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ORIGINAL ARTICLE

The true role of mRECIST guideline: Does it really estimate viable tumor or merely improve accuracy in hepatocellular carcinoma response evaluation?

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Summary

Purpose: *Modified Response Evaluation Criteria In Solid Tumors (mRECIST), developed by the American Association for the Study of Liver Diseases (AASLD) criteria measure changes in arterialized hepatocellular carcinoma (HCC) and aim at providing a common framework for the design of clinical trials. It still isn't determined whether mRECIST can be applied in routine clinical practice and whether mRECIST could estimate viable tumor correctly.*

Methods: *We retrospectively analyzed data from patients subjected to transcatheter arterial chemoembolization (TACE) as initial treatment for advanced HCC in our institution. Not suitable for using mRECIST standard cases and the agreement in response between RECIST and mRECIST were assessed. Then we selected HCC patients who achieved complete response (CR) according to mRECIST, following PET-CT examinations. We also compared arterial enhanced computed tomography (CT) or magnetic resonance imaging (MRI) with positron emission tomography (PET)-CT examination and analyzed their correlation.*

Results: *Out of 143 HCC patients, mRECIST evaluation appeared to be applicable for 128 (89.51%) assessable patients. In these 128 assessable patients, the objective response (OR) rates (complete/CR+partial response/PR) according to RECIST and mRECIST were 64.06% (82 of 128 patients) and 78.13% (100 of 128; p<0.001), respectively. Discordance in the response evaluations between the two methods was observed in 46 patients (35.94%) and was statistically significant (Kappa=0.491; p<0.001). The overall survival (OS) of patients who achieved an OR as assessed by mRECIST or by RECIST was significantly better than the survival of non-responding patients (stable disease/SD, or progressive disease/PD).*

Conclusions: *Although mRECIST criteria show a good correlation with prognosis, they demand strict requirements for patient selection and couldn't be useful as a tool for routine clinical practice. Furthermore, merely by means of contrast-enhanced CT or MRI, mRECIST couldn't estimate viable tumor sufficiently.*

Key words: *computed tomography, hepatocellular carcinoma, magnetic resonance imaging, mRECIST, PET-CT, viable tumor*

Introduction

For nonsurgical patients with advanced stage HCC, the use of a variety of therapies such as sorafenib, chemoembolization or radioembolization, has raised the issue of the best modality to measure response rate. Tumor response was initially measured according to the RECIST guideline [1]. The RECIST criteria which determine anatomic size and lesion changes during treatment as an indicator of response do not measure antitumor activity. Recent studies have shown a poor correlation between the RECIST criteria with the clinical benefit provided by new agents such as sorafenib or by locoregional interventional therapies [2,3]. In 2000, the HCC panel of European Association for the Study of the Liver (EASL) pointed out that tumor necrosis induced by treatment should be taken into account [4]. That pan-

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el considered estimation of the reduction in the viable tumor area using contrast-enhanced radiologic imaging as the optimal method to assess treatment response. Viable tumor was defined as uptake of contrast agent in the arterial phase of dynamic CT or MRI. The concept of viable tumor proposed has been subsequently endorsed by the AASLD. In 2010, AASLD has proposed a formal amendment of the RECIST criteria that take into consideration changes in the degree of tumor arterial enhancement, the so-called mRECIST [5].

According to mRECIST evaluation, several studies have demonstrated that patients responding to locoregional therapies have a better prognosis than non-responders. In the Edeline et al. study, patients who received sorafenib for advanced HCC and achieved an OR according to mRECIST, had a longer OS than non-responding patients with SD or PD [6]. As for patients receiving TACE, Kim et al. reached a similar conclusion [7].

