*TOPIC HIGHLIGHT*

**WJH 6th Anniversary Special Issues (2): Hepatocellular carcinoma**

# Assessment of clinical and radiological response to sorafenib in hepatocellular carcinoma patients

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Author contributions: All the authors provided substantial contributions to conception of the manuscript; helped drafting the article or making critical revisions related to important intellectual content of the manuscript; and approved the final version of the article to be published.

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## Abstract

Sorafenib is an effective anti-angiogenic treatment for hepatocellular carcinoma (HCC). The assessment of tumor progression in patients treated with sorafenib is crucial to help identify potentially-resistant patients, avoiding unnecessary toxicities. Traditional methods to assess tumor progression are based on variations in tumor size and provide unreliable results in patients treated with sorafenib. New methods to assess tumor progression such as the modified Response Evaluation Criteria in Solid Tumors or European Association for the Study of Liver criteria are based on imaging to measure the vascularization and tumor volume (viable or necrotic). These however fail especially when the tumor response results in irregular development of necrotic tissue. Newer assessment techniques focus on the evaluation of tumor volume, density or perfusion. Perfusion computed tomography and Dynamic Contrast-Enhanced-UltraSound can measure the vascularization of HCC lesions and help predict tumor response to anti-angiogenic therapies. Mean Transit Time is a possible predictive biomarker to measure tumor response. Volumetric techniques are reliable, reproducible and time-efficient and can help measure minimal changes in viable tumor or necrotic tissue, allowing the prompt identification of non-responders. Volume ratio may be a reproducible biomarker for tumor response. Larger trials are needed to confirm the use of these techniques in the prediction of response to sorafenib.

**Key words:** Hepatocellular carcinoma; Sorafenib; Response Evaluation Criteria in Solid Tumors; Perfusion computed tomography; Dynamic Contrast-Enhanced-UltraSound; Volumetric assessment

**Core tip:** The development of new treatment options for hepatocellular carcinoma has changed not only the way in which cancer is treated, but also how it is diagnosed

and especially the assessment of tumor response. The traditional radiologic methods, which are mainly based on the evaluation of variations in tumor size, are considered insufficiently sensitive and unreliable in determining tumor progression when targeted therapies like sorafenib are involved. New assessment tools trying to combine morphological and vascular functional data to obtain an accurate measurement of tumor characteristics such as volume, density or vascularization, showed positive results in assessing patient's response to therapy.

# INTRODUCTION

With an incidence doubled in the last decades, increased mortality rates, and important risk factors associated with its development, hepatocellular carcinoma (HCC) is considered the most common primary liver malignancy[1]. The management of HCC is complex and often requires a multidisciplinary approach in order to select the most appropriate treatment and to reduce toxicity[2].

The only medical treatment approved for HCC is the oral multikinase inhibitor sorafenib (SO)[3,4]. Its mechanism of action is based on the inhibition of a number of pro-angiogenic signaling pathways, that, stimulating angiogenesis, are responsible of the characteristic hypervascular pattern of HCC lesions[5]. The therapeutic response to SO correlates with changes in tumor structure, including decreased vascularization and increased tissue necrosis or cavitation, but it is not always associated with reduction in tumor size[6,7]. Clinical trials showed that SO is an effective treatment for advanced-stage HCC[8]. Moreover, the efficacy and safety of the combination of SO with other standard treatments for intermediate and advanced-stage HCC, such as Transarterial Chemo Embolization (TACE), is still under investigation[8-10].

Present research efforts are devoted to the refinement of prognosis prediction by molecular profiling and enhanced clinical characterization to further improve therapies and, in turn, increase life expectancy of patients[3].

The assessment of tumor progression during SO treatment is an open issue: traditional radiologic methods mainly based on the evaluation of changes in tumor size are considered insufficiently sensitive and unreliable[11]. The phase III SHARP trial[4] showed that the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1[12]

did not correlate with the SO-induced positive clinical outcome and that its ability to predict patient's response was very limited[4].

In this paper, we will review the new available tools that showed promising results for the assessment of HCC patients' response to Sorafenib treatment.

# TRADITIONAL ASSESSMENT TOOLS: MODIFIED RECIST AND THE EUROPEAN ASSOCIATION FOR THE STUDY OF LIVER

The modified RECIST (mRECIST) was recently proposed by the American Association for the Study of Liver Diseases (AASLD) as a new assessment method able to overcome the main limitations of RECIST criteria by including, among the evaluation criteria, the changes in tumor structure induced by anti-angiogenic treatments[13]. mRECIST assesses the vascularization of a lesion and the changes in tumor arterial enhancement through imaging techniques, such as the contrast-enhanced spiral computed tomography (CT) or dynamic magnetic resonance imaging (MRI). Neo-angiogenesis is in fact well-enhanced both in the arterial phase of MRI and in CT although MRI contrast agents provide better visualization[14]. However, for an appropriate evaluation, the AASLD guidelines recommend the assessment of tumor lesions also at baseline, as well as the optimization of image acquisition protocols and interpretation[13].

