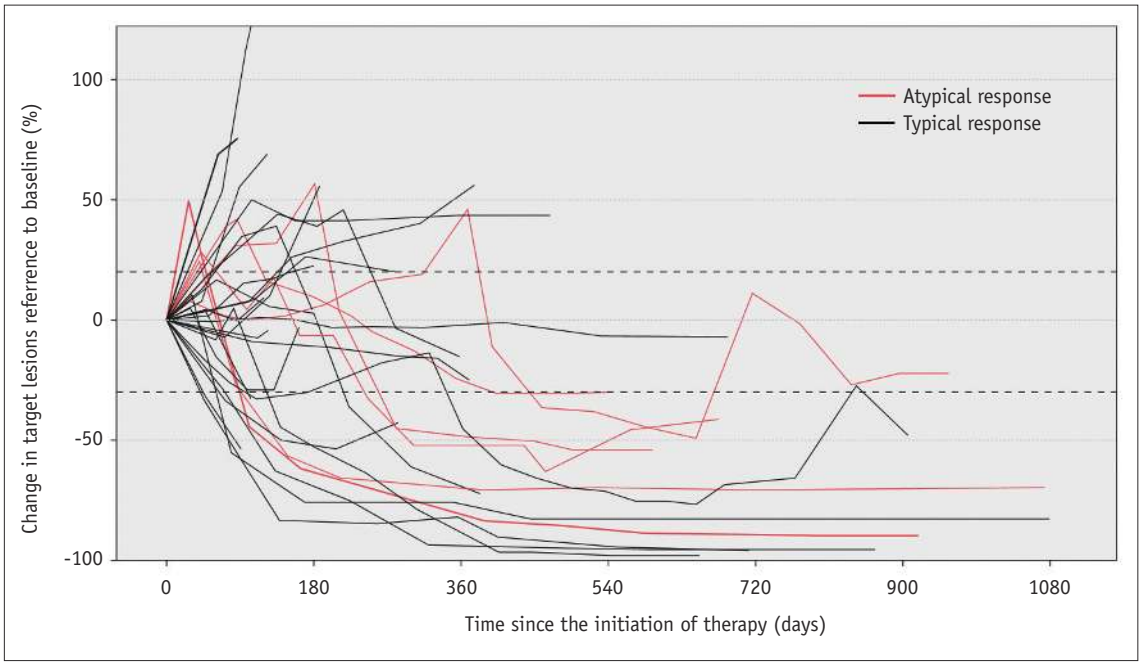

Fig. 3. Spider plot of percentage changes in sum of diameters of target lesions from baseline during PD-1 inhibitor therapy. PD-1 = programmed cell death-1

Table 4. Characteristics of 6 Pseudoprogression Patients

Patients' No.	Sex (M/F)	Age	IMDC	Prior Nephrectomy (Y/N)	Treatment	Treatment Line of Anti-PD-1	Date of Anti-PD-1 Initiation
1	M	47	Intermediate	Y	Nivolumab	3rd line	4/28/2018
2	M	49	Intermediate	Y	Nivolumab	3rd line	3/21/2017
3	M	62	Intermediate	Y	Nivolumab	4th line	12/9/2016
4	M	79	Intermediate	Y	Pembrolizumab	2nd line	6/12/2016
5	M	51	Intermediate	Y	Nivolumab	3rd line	2/27/2018
6	M	68	Poor	Y	Nivolumab	3rd line	12/18/2017

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Hyperprogression

None of the patients in this study demonstrated hyperprogression at the time of analysis, which was defined as a rapid increase in TGR (minimum twofold) compared to the expected growth rate (7). The median change in TGR was 57% (range: -526–132). An increase in the TGR since initiation of treatment was observed in 3 patients (10%) (Fig. 6). The most obvious increase in TGR was observed in a 59-year-old female patient during the first evaluation; she presented with continuous progression and died after 6