However, in these studies, mRECIST criteria were only used in oncology trials including locoregional therapies for the treatment of HCC. It still hasn't been determined whether mRECIST could be useful as a tool for routine clinical practice. In addition, although mRECIST showed a good correlation with prognosis, it needs to be determined whether mRECIST can estimate viable tumor correctly which was our original intention for modifying RECIST criteria. Whether MRI or CT could detect viable tumor has to be demonstrated. To achieve our goal in the present study we compared the value of mRECIST to predict OS in comparison to the RECIST criteria in patients with HCC undergoing TACE as initial treatment modality. Then, we evaluated the correlation between mRECIST and tumor recurrence and the accuracy of mRECIST criteria compared to PET-CT data.

Methods

Data collection

We retrospectively analyzed data from patients who received TACE as initial treatment for advanced HCC and followed-up at our institution between January 2010 and December 2012. At initial diagnosis, all patients had disease proven histologically or confirmed by clinical, laboratory and imaging examinations, and had at least one index lesion measuring 1 cm or larger in diameter with a baseline CT scan obtained at least 1 month before treatment. Patients had well-preserved liver function without ascites (Child-Pugh class A) and intermediate-stage multifocal HCC with absence of symptoms (Barcelona Clinic Liver Cancer/BCLC, stage B). None of the patients had other disease that could influence survival. Our standard imaging follow-up in patients who received TACE was a CT scan in the first and second months and every 2 months thereafter.

TACE protocol

Digital Subtraction Angiography (Multistar, Siemens, Erlangen, Germany) of hepatic and mesenteric arteries was performed immediately before TACE to map vascular liver anatomy and to identify arterial feeders of the tumor. All the procedures were performed under local anesthesia and antiemetic drugs. TACE was performed by selective catheterization of the hepatic segmental arteries supplying the lesions, using either 5-F catheters or 3-F coaxial microcatheters. TACE was performed by infusion of a mixture of lipiodol contrast medium (10–20 mL, Lipiodol; Guerbet, Aulnay-sous-Bois, France) and 50 mg doxorubicin hydrochloride (Adriblastina; Pfizer Italia srl, Borgo San Michele, Italy), followed by embolization of feeding arteries using gelatin sponge particles (Cutanplast; MasciaBruneili Spa, Milano, Italy). A second TACE was scheduled at 6 to 8-week intervals when a residual viable tumor was detected in the liver at follow-up assessment.

Image analysis

The diagnosis of HCC and assessment of treatment responses were carried out with a dynamic imaging study involving 4 phases (precontrast, arterial, portal and equilibrium phases) using contrast-enhanced spiral CT or gadolinium-enhanced MRI as appropriate. It is necessary to keep in mind that it is mandatory to use contiguous slices for image reading and interpretation, to avoid missing small lesions.

Two independent radiologists reviewed pre-procedural and post-TACE imaging data to assess tumor response (response evaluation of target lesions, non-target lesions, and new lesions) according to RECIST and mRECIST.

Assessment of treatment responses using RECIST and mRECIST criteria

According to RECIST, CR is the disappearance of all target lesions; PR is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; PD is at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since when treatment started or the appearance of one or more new lesions; SD is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since the treatment started.

According to mRECIST, CR is the disappearance

of any intratumoral arterial enhancement in all target lesions; PR is at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions; PD is an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment started. SD is any case that did not qualify for either PR or PD.

Complete response in mRECIST vs PET-CT examinations

We selected HCC patients who achieved CR after therapy at our institution according to contrast-enhanced CT or MRI. All patients underwent PET-CT examinations and were followed up. From January 2010 to December 2012, the final study population included 9 patients (M/F = 7/2; mean age 58 ±12.17years, range 42–78 years).

Correlation between arterial enhanced CT or MRI and PET-CT examination

From March 2011 to June 2013, we compared arterial enhanced CT or MRI with PET-CT examination in 69 patients with an initial diagnosis of HCC (M/F=55/14; mean age 57.61 ±13.62 years, range 28–82 years) and analyzed their correlation.