The European Association for the Study of Liver (EASL), in 2000, suggested a similar approach that included the evaluation of changes in tumor enhancement through contrast-enhanced imaging also to establish variations in viable tumor and necrotic areas[15].

The ability of mRECIST and EASL criteria to assess patients with HCC treated both with loco-regional therapy or systemic agents were compared with the traditional RECIST criteria in different studies[16-21]. Results showed that mRECIST and EASL criteria are sufficiently reliable in assessing response to loco-regional treatment, but some uncertainties remain whether using these criteria after target agents[22]. Necrotic areas after loco-regional therapy are usually predictable and well-defined necrotic areas. Conversely, SO can result in an irregular and unpredictable development of necrosis since the decreased tumor vascularization does not always translate in necrotic tissue[20,23]. A recent study however showed that EASL and mRECIST responses are independent predictors for overall survival in patients treated with the combination of SO and TACE, and that this response can be evaluated early (3 mo)[21].

This scattered scenario suggests that criteria based on an overall visual assessment can be misleading and may lead to inaccurate measurements; therefore, there is a strong need to develop new and more reliable assessment tools.

# NEW ASSESSMENT TOOLS

The research effort towards the development of new assessment tools for SO response grounds on the consideration that, provided the high impact of SO on tumor vascularity, techniques able to combine morphological and vascular functional data can be more effective than the traditional criteria[24]. In addition, EASL and AASLD guidelines underline that the portion of viable tumor, and not the whole tumor mass, is the most important evaluation parameter, which depends on the blood flow within and vascularization of the lesions.

Hence, perfusion-CT (pCT) and Dynamic Contrast-Enhanced-UltraSound (D-CEUS) are at the basis of some current strategies for the evaluation of tumor perfusion and tumor density[24-26], whereas other authors propose volumetric assessment of tumor as possible marker of progression[27-29].

Last, several tumor biomarkers are under investigations as possible prognostic and predictive factors for SO response aimed to help identifying candidate resistant patients, possibly candidate with alternative treatments, and avoiding unnecessary toxicities.

## New tools for the evaluation of tumor perfusion and density

pCT and D-CEUS were recently identified as possible practical and non-invasive radiological techniques that, enabling the visualization of tissue microcirculation, are able to provide information related to the diagnosis, stratification, and prediction of the response to treatment in oncologic patients[30,31]. Moreover, the sensitivity, rapidity, and efficacy of these imaging techniques was further advanced with the introduction of multidetector CT scanners and of commercially-available software for data analysis[32]. Provided their ability to evaluate tissue vascularization, these techniques were also explored as possible tools to measure the efficacy of anti-angiogenic therapies[31,33,34]. The studies investigating pCT and D-CEUS ability to measure treatment response were conducted both in patients treated with SO and in patients treated with bevacizumab. These two therapies are comparable in terms of tumor response, that is similar with the two molecules; however, from a clinical viewpoint, they greatly differ in relation to HCC treatment as bevacizumab is not used to treat HCC patients.

Another very recent approach concerned the use of the apparent diffusion coefficient (ADC), reflecting diffusion of water in tissue, measured by DW-MRI that was already demonstrated to correlated with response to chemotherapy[35].

**pCT parameters:** pCT parameters such as blood flow (BF), blood volume (BV), mean transit time (MTT) and permeability surface area (PS) are significantly different in HCC lesions compared with normal liver tissue and correlate to the tumor stage[26,30,36]: whereas BF, BV, and PS were reported to be higher in advanced HCC than in moderately differentiated HCC tissue, MTT was lower in advanced HCC[30].

pCT was compared to RECIST and tumor density in a phase Ⅱ clinical trial involving 23 patients with advanced HCC undergoing bevacizumab for the evaluation of the response to treatment[33]. Whereas no variations in tumor size (RECIST) and only a mild reduction in tumor density were observed, pCT parameters significantly correlated to patient's response [progression free survival (PFS)]: higher MTT baseline values were directly correlated to better clinical outcome and 6-mo PFS[33]. Similar results were reported on 33 advanced HCC patients under bevacizumab, who showed a significant decrease in tumor perfusion and an increase in MTT values after treatment administration[31]. Also, patients in which the disease progressed had lower baseline MTT levels that highly increased after treatment when compared to those with partial or complete response to treatment[31].

