Assessing Tumor Response in Hepatocellular Carcinoma: Review of Conventional, New, and Emerging Concepts

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Learning objectives

The purpose of this exhibit is to

1.- Know the different tumor response evaluation criteria

2.- Discuss the limitations in the evaluation of tumor response when employing conventional response criteria

3.- Review the utility of new and emergent concepts in the evaluation of tumor response in the era of targeted therapies
Background

Hepatocellular carcinoma (HCC) is the most common primary malignant disease of the liver. Response to treatment is a crucial aspect in cancer therapy and represent a marker of improved survival. There are multiple imaging based tumor response criteria proposed to achieve objective assessment of treatment response. Most of these criteria were developed to standardize response in trials but are used commonly on clinical practice [1].
Findings and procedure details

HCC response criteria

Conventional:

In 1979 The World Health Organization (WHO) defined criteria for tumor response based on imaging findings that became the most commonly used by investigators around the world [2]. The Response Evaluation Criteria in Solid Tumors (RECIST) was published in 2000 by the National Institute of Cancer [3] to standardize response evaluation criteria, in 2009 was released the version 1.1 with some modifications [4]. Both, WHO and RECIST rely only in tumor size, and not tumor viability, this can lead to an incorrect assessment of clinical benefit provided by some therapies. Information to measure response is obtained on anatomic images.

New:

The European Association for the Study of Liver Disease (EASL) guidelines [5] and the modified RECIST (mRECIST) [6] took into account viable tumor, as lesion that remained with arterial enhancement after treatment (Table 1). This implies a change from anatomic to dynamic imaging. Since locoregional therapies aim to produce necrosis, changes in tumor enhancement represent a better way to measure response. Both, EASL and mRECIST have proven better results when used to measure response in HCC [7,8] (Figure 1-4).

The EASL and mRECIST guidelines differ in terms of number of target lesions and calculation method (bidimensional vs. unidimensional). Kim et al. compared the prognostic values of mRECIST to predict overall survival with reference to EASL criteria in patients with HCC undergoing chemoembolization, they demonstrated that both methods were equivalent, being the mRECIST criteria a easier method to asses response [9].

Also mRECIST should be used for the assessment of treatment efficacy in patients who are receiving antiangiogenic drugs [10].

<table>
<thead>
<tr>
<th></th>
<th>WHO</th>
<th>RECIST 1.1</th>
<th>mRECIST</th>
<th>EASL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of lesions</td>
<td>Not established</td>
<td>5 target lesions</td>
<td>5 target lesions</td>
<td>All measurable lesions with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Maximum 2 per organ)</td>
<td>(Maximum 2 per organ) with</td>
<td>enhancement</td>
</tr>
<tr>
<td>Size of lesions</td>
<td>Not established</td>
<td>&gt; 10 mm</td>
<td>&gt; 10 mm</td>
<td>Not established</td>
</tr>
<tr>
<td>Measurements</td>
<td>Bidimensional: Sum of the lesion areas (Product of the longest diameter and greatest perpendicular diameter)</td>
<td>Unidimensional: Sum of the longest diameter of the lesion</td>
<td>Unidimensional: Sum of the longest diameter of enhancing lesions</td>
<td>Bidimensional: Sum of the lesion areas (Product of the longest diameter and greatest perpendicular diameter)</td>
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</tr>
<tr>
<td>Complete response (CR)</td>
<td>Disappearance of all known disease</td>
<td>Disappearance of all target lesions</td>
<td>Disappearance of any intratumoral arterial enhancement in all target lesions</td>
<td>Disappearance of any intratumoral arterial enhancing liver lesions</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>Decrease greater than 50% from baseline</td>
<td>At least a 30% decrease in the sum of the longest diameters</td>
<td>At least a 30% decrease in the sum of diameters of enhancing lesions</td>
<td>At least a 50% decrease in the sum of the areas of enhancing lesions</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Any cases that do not qualify for PR or PD</td>
<td>Any cases that do not qualify for PR or PD</td>
<td>Any cases that do not qualify for PR or PD</td>
<td>Any cases that do not qualify for PR or PD</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>At least 25% increase in the sum of the area</td>
<td>An increase of at least 20% in the sum of the diameters</td>
<td>An increase of at least 20% in the sum of the diameters of enhancing viable enhancing lesions</td>
<td>An increase of at least 25% in the sum of the areas of enhancing lesions</td>
</tr>
</tbody>
</table>

Emerging:

Diffusion-weighted imaging (DWI), can identify tumor response weeks earlier than anatomical and dynamic imaging. It has been demonstrated that tumor necrosis increases apparent diffusion coefficient (ADC) values, this allows differentiation between viable and necrotic portions of tumor. In the study by Chung et. al. [11] a intraprocedural ADC change greater than 15% predicted 1 month anatomical response (Figure 5). Different studies have shown differences between responders and not responders in
terms of ADC. [12-14] Still there is no currently universally accepted value for ADC change.

Colin levels have also been shown to change early after therapy (3-5 days) [15]. CT perfusion and dynamic contrast-enhanced MRI have been used for quantifying tumor vascularity and for monitoring treatment response with promising results [16,17].

These functional techniques potentially could identify responders from non responders and to plan follow up and treatment early after procedures.
Fig. 1: 64 yo male with cryptogenic cirrhosis A) Dynamic MR shows 19 mm hypervascular lesion in segment IV (arrow) B) The lesion was treated with RFA. C) In the follow up the lesion increased 94% in the diameter but shows no arterial enhancement (arrowhead). According to RECIST it represents PD, according to mRECIST it represents CR.

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Fig. 2: 55 yo female with HCV infection and cirrhosis. A) CT in portal phase shows hypervascular lesion in segment VIII. B) The patient received treatment with TACE. C) 3 months after treatment MR with digital subtraction images show no change in the size of the tumor but no arterial enhancement. According to mRECIST it corresponds to CR and according to RECIST it corresponds to SD.

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**Fig. 3:** 63 yo male with HCV and cirrhosis. A) Dynamic MR in arterial phase shows an hypervascular lesion corresponding with HCC. B) and C) The patient received combined treatment with TACE and RFA. 3 months after treatment the lesion is hyperintense in the non contrast phase (D) with no arterial enhancement (E) corresponding with CR according to mRECIST and SD according to RECIST.

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**Fig. 4:** Dynamic MR in arterial phase showing HCC lesion 6 months after TACE. (A) and (B) show unidimensional criteria for assessing treatment response (A) RECIST (B) mRECIST. (C) and (D) show bidimensional criteria (C) WHO (D) EASL criteria. The image illustrates the importance of mRECIST and EASL criteria taking into account the viable (enhancing) portion of the tumor.

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**Fig. 5:** 64 yo woman with HCV infection and HCC. (A) Dynamic MR shows a 47 mm lesion with arterial enhancement. ADC maps pre (B) and post treatment (C) show a 44% increase in ADC values (0.9X 10^-3 mm/s² vs 1.3 X 10^-3 mm/s²). (D) After 6 months the HCC shows partial response according to mRECIST.

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Conclusion

Evaluation of tumor response in HCC has been evolving during the last years. The abandonment of purely anatomic measurements has proven useful. Since the use of mRECIST and EASL a better identification of patients with tumor response had helped to deliver adequate treatment for patients. Recently functional imaging methods promise to help physicians to deliver individualized treatment and follow up for patients with HCC, however more evidence and standardizations is needed.
Personal information

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References