Statistics

Statistical analysis was performed with SPSS 20.0 software. A P value of less than 0.05 was considered statistically significant. Correlation was calculated by the weighted kappa (k) test and x^2 test. Survival data were analyzed by using the Kaplan-Meier method with the log-rank test.

Results

Not suitable for mRECIST standard analysis

Of 143 HCC patients mRECIST evaluation appeared to be widely applicable for 128 (89.51%) assessable patients. The final study population included 128 patients (M/F=116/12; mean age 55.68 ± 12.75 years, range 25–83 years). All HCC lesions were suitable to RECIST criteria, nonetheless 15 patients were excluded because they couldn't be evaluated by mRECIST. Among the unsuitable conditions, infiltrative-type HCC mass showing ill-defined borders, and lipiodol asymmetry distribution in tumor were the main reasons (12/15). The metastatic lesions of 2 patients didn't show intratumoral arterial enhancement on contrast-enhanced CT. The cases of not suitable for mRECIST usage are reported in Table 1.

Correlation between RECIST and mRECIST

Of the 128 assessable patients, the OR rates according to RECIST and mRECIST were 64.06% (82 of 128 patients) and 78.13% (100 of 128) (p<0.001), respectively. Among 64 patients who were classified as PR by RECIST, 28 (43.75%) were reclassified as CR by mRECIST, and 36 (56.25%) were reclassified as PR. Among the 24 patients who were classified as SD by RECIST, 2 patients (8.33%) were reclassified as CR by mRECIST, 16 (66.67%) were reclassified as PR by mRECIST, and 6 (25%) were reclassified as SD. Overall, a discordance between the response evaluations between the 2 methods was observed for 46 patients (35.94%). Differences in distribution of responses according to RECIST and mRECIST (Table 2) were statistically significant (Kappa=0.491<0.75, x^2=189.2, p<0 .001). Responses as assessed by RECIST and mRECIST are reported in Table 2.

Survival analysis

The Kaplan-Meier estimates of OS after response evaluation by RECIST and mRECIST are presented in Figure 1. Both methods provided good correlation of OS according to response (log-rank test:p<0.001 for RECIST; p<0.001 for mRECIST). The median OS for patients with CR, PR, SD, and PD was 25.47 months (95% CI 20.50-30.43), 17.42 months (95% CI 15.75-19.10), 11.18 months (95% CI 9.01-13.35) and 5.39 months (95% CI 4.14-6.64) respectively for RECIST, and 21.95 months (95%

Table 1. Cases not suitable for mRECIST usage

Reasons	*Numbers*
Tumor bleeding interference	1
Ill-defined mass borders	8
No enhanced metastasis	2
Lipiodol asymmetric distribution	4
Total	15

Table 2. Response evaluation according to RECIST and mRECIST

RECIST	mRECIST				
	CR	*PR*	*SD*	*PD*	*Total*
CR	18	0	0	0	18
PR	28	36	0	0	64
SD	2	16	6	0	24
PD	0	0	0	22	22
Total	48	52	6	22	128