The results obtained in patients treated with bevacizumab and evaluated through pCT were recently confirmed in a series of 10 patients treated with SO[26]: at 3 mo after the initiation of SO treatment, patients showed a progressive decrease of BF, BV, and PS and a significant increase of MTT compared to baseline values[26]. All together, these results support the hypothesis that pCT, and, more specifically, MTT, can be a valuable candidate predictive biomarker for SO response in HCC patients[26].

**D-CEUS:** D-CEUS was used to study tumor perfusion and dynamic changes in tumor vascularity in patients under bevacizumab treatment[34]. Changes were detected as early as 3 d after bevacizumab administration, suggesting that they could be used to predict tumor response and, in turn, measure the effectiveness of anti-angiogenic therapies[34]. In patients treated with SO, positive tumor response and longer survival rates were associated to increased or unchanged time to peak intensity (Tp) and MTT values, as well as decreased area under the curve (AUC)[37]. Moreover, AUC, Tp and slope of wash in (Pw) positively correlated to PFS, thus suggesting that D-CEUS is able to provide a measure of the efficacy of anti-angiogenic therapy and a reliable help in the selection of patients who could benefit from SO treatment[37].

pCT and D-CEUS as measure of tumor response were recently compared in 11 HCC patients treated with SO[24]. Despite decreasing consistently after treatment, pCT parameters were not able to discriminate between responders and non-responders. Conversely, a decrease of more than 40% in the AUC measured through D-CEUS after 1-mo treatment was found as a strong predictor of lack of progression at 2-mo, thus enabling the differentiation between patients who responded to therapy and those who did not[24]. D-CEUS was then suggested as possible marker of SO response, although the results of pCT analysis may have been biased by the small number of patients[24]. As a further application of CEUS, in a murine HCC mode CEUS obtained using vascular endothelial growth factor receptor-2 (VEGFR-2)

targeted microbubbles was demonstrated to be effective in measuring SO response: the differential targeted enhancement due to bound microbubbles in the tumor significantly decreased in the mice treated with SO, and was able to discriminate the non-responder group from the responders[38].

Last, the ADC obtained from DW-MRI was applied in mice to investigate its ability as an indicator of response to SO in HCC. Lower ADC values and a stronger progressive ADC decrease were observed in mice treated with SO than in the control group, thus prompting further research on this technique for the evaluation of SO response[35].

### New tools for volumetric assessment

Volumetric techniques are regarded to as possible alternative methods to measure the whole tumor volume instead of the traditional approach of RECIST and EASL that, being based on the evaluation of a representative axial slice of the tumor, do not take into account its entire volume[22,27-29]. In fact, SO and other anti-angiogenic treatments induce the development of an often irregular and not-homogeneous necrotic area, so that the area selected for evaluation may not be representative of the whole tumor. Volumetric techniques take into consideration the entire tumor load and are able to detect even minimal changes in viable tumor or necrotic tissue, thus allowing the prompt identification of non-responders[22]. In addition, the introduction of automatic and semi-automatic software for image segmentation, have provided faster, more reliable and user-friendly tools for volume measurement, leading to rapid spread of these techniques[27-29].

In 17 HCC patients treated with TACE, semi-automatic 3D volume segmentation technique based on a voxel-by-voxel analysis for measuring tumor volume and enhancement pattern was reported to be reproducible and time-effective, and to provide a more accurate estimation of tumor burden than 2D techniques[28]. Similarly, HCC necrosis measured by volumetric assay was more reproducible than that obtain with the 2D measurement in 29 HCC patients, treated with yttrium-90 radioembolization[29]. According to the results of this study, the mean values of necrosis obtained with the two methods significantly differed[29].

In small retrospective involving 23 HCC or liver metastasis patients undergoing radioembolization, volumetric assessment demonstrated good intra/intra-observer reproducibility[27]. Both whole tumor and necrotic areas were measured providing good accuracy and reliability. Also, the authors observed a significant difference in survival time, in a Kaplan-Meier analysis, between patients whose change in necrotic area was $\geq$ 10% compared with those with necrosis $\leq$ 10%, thus suggesting a possible correlation between survival rates and tumor necrosis measured through this technique[27].

