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How to better understand mRECIST – novel refinements for evaluating HCC

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ABSTRACT

Hepatocellular carcinoma (HCC) ranks as the sixth most common cancer and fourth leading cause of cancer-related mortality worldwide. Previous research indicates that molecular targeted therapies can contribute to increased survival rates in patients with HCC due to its unique antiproliferative and antiangiogenic function. Thus, accurate assessment of treatment efficacy using molecular targeted therapies is essential for routine anti-cancer treatment, as well as clinical trials.

Modified RECIST (mRECIST) criteria was developed to overcome the limitations of conventional RECIST 1.1 criteria, which could produce inaccurate assessments of disease progression, due to clinical events related to the natural progression of chronic liver disease (e.g., enlargement of lymph nodes, ascites, etc.). This revised criterion focuses on measuring only the viable tumor, which is defined as the contrast-enhanced portion of the tumor on hepatic arterial phase images, rather than the whole lesion as in RECIST 1.1.

Moreover, mRECIST has now firmly established itself as the standard tool for measuring radiological endpoints at advanced tumours or earlier stage unsuitable for surgical resection or locoregional therapies of HCC with molecular targeted therapies, as endorsed by recognized bodies such as the European Association for the Study of the Liver (EASL) and the European Society for Medical Oncology. The National Comprehensive Cancer Network also recommends both methods mRECIST and RECIST 1.1 at advanced stages of HCC.

This document aims to improve the understanding of the mRECIST criteria, specifically by exploring the key distinctions between mRECIST and RECIST 1.1 from the perspective of lesion measurement and collection of Case Report Forms (CRFs), with a focus on common efficacy endpoints for HCC evaluation. Overall, this approach provides practical guidance while also aiding readers in comprehending the nuances of mRECIST criteria.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and represents a leading cause of cancer-related mortality worldwide [1]. There have been significant advances in treatment for HCC over the past decade. Available treatment options include surgical resection, liver transplantation, ablative techniques, transarterial chemoembolisation, transarterial radioembolisation, radiotherapy and molecular targeted therapies [2]. Despite the development of novel molecular targeted therapies for HCC, accurate assessment of treatment efficacy remains a challenge.

Nowadays, the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and modified RECIST (mRECIST) criteria are the most used criteria to assess tumour response in clinical trials [3]. The conventional RECIST 1.1 criteria have limitations for measuring lesion diameter and assessing treatment response in HCC patients, due to the heterogeneous nature of these tumors and interference from hepatic arterial circulation. To tackle these constraints, modified RECIST (mRECIST) criteria were introduced in 2010, specifically designed for assessing and treating hepatocellular carcinoma (HCC) [4]. In contrast to RECIST 1.1, mRECIST predominantly emphasizes the evaluation of the viable tumor segment, which is identified as the contrast-enhanced area on hepatic arterial phase images. This targeted measurement demonstrates significant prognostic potential in predicting overall survival (OS) [5].

This document aims to provide an in-depth overview of the mRECIST criteria, specifically exploring the key distinctions between mRECIST and RECIST 1.1 for image acquisition, lesion measurement and collection of Case Report Forms (CRFs), with a focus on common efficacy endpoints for HCC evaluation.

By doing so, this paper aims to provide practical guidance to aid readers in understanding the nuances of mRECIST criteria, and to emphasize its essential role in accurate HCC assessment and treatment.

COMPARISON OF RECIST 1.1 AND MRECIST

From the category of overall time-point responses, the principles used to establish objective tumor response are unchanged from RECIST 1.1. There are five response categories in RECIST 1.1 including Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE) [6]. And in mRECIST for HCC, identical to RECIST 1.1, overall patient response is a result of the combined assessment of target lesions, nontarget lesions, and new lesions. However, there are differences in the image acquisition, lesion measurement at baseline and treatment response.