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

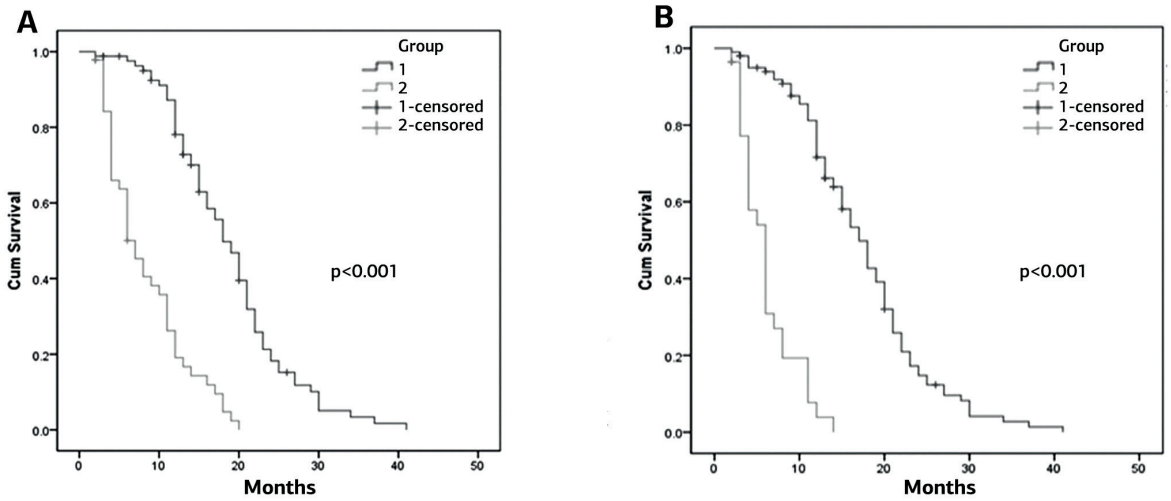

Figure 1. Kaplan-Meier estimates of overall survival for responders (group 1) and for non-responders (group 2). Survival was calculated according to response assessed by RECIST (**A**) and mRECIST (**B**).

CI 19.69-24.22), 14.04 months (95% CI 12.31-15.79), 9.4 months (95% CI 7.03-11.77) and 5.39 months (95% CI 4.13-6.64) respectively for mRECIST. The survival of patients who achieved an OR as assessed by RECIST or by mRECIST was significantly better than the survival of non-responding patients (SD or PD) (p<0.001) (Figure 1 A,B).

Of the 64 patients who were classified as PR according to RECIST, response according to mRECIST revealed a significantly different prognosis (Figure 2 A), with a median OS of 20.27 months (95% CI 17.88-22.67) and 15.47 months (95% CI 13.42-17.52) in patients who had CR (N=28) or PR (N=36) (p=0.006). In the 52 patients who were classified as PR according to mRECIST, response according to RECIST demonstrated a significantly different prognosis (Figure 2 B), with a median OS of 15.47 months (95% CI 13.42-17.52) and 10.68 months (95% CI 8.07-13.31) in patients with PR (N=36) or SD (N=16) (p=0.01). In the 48 patients who were classified with CR according to mRECIST, response according to RECIST determined a significantly different prognosis (Figure 2 C), with a median OS of 25.47 months (95% CI 20.50-30.43) and 20.27 months (95% CI 17.88-22.67) in patients classified as CR (N=18) or PR (N=28) (p=0.049).

Complete response in mRECIST vs PET-CT examinations

Of the 9 HCC patients who achieved complete tumor response after therapy according to contrast-enhanced CT or MRI, 5 patients showed abnormal viable tumors' determined by a dense accumulation in PET-CT imaging (an example of CR according to contrast-enhanced CT and positive in PET-CT examinations is shown in Figure 3A and B). After being followed up to the 7th month, all 5 patients showed tumor recurrence, while the other 4 patients remained as complete responders till the end of the study. Comparison in CR between

Table 3. Complete response in mRECIST vs PET-CT examinations

No.	*Gender*	*Age (years)*	*Therapies*	*Response*			*Follow-up (months)*	*Recurrence*
				RECIST	*mRECIST*	*PET-CT*		
1	F	68	RFA	PR	CR	-	13	No
2	M	62	RFA+Sorafenib	PR	CR	+	7	Yes
3	M	49	RFA	CR	CR	+	1	Yes
4	M	42	RFA	PR	CR	+	2	Yes
5	M	50	Surgery	CR	CR	-	24	No
6	M	56	TACE	PR	CR	-	13	No
7	M	47	Surgery	CR	CR	+	3	Yes
8	M	78	TACE	PR	CR	+	1	Yes
9	F	70	Surgery	CR	CR	-	3	No

