New Data Supporting Modified RECIST (mRECIST) for Hepatocellular Carcinoma

Running Title: Modified RECIST (mRECIST) for Hepatocellular Carcinoma

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Abstract

The modified RECIST (mRECIST) guideline has introduced specific amendments to standard RECIST to address the unique complexities involved in the evaluation of tumor response in hepatocellular carcinoma. A growing amount of data suggests that mRECIST—designed for response assessment in clinical trials—may translate into a tool for clinical practice.
In this issue of *Clinical Cancer Research*, Kim and colleagues (1) show that assessment of tumor response by modified RECIST (mRECIST) criteria (2) predicts overall survival in patients with hepatocellular carcinoma (HCC) treated by transcatheter arterial chemoembolization (TACE). The study confirms the results of several recent investigations conducted in the United States, Europe, and Asia (3-5).

The development of imaging criteria for response assessment in patients with HCC has been a long process (Fig. 1). In 2000, the European Association for Study of Liver (EASL) first proposed an amendment to the World Health Organization (WHO) criteria, the ones most commonly used at that time (6). The WHO criteria were designed for the evaluation of cytotoxic agents and recommended the use of the product of the two longest perpendicular diameters to monitor changes in tumor size. These criteria were unable to capture the anticancer activity of tumor-directed therapies used in the treatment of HCC, such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and TACE. The EASL guideline recommended to take into account treatment-induced tumor necrosis and to measure the product of the longest diameters of the viable portion of the tumor – as recognized by contrast-enhanced radiological imaging – instead of the product of the longest diameters of the whole tumor mass. Assessment of tumor response according to the EASL amendment has been used in HCC patients receiving tumor-directed treatments for more than a decade. The article by Kim and colleagues in this issue of *Clinical Cancer Research* (1) confirms that this approach still has value in this setting.

A limitation of the 2000 EASL guideline is that it only provides recommendations for the evaluation of target lesions. With the advent of systemic treatments for HCC, the need for a comprehensive model for response assessment has been widely acknowledged (7, 8). In the meantime, the WHO criteria were largely replaced by the RECIST criteria in oncology trials. The introduction of RECIST has been a major advancement in the standardization of response assessment. The RECIST model clearly defines the categories of target lesions, non-target lesions,
and new lesions, and provides overall response classifications resulting from the different combinations of the responses observed in each of these categories. In addition, the RECIST criteria simplified the assessment of the target lesions by recommending the use of unidimensional measurements and the sum of the longest tumor diameters instead of the bidimensional approach of the WHO method including two measurements and the sum of the products. The original 1.0 RECIST guideline recommended to measure up to a maximum of 5 target lesions per organ and 10 target lesions in total, representative of all involved organs, while the revised 1.1 RECIST recommendations have reduced to 2 the maximum number of target lesions to measure per organ and to 5 the maximum total number of target lesions.

The RECIST panel acknowledged that amendment to the guideline could be needed for specific tumors or anatomic sites presenting unique complexities. Specific refinements to standard RECIST criteria in the setting of HCC clinical research were introduced at the time of the SHARP trial comparing sorafenib versus placebo (2). The SHARP study identified a distinct overall survival benefit for sorafenib as compared to placebo. The assessment of the secondary endpoints, time-to-progression (TTP) and disease control rate (DCR), was conducted by an independent blinded radiological panel following specific recommendations for image interpretation aimed at preventing incorrect diagnoses of progression. In fact, in the SHARP trial, TTP and DCR data were consistent with overall survival. However, the objective response rate (ORR) in the sorafenib arm – calculated by standard RECIST metrics – was negligible.

A number of novel molecular targeted compounds that produce ORR of less than 10% by standard RECIST have shown significant improvement in survival in a variety of cancers in randomized controlled trials (7). Both the original 1.0 and the revised 1.1 RECIST guidelines, similar to the WHO criteria, are based on the concept of tumor shrinkage as the only measure of antitumor activity. These agents no longer induce tumor shrinkage and, thus, ORR is no longer a surrogate for overall survival (7).
In 2008, a group of experts was convened by the American Association for the Study of Liver Diseases (AASLD) to develop a set of guidelines aimed at providing a common framework for the design of clinical trials in HCC (7). This panel addressed the issue of the lack of correlation between response by conventional size-based criteria and survival observed in HCC trials with both tumor-directed therapies and molecular targeted agents, and produced formal amendments to standard RECIST (Fig. 1). The resulting criteria were named mRECIST for HCC (2). Several changes were based on the recommendations produced at the time of the SHARP trial to prevent incorrect diagnoses of progression. In addition, the mRECIST criteria adapted the concept of viable tumor proposed by the 2000 EASL guideline to comply with the unidimensional approach of standard RECIST, by recommending to measure the longest diameter of the viable portion of the target lesions.

mRECIST appears to have broader applicability with respect to the EASL criteria. By keeping the accepted standard RECIST model as a reference, mRECIST enables assessment of overall response by taking into account target lesions response, non-target lesions response, and presence or absence of new lesions. The important new information brought by the article by Kim and colleagues in this issue of Clinical Cancer Research (1) is that the ability of mRECIST criteria to predict survival in HCC patients receiving TACE is not dependent on the maximum number of target lesions that are measured in the liver. Measurement of up to 5 target lesion – following the original 1.0 RECIST guideline – was as efficacious as measurement of up to 2 target lesions – according to the revised 1.1 RECIST recommendations. Thus, mRECIST appears to be suitable for use with either the 1.0 or the 1.1 standard RECIST models for target lesions assessment.

The mRECIST guidelines have been increasingly adopted in HCC clinical research. Several key recommendations, such as those concerning the classification of ascites, hepatic hilar lymph nodes, vascular invasion, and new lesions – all of which may have a major impact on the assessment of TTP and DCR – have been incorporated into the radiology charters of clinical trials,
even when target lesions measurements were conducted according to standard metrics and, therefore, the criteria were formally named standard RECIST. The main open question is whether the use of the mRECIST viable tumor concept for target lesions measurements can bring ORR back as a surrogate for survival. Several clinical trials from investigators around the globe have suggested that this is indeed the case in patients receiving tumor-directed therapies (1, 3-5). In patients treated with TACE, mRECIST ORR of 32-57% were observed, with significant correlation between response and overall survival (3, 5). Data in patients treated with molecular targeted agents are still limited. Studies in patients receiving sorafenib have reported ORR ranging 9-23% according to mRECIST: in these series, patients who achieved an objective response had a longer overall survival than patients with stable disease or progression (9, 10). However, further research is needed to understand the prognostic value of ORR as per mRECIST in the setting of systemic treatments.

In conclusion, a growing body of scientific evidence suggests that mRECIST– designed for response assessment in clinical trials – may translate into a tool for clinical practice, a process that has already started with the recommendations issued in the recent clinical practice guidelines produced by the EASL and the European Organization for Research and Treatment of Cancer (11) and by the European Society of Medical Oncology and the European Society of Digestive Oncology (12).
References


Legend to figure

Figure 1. Key steps in the development of response evaluation criteria for hepatocellular carcinoma and in the translation from clinical research to clinical practice.
Figure 1:

2000

- EASL amendment to WHO criteria
- Original RECIST guideline (version 1.0)

2012

- AASLD-JNCI guidelines for HCC research
- Revised RECIST guideline (version 1.1)
- AASLD practice guidelines
- Modified RECIST (mRECIST) for HCC
- EASL-EORTC clinical practice guidelines
- ESMO-ESDO clinical practice guidelines

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