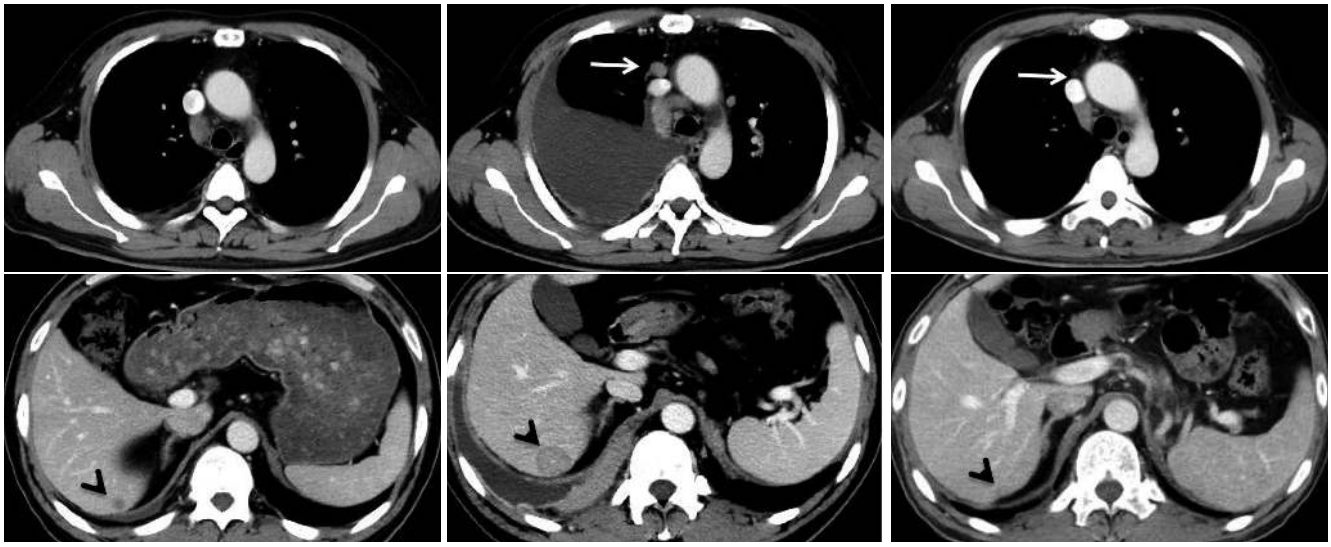

Fig. 4. Axial contrast-enhanced CT images in a 47-year-old male patient with clear cell renal cell carcinoma metastatic to the liver undergoing PD-1 inhibitor therapy with nivolumab.
A. Image obtained at baseline shows a solid liver nodule (arrowhead). **B.** Image obtained after 10 weeks demonstrates a new mediastinal nodule lesion (arrow), pleural effusion as new non-target lesion, and significantly increased size of the liver lesion (arrowhead). **C.** CT image obtained at week-47 shows complete regression of mediastinal lymph node (arrow), pleural effusion and liver metastasis (arrowhead).