RFA: radiofrequency ablation, TACE: transcatheter arterial chemoembolization.For other abbreviations see footnote of Table 2

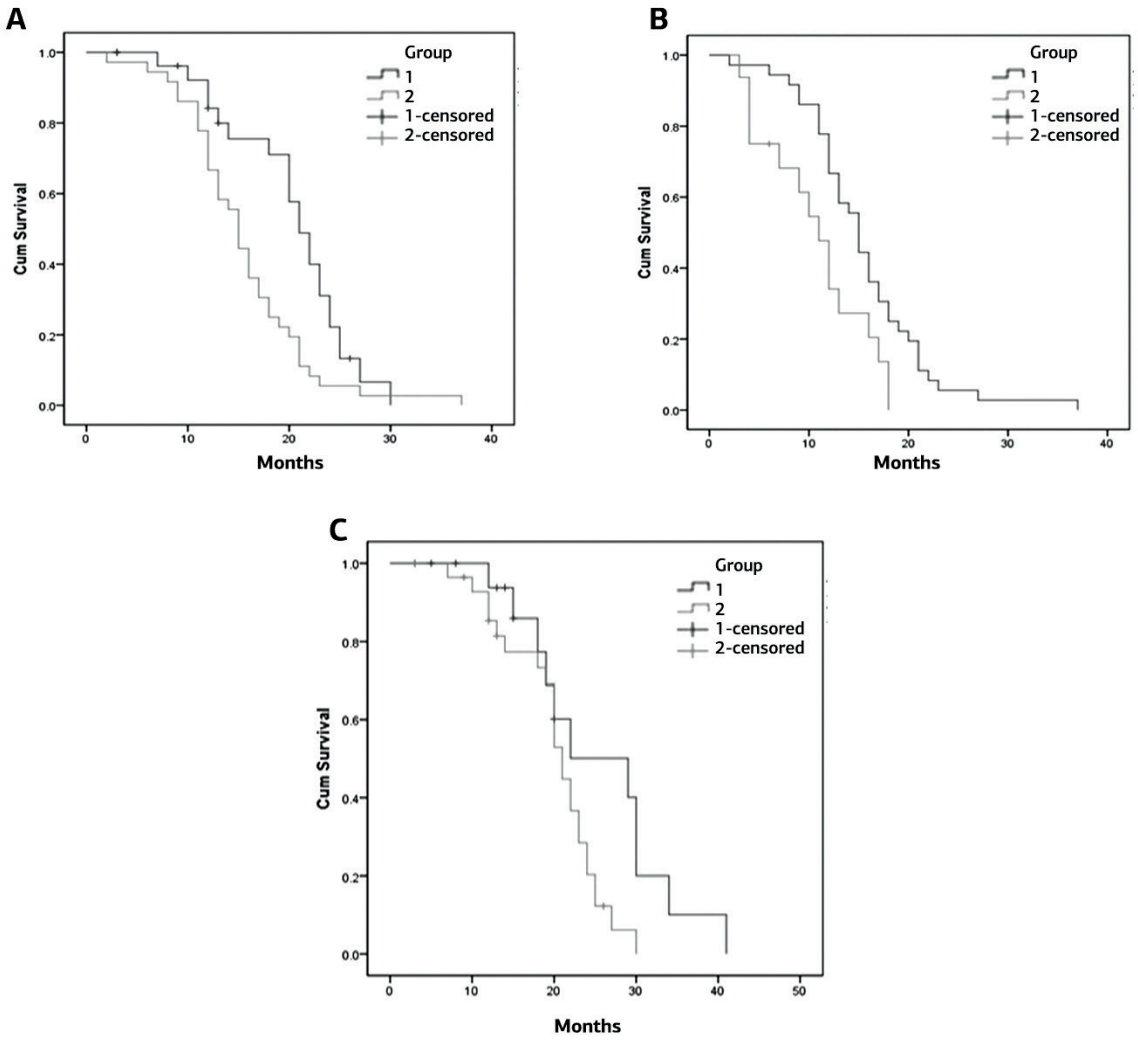

Figure 2. A: Survival of patients with complete response (group 1) or partial response (group 2) according to mRECIST, and PR according to RECIST (p=0.006). **B:** Survival of patients with partial response (group 1) or stable disease (group 2) according to RECIST, and partial response according to mRECIST (p=0.01). **C:** Survival of patients with complete response (group 1) or partial response (group 2) according to RECIST, and complete response according to mRECIST (p=0.049).