1. **Difference of image acquisition:** Except examinations with (contrast-enhanced spiral computed tomography (CT) or contrast-enhanced dynamic magnetic resonance imaging (MRI) in conventional RECIST 1.1, it is mandatory to obtain a dual-phase imaging of the liver in mRECIST. Every effort should be made to time the contrast administration so that high-quality arterial-phase imaging is obtained throughout the liver on the first run, and high-quality portal venous-phase imaging is obtained throughout the liver on the second run. And this information would be used for the viable tumor area measurement. [4]

2. **Difference of lesion measurement at baseline:** The mRECIST has also categorized tumour lesions/lymph nodes into measurable or non-measurable as well as truly non-measurable lesions like RECIST 1.1. And the number of lesions selected as target lesions were a maximum of two lesions per organ and five lesions in total. For nonhepatic lesions, if present, could be considered as target lesions under the RECIST 1.1 criteria, without considering their vascularization.
   However, intrahepatic lesions selected as a target lesion using mRECIST should meet below criteria [4]:
   - The lesion can be classified as a RECIST measurable lesion (i.e., the lesion can be accurately measured in at least one dimension as 1 cm or more).
   - The lesion is suitable for repeat measurement.
   - The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI. And the HCC lesions measurement would base on viable tumor excluding partial internal necrosis part (Fig. 1).

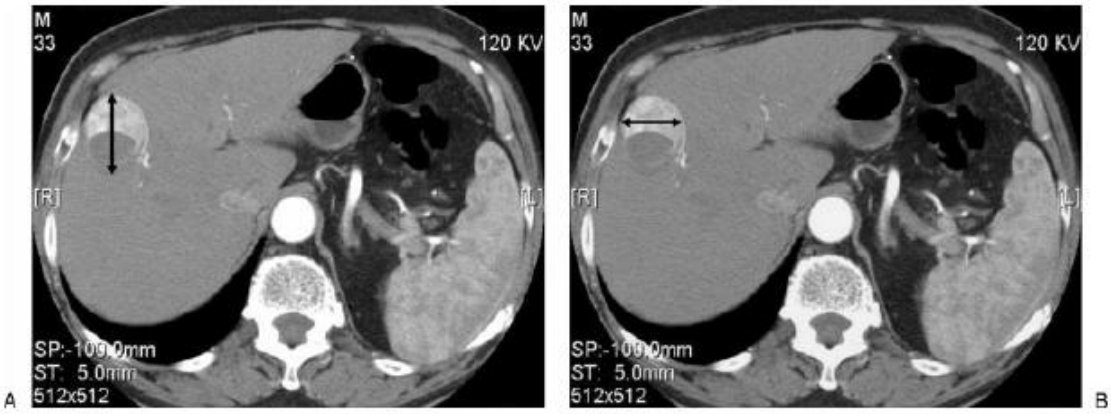

Figure 1 Application of mRECIST assessment for hepatocellular carcinoma (HCC). Target tumor response measurements on arterial-phase computed tomography (CT) scans. (A)Measurement of longest overall tumor diameter according to conventional RECIST, and (B) measurement of longest viable tumor diameter according to mRECIST for HCC. [4]

3. **Difference of defining treatment response**

Same with RECIST 1.1, the overall tumor response is determined by considering the criteria for the target lesions, non-target lesions, and new lesions. Progressive disease should be declared regardless of favorable responses of the target or non-target lesion. Here is the difference between mRECIST and RECIST 1.1 in the response criteria for target and non-target lesions (Table 1, 2).

The newly adopted criteria for identifying new lesions, as defined by mRECIST, are as follows:

- A new intrahepatic lesion is defined as a lesion larger than 10 mm that exhibits arterial hyperenhancement and portal venous/delayed washout.
- Liver lesions larger than 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1-cm-interval growth in subsequent scans.
- An individual radiologic event will be adjudicated in retrospect as progression at the time it was
  first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing [4].