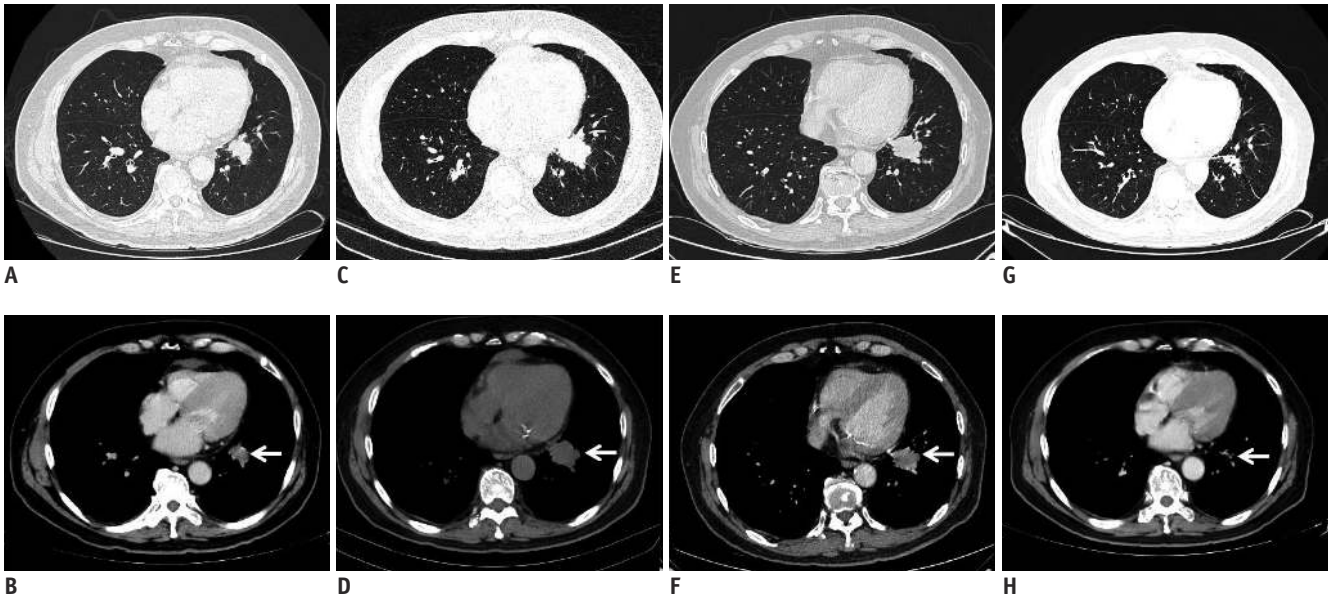

Fig. 5. Axial contrast-enhanced CT images in a 68-year-old male patient with clear cell renal cell carcinoma metastatic to the lung undergoing PD-1 inhibitor therapy with nivolumab.
A, B. Contrast enhanced axial CT image obtained at baseline shows a metastatic nodule (arrow) in the left-lower-lobe measuring 26 mm in the longest diameter. **C, D.** Follow-up axial CT image at week-6 of therapy shows an increase in the lesion, which now measures 33 mm (arrow), indicating progressive disease according to RECIST 1.1. **E, F.** Further follow- up axial CT image at week-14 of therapy shows a decrease in size of the lesion, which now measures 26 mm (arrow), representing tumor response. **G, H.** On the final assessment scan (week-35), the left-lower-lobe nodule has further decreased in size, measuring 9 mm in lung window (arrow).

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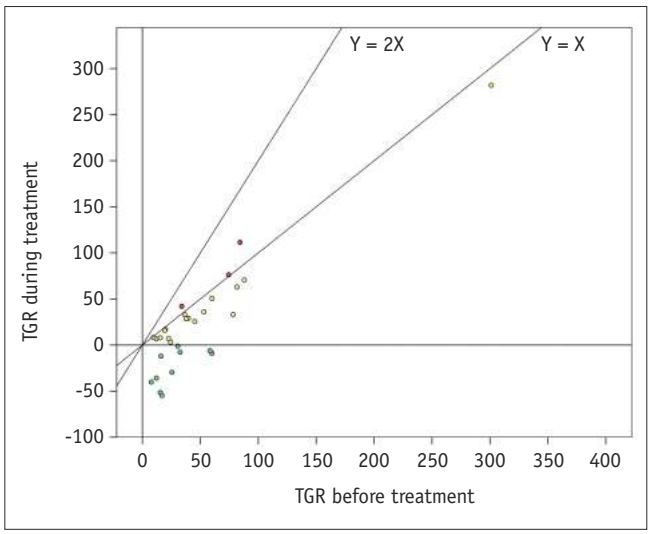

Fig. 6. Analysis of the TGR during and before the PD-1 inhibitors. Each dot represents a patient. Red dots are set for patients with accelerated TGR, yellow dots show patients with declined TGR, green dots show patients with tumor regression. TGR = tumor growth rate

months of initiation.

DISCUSSION

The present study evaluated the tumor response patterns of mccRCC patients treated with commercial PD-1 inhibitor agents and compared the assessment outcomes based on the iRECIST and RECIST 1.1 radiological criteria. Twenty-two patients demonstrated dissociated responses, of which 6 experienced pseudoprogression during the study period. Pseudoprogression was more accurately captured and identified when iRECIST was used than when RECIST 1.1 was used. This suggests that the RECIST 1.1 criteria, by initially classifying these cases as progressive, underestimated the benefits of PD-1 inhibitors.

Pseudoprogression, or initial progression followed by a subsequent response, has been increasingly encountered in practice and it is often considered as a representative phenomenon of immune-related tumor response in other cancer types (20). The incidence of pseudoprogression is approximately 10% or lower in patients with metastatic melanoma treated with immune checkpoint inhibitors (17, 25, 28) and 5% or lower in patients with advanced non-small cell lung cancer (NSCLC) (29-31). In mccRCC, recent data derived from patients treated beyond progression in clinical trials reported comparable results, with a rate of approximately 5–15% (5, 8, 32). In our study, all 6 patients with pseudoprogression received PD-1 inhibitors for more than 18 months, and an ongoing CR was observed during the data analyses. This indicated favorable outcomes for patients with pseudoprogression. The incidence of pseudoprogression in our cohort was higher than that in other studies, and the pseudoprogression patterns of the 6 patients demonstrated high complexity. A potential explanation is that this study focused on advanced renal cell carcinoma patients treated with PD-1 inhibitors as a second - or third-line therapy, and all the target lesions were metastases located in different organs without detectable primary tumors. The biopsies of the target lesions were not performed in this study, and the mechanism of the observation was uncertain; it may be associated with the biological rationale of PD-1 inhibitors. The first hypothesis is that the delayed onset of an immune response may enable the tumor to initially grow. The second potential explanation is that pseudoprogression is associated with the infiltration of the tumor lesion by active T cells and other immune cells because of the immune response induced by PD-1 inhibitors (4).