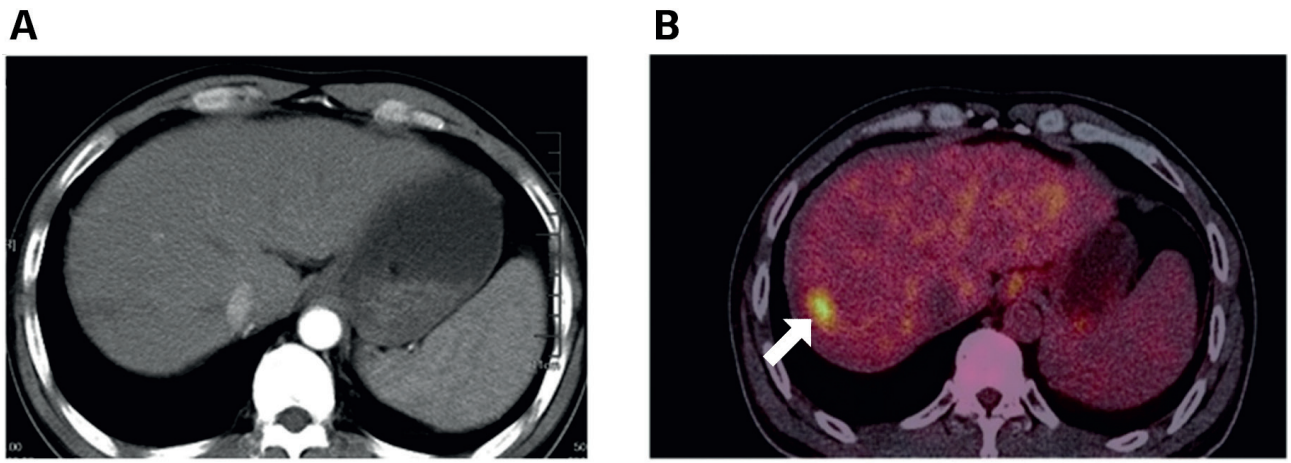

Figure 3. These images illustrate an example of a patient who achieved complete response after therapy according to contrast-enhanced CT which appears normal (**A**); Yet, PET-CT shows abnormal viable tumor (arrow) (**B**).

Table 4A. Comparison between CT/MRI and PET/CT for nodules less than 3cm

	PET-CT		
CT/MRI	*+*	*-*	*Total*
+	25	23	48
-	13	2	15
Total	38	25	63

p=0.017

Table 4B. Comparison between CT/MRI and PET/CT for nodules more than 3cm

	PET-CT		
CT/MRI	*+*	*-*	*Total*
+	41	1	42
-	3	0	3
Total	45	1	45

p=0.79

mRECIST and PET-CT is presented in Table 3.

Correlation between arterial enhanced CT or MRI and PET-CT examination

In the 69 initial HCC patients who had arterial enhanced CT or MRI and PET-CT examination, the tumor nodules number was 108. Assuming the correspondence with positive and negative radiology images, the correlation between arterial enhanced CT or MRI with PET-CT was 62.96% (73/108). Difference between arterial enhanced CT or MRI and PET-CT examination was primarily in the small nodules. The correspondence rate was 42.86% (p=0.017) in nodules less than 3cm (Table 4 A) and 91.11% (p=0.79) in nodules more than 3cm (Table 4 B). In those positive nodules in both arterial enhanced CT/MRI and in PET-CT examination, the tumor diameter showed no difference (p=0.648).