To our knowledge, response to SO using tumor volume assessment was investigated only in one prospective study involving 22 HCC patients in which the response to therapy was evaluated by multiple criteria[22], including traditional radiological criteria (RECIST1.1., EASL and mRECIST). The results showed that none of the three radiological criteria showed a significant correlation with patients' survival and that the only parameter associated with survival was volume rate: an increase $\geq$ 10% in tumor volume after 2-mo was found as negative predictive factor for survival. The study also confirmed[27-29] the reproducibility of measurements, with high degree of inter- and intra-observer agreement, thus suggesting that, whereas traditional criteria to measure tumor response are not reliable in the case of SO administration, volume assessment seem to be an early and reproducible biomarker for tumor response[22].

Despite these promising results, larger trials are needed to confirm data on volumetric assessment as tool for measuring tumor volume in HCC patients, especially if treated with SO, and to investigate the correlation between measurement of changes in tumor volume and response to therapy.

### The prognostic and predictive values of tumor biomarkers

Several studies are investigating new and more accurate predictive and prognostic factors for response to SO. They include the evaluations of alpha-fetoprotein (AFP) levels[26,39-44], genotype and phenotype features, such as VEGF family single nucleotide polymorphisms (SNPs)[45,46], and the differential blood cell counts, particularly the neutrophil-lymphocyte ratio (NLR)[47-49].

AFP is a glycoprotein secreted in approximately 70% of HCC, and it is considered as an useful biomarker for HCC diagnosis[39,40]. The mechanism of action could be related to SNPs in human AFP promoter that lead to uncontrolled transcriptional activities[50]. It has also been suggested that AFP could act possible predictor of response to anti-cancer and anti-angiogenic treatment[39-41,43]. The role of AFP in measuring the response to SO is however debated and deserves further considerations[43,51] since authors reported heterogeneous results[22,40-44].

Some studies suggest that, in patients treated with SO, AFP decrease is an independent predictors of good response to sorafenib[41,44] and that the early increase in AFP is associated with poor survival[40]. In a nationwide retrospective study, high AFP levels at baseline were consistently shown to be prognostic for a shorter survival, and SO responders showed a significant decline in AFP during the first month treatment[43]. Conversely, in the study evaluating different measures of tumor progression in 10 patients receiving SO, authors reported an inverse correlation between baseline MTT values, that were predictive of SO response, and changes in AFP after 3 mo, but changes in AFP levels were not associated with response rate[26].

Gene expression is believed as one of the main responsible of responsiveness to treatments in HCC patients[52]. The lack of response to SO in HCC patients was shown to be correlated to a mesenchymal-like phenotype and expression of CD44, linked to activation

of the transforming growth factor-β pathway[53] and the combined HTATIP2 expression and microvessel density was found to be a predictor of SO response[54]. Some studies also highlighted the role of VEGF[45], suggesting that patients responsiveness to SO may be well defined through the analysis of VEGF and VEGFR SNPs[46].

NLR was investigated as prognostic factor both in patients receiving SO[47,48] and in those not receiving SO[49]. In HCC patients not treated with SO, low NLR was associated with higher survival[49]. Similarly, high periprocedural NLR was associated with poor survival in patients with unresectable HCC on SO treatment[47,48] even if these results deserve further consideration[55].

## CONCLUSION

The traditional assessment criteria for the evaluation of SO response in HCC treatments demonstrated to be inappropriate to reliably predict the clinical response to treatment. Despite adjustments resulting in the development of modified criteria such as mRECIST and EASL, these tools still show important limitations, especially when the tumor response results in irregular development of necrotic tissue. The introduction of new and efficient biomarkers to measure patients' response to SO could enable the early assessment of patients' response, reducing unnecessary costs and adverse events, and improving final patients' outcome.

New tools for the evaluation of tumor progression were developed and are under investigation. They focus on providing a precise estimate of the changes in viable tumor volume, through the measurement of tumor perfusion or through volumetric assessment. More specifically, the perfusion parameter MTT and the volume ratio were identified as predictive biomarkers of therapeutic response.

Despite these promising positive results of both these techniques, available data are still scant and prompt new larger systematic validation studies. Although there is no gold standard for response evaluation in HCC, these validation studies should be based on the suggestions reported in current guidelines. As already done in the available studies, the validation of these new approaches should rely on the comparison between their results and those obtained through standard assessment methods (EASL, mRECIST), while bearing in mind the limitations of each approach.

Once the necessary technological advancements will be completed, it is expected the introduction of these new assessment methods in the clinical practice, enabling the prompt identification of subjects not responding to a specific therapy, resulting in a reduction in adverse events and unnecessary costs and leading to a more rapid identification of the best treatment approach for each subject.

## ACKNOWLEDGMENTS

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