Hyperprogression is a new pattern of progression observed in a fraction of patients, which should be approached with caution in patients using PD-1 inhibitors (7). No consensus has been reached on the definition of hyperprogression. In a study of 218 patients with solid tumors or lymphoma treated with PD-1 or PD-L1 inhibitors, Champiat et al. (7) defined hyperprogressive disease as a twofold increase in the expected TGR (which is an estimation of the increase in tumor volume over time). On the other hand, Ferrar et al. (24) defined hyperprogression as a RECIST 1.1 progression during the first evaluation with at least an increase of 50% ΔTGR (the variation of TGR before and during treatment) in a multicenter retrospective study of 406 NSCLC patients. We adopted the same methodology used by Champiat et al. (7) in the present study, and none of the patients experienced hyperprogression during the treatment period, which could be due to the small number of patients and the appreciably higher ORR. Hyperprogression is a very poorly investigated phenomenon, and further studies are required to determine its incidence in mccRCC patients and the underlying mechanisms.

Direct comparisons between the iRECIST and RECIST 1.1 assessments are lacking in clinical trials and real-world clinical experiences in mccRCC patients undergoing immune checkpoint inhibitor therapy. Tazdait et al. (14) compared RECIST 1.1, irRECIST, and iRECIST criteria using NSCLC patients undergoing anti-PD1 therapy and confirmed

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that 11% (13 of 120) of treated patients characterized as PD according to the RECIST 1.1 criteria benefitted from treatment. In this cohort with 6 pseudoprogression cases, the category of SD/iSD was fully concordant, and the discrepancies among the CR/iCR, PR/iPR, and PD/iCPD assessments based on RECIST 1.1 and iRECIST were significant. The differences between the response assessments based on the two criteria were observed only in progressive patients, as expected. The iRECIST criteria inherit the definition of target and non-target lesions and the categorization of tumor response, whereas they have a major change in the assessment criteria of PD. According to the iRECIST criteria, iUPD refers to RECIST 1.1 PD, and it needs to be confirmed by a follow-up examination, which contributes to the longer TTP per iRECIST than the TTP per RECIST 1.1. Our results confirm that RECIST 1.1 underestimates the number of mccRCC patients who benefit from PD-1 inhibitors.

Although imperfect, ongoing and published clinical trials evaluating PD-1 inhibitor agents have predominantly used the RECIST 1.1 criteria for assessing response; some have also used irRECIST or iRECIST as secondary response criteria. It has been increasingly accepted that iRECIST is more accurate in capturing a subtype of atypical response patterns in immunotherapeutics. However, given the lack of extensive validation, iRECIST is recommended by the RECIST working group for the application of clinical trials rather than being adopted to support accurate clinical decision-making and patient management. Our cohort included 14 patients receiving anti-PD-1 treatment beyond progression, whereas all 14 patients demonstrated good tolerability and acceptable performance status, with no impending end-organ damage and ongoing severe toxic effects. In brief, iRECIST was derived from expert consensus, and further efforts are required to validate the superiority and applicability of this novel system.

Another shortcoming of the current strategy for immune response evaluations is related to the duration between pseudoprogression and subsequent tumor reduction (20). According to the iRECIST guidelines, the subsequent assessment after initial RECIST 1.1-defined progression should be ≥ 4 weeks and no longer than 8 weeks later to ensure that patients can undergo salvage therapies (21). Five of 6 pseudoprogression cases in the present study experienced subsequent response within 8 weeks, whereas one patient had pseudoprogression from week 13 through week 18, followed by tumor shrinkage, which demonstrated significantly delayed tumor response. This questions whether the currently recommended duration of a maximum of 8 weeks for confirmed PD is adequate to capture all patients with delayed tumor response. Specifically, there is the need for scientific evidence for optimizing the time intervals during treatment monitoring.

Intra-observer agreement of the tumor response assessments based on the two criteria were substantial, whereas the κ value for iRECIST was lower than that for RECIST 1.1, due to the presence of iUPD in the iRECIST response categorization. The inter-observer agreement for iRECIST was almost perfect, indicating high reproducibility and agreement for this new criterion.

The current study has some limitations. First, a relatively small number of patients treated at a single institution were included. More data are needed to confirm the proportion of atypical patterns of responses to extrapolate these results to the wider mccRCC population. Second, a biopsy of pseudoprogression lesions for pathologic review was not performed. Finally, there were nonhomogeneous CT monitoring intervals for assessing tumor response due to the retrospective nature of the study and the different clinical routines, which may have resulted in bias.

In conclusion, iRECIST is more capable of capturing immune-related atypical responses, whereas conventional RECIST 1.1 may underestimate the benefit of PD-1 inhibitors. Pseudoprogression is not rare in mccRCC patients during PD-1 inhibitor therapy, and it may last beyond the timeframe recommended for a maximum of 8 weeks, indicating a limitation of the current strategy for tumor response monitoring. Hyperprogression remains an almost undiscovered entity. Given the small number of patients studied, further research is urgently needed to understand the underlying mechanisms.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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