Discussion

mRECIST were first designed specifically for HCC clinical trials so that the suitable patients be strictly limited. It is demanded that only well-delineated, arterially enhanced lesions can be selected as target lesions for mRECIST [5]. To demonstrate whether mRECIST are suitable in routine clinical practice, we retrospectively analyzed data from 143 HCC patients who received TACE as treatment for advanced HCC in our institution. Patients for whom the tumor couldn't be measured using contrast-enhanced CT were excluded from the study. Our study showed that among those patients who were assessable by RECIST , mRECIST evaluation appeared to be suitable for 128 patients (89.51%). The main factors that caused a difference between the two were infiltrative-type HCC masses with ill-defined borders or lipiodol asymmetric distribution. Other conditions included metastatic lesions that didn't show intratumoral arterial enhancement on contrast-enhanced CT and tumor rupture bleeding interference. RECIST criteria are simple, convenient and comprehensive and can be used in broader clinical situations. If mRECIST are used to replace RECIST as evaluation criteria of clinical efficacy for HCC, then inevitably some patients cannot be evaluated using mRECIST, thus they will be evaluated reusing RECIST. Therefore, when it is needed to carry out a unified study on the curative effect in a group, we'll get in trouble because it is impossible to use two curative effect evaluation criteria at the same time under the circumstances.

RECIST, which do not address measurements of antitumor activity other than tumor shrinkage, can be misleading because tumor necrosis may not always be paralleled by a reduction in tumor size. RECIST underestimate tumor response. The correlation between CR rate and the response rate obtained using mRECIST were higher than those obtained using RECIST (37.5 vs 14.06%, $p<0.05$; 78.13 vs 64.06%, $p<0.05$). Among 64 patients who were classified as PR by RECIST, 28 patients (43.75%) were reclassified as CR by mRECIST. Among 24 patients who were classified as SD by RECIST 2 patients (8.33%) were reclassified as CR by mRECIST, and 16 (66.67%) were reclassified as PR by mRECIST. Compared to RECIST, mRECIST apply to a much larger population of responders. The results were consistent with the findings of Yozo et al. [8]. As for prognosis, Ju Hyun Shim demonstrated that mRECIST were independent predictors of OS and more accurately helped predict long-term survival in HCC patients [9]. In our study, according to mRECIST or RECIST evaluation, all responders had a better prognosis than non-responders. The main difference between mRECIST and RECIST was that mRECIST could differentiate responders more quantitatively and more accurately.

Although both mRECIST and RECIST assessment of response to tumor therapy provided good correlation of OS, there were still differences in the subgroups. In the subgroup of patients who were classified as PR according to RECIST, patients that were classified as CR with mRECIST had a prolonged OS than those that were classified as PR (p=0.006). In the subgroup of patients who were classified as PR according to mRECIST, those

who were classified as PR with RECIST had a prolonged OS than those classified as SD (p=0.01). In the subgroup of patients who were classified as CR according to mRECIST, CR patients according to RECIST had a prolonged OS than those who had PR (p=0.049). Mansmann et al. conducted a study on metastatic colorectal cancers to particularly explore the relationship between the degree of early tumor shrinkage (ET5) after treatment and the patient prognosis [10]. ETS in patients with metastatic colorectal cancer was an important predictor of favorable outcome. PFS and OS were significantly superior in ETS ≥ 20% patients compared to non-ETS [11]. Similar to colorectal cancer, the extent of HCC tumor shrinkage could be prognostic of OS. We found that those patients who were classified as CR had a better OS than other patients. TACE for HCC is one of the most commonly used locoregional treatment. However, usually the first TACE does not achieve the best treatment response. So it is necessary to repeat TACE to achieve maximal tumor response. Georgiades et al. showed that patients who underwent chemoembolization for HCC showed a favorable response and improved survival following the second chemoembolization [12].