Table 1. Definitions of target lesion response according to RECIST version 1.1 and mRECIST [7]

Criterion		RECIST version 1.1	mRECIST
Measurable lesion		A tumor ⩾10 mm, lymph node with a short axis ⩾15 mm	A **non-interrupted arterially enhancing** portion of the hepatic lesion ⩾ 10 mm, **porta hepatis lymph node** ⩾ 20 mm.
Measurement method		Sum of the largest diameters of the measurable lesions (short axis for lymph nodes)	Same as RECIST 1.1
Response criteria	Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (wheather target or non-target) must have a reduction in the short axis to <10 mm	Disappearance of any **intratumoral arterial enhancement** in all target lesions
	Partial response (PR)	A decrease of at least 30% from baseline in the sum of the diameters of the target lesions	A decrease of at least 30% from baseline in the sum of diameters of **viable** (enhancement in the arterial phase) **target lesions**
	Stable disease (SD)	Any cases that do not qualify for CR, PR, or PD	Same as RECIST 1.1
	Progressive disease (PD)	An increase of at least 20% in the sum of the diameters of the target lesions, taking as reference the smallest sum that was studied (including the baseline sum if that is the smallest). The sum must also demonstrate an absolute increase of at least 5 mm.	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 the viable (enhancing) target lesions. The sum must also demonstrate an absolute increase of at least 5 mm.

Table 2. Definitions of non-target lesion responses according to RECIST version 1.1 and mRECIST [7]

Criterion	RECIST version 1.1	mRECIST
Complete response (CR)	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis)	Disappearance of all non-target lesions (**intratumoral arterial enhancement for intrahepatic lesion**). All lymph nodes must be non-pathological in size
Incomplete response/non-progressive disease (non-CR/non-PD)*	Persistence of 1 or more non-target lesion(s)	Persistence of 1 or more non-target lesions (**intratumoral arterial enhancement for intrahepatic lesion**)
Progressive disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression)†	Same as RECIST version 1.1‡

* mRECIST uses the terms “incomplete response” and “stable disease.”

† Determining a non-target lesion to be an instance of progressive disease (PD) should only be limited to cases where a significant difference is exhibited before and after treatment. Minor changes in certain lesions should not be determined as indicative of PD.

‡ mRECIST only defines cases as progressive disease when effusion (in which the cytological diagnosis has been advanced) newly arises or when the amount increases. This is because regardless of the state of HCC, ascites and pleural effusion could occur as a result of the underlying liver disease, and because the peritoneal and pleural metastasis of HCC is relatively rare.

Given these discrepancies, it is preferable to gather the specifics of each target, non-target, and new lesion separately when utilizing both RECIST 1.1 and mRECIST in the analysis. Refer to Figure 2 for an example of a case report form for response with mRECIST.

Figure 2 Case report form example for Time-Point Response Assessment with mRECIST

BEST OVERALL RESPONSE in MRECIST

The principles of best overall response closely follow RECIST 1.1. Below is the statistical logic of mRECIST based on existing RECIST 1.1 in practice.

For unconfirmed BOR in mRECIST, first select all the overall responses up to first PD date or New Anti-Cancer Treatment Start Date (pre-specified in protocol or SAP), whichever earlier, or select all tumor assessments if both dates are missing; Then pick the best of CR-PR-SD (or NON-CR/NON-PD)-PD-NE in this order with CR the best, and NE the worst; In case SD (or NON-CR/NON-PD) is the best response found: keep as SD (or NON-CR/NON-PD) only if at least one objective status of stable or better documented (i.e. CR/PR/SD (or NON-CR/NON-PD) at least lasted for more than X days. X is often 6 weeks but should reflect a duration of clinical relevance for the disease under study and should be pre-specified in the protocol and SAP), else set to "PD" if timepoint overall response PD exists, else set to "NE" [8].

Confirmation of response is not required when using mRECIST 1.1, except in non-randomised trials, and this approach is also recommended for mRECIST. For BOR based on confirmed response, the CR and PR should be confirmed. The confirmed CR, PR logics are same for both RECIST 1.1 and mRECIST including two objective statuses of CR a minimum of four weeks apart documented to be derived as confirmed CR and two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of four weeks apart documented to be derived as confirmed PR [8].