Although mRECIST demonstrated a good correlation with prognosis, they did not estimate viable tumor correctly, which was the original intention of mRECIST. In our study, among the 9 HCC patients who achieved CR according to contrast-enhanced CT or MRI, 5 patients showed abnormal viable tumors determined by dense accumulation in PET-CT imaging. After being followed up to the 7th month, all 5 patients showed tumor recurrence. Contrast-enhanced CT or MRI may overestimate tumor response with a relatively low specificity (4/9) in detecting viable tumor. Bargellini et al. retrospectively evaluated the correlation between mRECIST assessed at CT and pathology in 178 patients with HCC who underwent transplantation following TACE [13]. Their results demonstrated that overall correlation between mRECIST and pathology was obtained in 67.4% of the patients. CT may overestimate tumor necrosis and underestimate tumor response. In fact, almost 30% of the nodules that were classified as CR showed only a few clusters of viable cells at pathology. RECIST could both overestimate and underestimate tumor response and are not more specific than mRECIST in detecting viable tumors. Although 3 patients who had tumor recurrence were classified as PR by RECIST, there were 2 patients who were classified as PR by RECIST and who did not have tumor recurrence till the end of our study.

Of the 9 HCC patients with CR according to mRECIST, 5 patients who showed viable tumors in PET/CT developed recurrent tumors, while the other 4 patients who had no viable tumors as determined by PET/CT imaging remained complete responders till the end of the study. A study showed that there is no difference in the measurement of HCC between enhanced CT seen and enhanced MRI scan [14]. Therefore, we performed a group comparison in patients who had undergone enhanced CT or MRI scan and PET/CT imaging. The patients with enhanced CT or MRI composed one group, and those with PET/CT a second group and the difference in the detection rate of tumor nodules was compared between the two groups.

In 108 tumor nodules of 69 initial HCC patients, the correlation of arterial enhanced CT or MRI with PET/CT was 62.96% (73/108). Differences between arterial enhanced CT or MRI and PET/CT examination were mainly seen in cases with small nodules. The correspondence rate was 42.86% (p=0.017) in nodules less than 3cm and 91.11% (p>0.05) in nodules more than 3cm. There were 16 nodules that were characterized as positive by PET/CT, while contrast-enhanced CT or MRI characterized them as negative. Among them, 5 (31.25%) nodules were more than 1cm. To make as sure as possible, lesions showing intratumoral arterial enhancement on contrast-enhanced CT or MRI, it has been determined that mRECIST can only be applied in cases of typical lesions that can be accurately measured in at least one dimension as 1 cm. Our study showed that even when we excluded nodules less than 1 cm, we still couldn't guarantee viable tumor with contrast-enhanced CT or MRI. At the same time, contrast-enhanced CT or MRI showed 24 positive nodules while PET/CT diagnosed them as negative.

The role of PET in detecting hepatobiliary malignancies has not yet been clearly defined. Myeong et al. reported that ^{18}F-fluorodeoxyglucose PET/CT examination was significantly associated with tumor burden including tumor size, number of lesions, α-fetoprotein levels and tumor stage [15]. Lan et al. suggested that literature on PET more strongly supports clinical roles for restaging of hepatobiliary malignancies, and for identifying metastatic disease [16]. The results of our study showed that both contrast-enhanced CT or MRI and PET/CT could present false positive results and were not sufficient to estimate viable tumor.

In conclusion, mRECIST criteria take into account tumor necrosis induced by treatment and show a good correlation with prognosis. Although mRECIST are superior to RECIST for performing tumor response evaluations in clinical trials, they need strict requirements and can't be useful as a tool for routine clinical practice. Furthermore, merely resorting to contrast-enhanced CT or MRI for diagnosis, mRECIST can't estimate viable tumor sufficiently.

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