However, the performance of both criteria in assessing disease progression is identical. A latest meta-analysis including 23 studies comprising 2574 patients after molecular targeted therapies in hepatocellular carcinoma (HCC) was performed and found there was a considerable discrepancy in the assessment of OR between the RECIST 1.1 and mRECIST criteria that the ORR according to mRECIST is higher than RECIST1.1 (15.9% vs 7.8%, p<0.001) while both criteria equally able to discriminate disease progression and non-progressors [9]. There are several possible reasons. First, molecular targeted therapies are based on the inhibition of several proangiogenic signalling pathways, which stimulating angiogenesis, are responsible of the characteristic hyper-vascular pattern of HCC lesions. The therapeutic response after molecularly targeted therapy is closely associated with structural changes, mainly including decreased vascularisation and increased tissue necrosis or cavitation, but it is not always reflected in the reduction in tumour size. Second, HCC and cirrhosis coexist in more than 80% of cases. The inherent pathogenic factors and haemodynamic changes of cirrhosis may mimic or mask intrahepatic tumours [9].

SURVIAL ANALYSIS in MRECIST

Same with RECIST 1.1 criteria, progression-free survival is the time from start date to date of event which includes first documentation of PD or death due to any cause. And overall survival is the time from start date to date of death due to any cause.

Phase III studies assessing primary and adjuvant therapies in HCC propose overall survival and time to recurrence as primary endpoints, while composite endpoints like disease-free survival (DFS) or progression-free survival (PFS) should be included as secondary endpoints, especially when the target population is not clearly defined. Randomized phase II studies, which traditionally consider response rate as the gold standard for efficacy, were deemed crucial before conducting phase III trials in HCC.

mRECIST can assist in predicting overall survival (OS) in patients undergoing molecular targeted therapies, with patients achieving objective response (OR) showing significantly better survival outcomes than those who only achieve stable disease (SD) or progressive disease (PD) [9]. However, according to RECIST 1.1, the OS of patients classified as OR is not significantly different from that of non-responders. Edeline et al. conducted a study showing that among patients classified as stable according to RECIST 1.1, the implementation of mRECIST allowed for the identification of distinct prognostic subgroups. Responding patients had a significantly better median overall survival (OS) of 17.1 months compared to 9.7 months for stable patients and 3.7 months for patients with progressive disease (PD) [10].

Therefore, mRECIST may offer a suitable alternative to RECIST in phase II clinical trials, in which detection of an efficacy signal is paramount. In other words, if the patient is classified as a responder by mRECIST, it is important to provide supportive care to ensure they continue taking targeted therapies. Conversely, if the patient is classified with progressive disease (PD) by mRECIST, it is advisable to discontinue sorafenib as it is unlikely to benefit the patient significantly [9,10].

Due to the universal use of RECIST 1.1, almost every company has efficacy analysis process and efficacy ADaM specs for RECIST 1.1. Therefore, creating a set ADaM spec with mRECIST criteria based on RECIST 1.1 efficacy ADaM specs could quickly and effectively analyze the efficacy results with mRECIST.

CONCLUSION

This article aims to investigate the significant distinctions between RECIST 1.1 and mRECIST with regards to lesion selection, measurement, and the correlation between objective response rate (ORR) and overall survival (OS). By presenting this exploration, readers will gain a deeper understanding of mRECIST and how to effectively derive and validate efficacy endpoints such as best overall response (BOR), progression-free survival (PFS), and duration of response (DOR) using pre-existing RECIST 1.1 efficacy analysis data. Ultimately, this knowledge could help clinicians in making informed decisions for their patients and determining the direction of phase II clinical trials. Examples presented in this paper are hypothetical and for illustrative purpose only, and this paper puts forward a special view of criteria difference, data collection and endpoints interpretation with mRECSIT criteria based on RECIST 1.1. Further detailed analysis process could depend on study protocol and statistical analysis plan (SAP),

independent review charter (IDMC) charter, CDISC ADaM Guidance, as well as these two guidelines. Fully understand the differences between these two guidelines can lead to the standardization of the process of derivation of efficacy endpoints and keep analysis result with high quality with mRECIST criteria, and thus saving time and resources based on exiting RECIST 1.1 analysis frame.

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