Treatment Response Evaluation and Follow-up in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is one of the major causes of morbidity, mortality and healthcare expenditure in patients with chronic liver disease. The management of HCC is evolving because of recently introduced novel therapeutic approaches. Optimal outcome requires an early and accurate assessment of tumor response to therapy. Current imaging modalities, such as computed tomography (CT) and magnetic resonance (MR) imaging; provide reliable and reproducible anatomical data in order to demonstrate tumor burden changes. However, in the setting of novel targeted therapies and liver directed treatments, simple tumor anatomical changes can be less informative and usually appear later than biological changes. There has been a growing interest to monitor the therapeutic response, at an early phase of treatment, by measuring tumor viability and/or perfusion. Therefore the importance of tumor viability assessment is increasingly being recognized. The tumor viability measurement guidelines have recently been amended to include the measurement of only the longest diameter of the enhancing tumors to formally amend RECIST to modified RECIST (mRECIST). Viable tumor should be defined as uptake of contrast agent in the arterial phase. In this review, we discuss criteria of response evaluation in HCC and further follow-up of patients receiving curative and palliative treatment. (J Clin Exp Hepatol 2014;4:S126–S129)

Treatment

Hepatocellular carcinoma (HCC) is one of the major causes of mortality among patients with cirrhosis. The incidence of HCC is rising in India and is poised to become the leading GI cancer. The management of HCC is evolving because of recently introduced novel therapeutic approaches. Optimal outcome requires an early and accurate assessment of tumor response to therapy. Current imaging modalities, such as computed tomography (CT) and magnetic resonance (MR) imaging; provide reliable and reproducible anatomical data in order to demonstrate tumor burden changes. Traditionally, therapeutic response has been assessed by serial tumor burden measurements according to Response Evaluation Criteria in Solid Tumors (RECIST), World Health Organization (WHO) criteria, or European Association for the Study of the Liver (EASL) criteria.[1–4] These established response criteria based on size for tumor burden measurement continues to be used as size measurement could easily be obtained by these simple imaging modalities. However, in the setting of novel targeted therapies and liver directed treatments, simple tumor anatomical changes can be less informative and usually appear later than biological changes. There has been a growing interest to monitor the therapeutic response, at an early phase of treatment, by measuring tumor viability and/or perfusion. Therefore the importance of tumor viability assessment is increasingly being recognized. Other advances in MR imaging such as diffusion weighted imaging (DWI) are also emerging as biomarkers of cellular integrity.[5] In addition, positron emission tomography (PET) can also be used to investigate tumor metabolism.[6] With the availability of so many imaging techniques, it is challenging to determine the most appropriate image criteria to serve as a surrogate end point of treatment response. In this review, we discuss criteria of response evaluation in HCC.

TREATMENT RESPONSE EVALUATION FOR HEPATOCELLULAR CARCINOMA

The most important parameter for any cancer treatment response evaluation is overall survival. Nonetheless, tumor response and time-to-progression have been considered pivotal for surrogate assessment of efficacy.

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Abbreviations: AASLD: American Association for the Study of Liver Diseases; CR: complete response; CT: computed tomography; DWI: diffusion weighted imaging; EASL: European Association for the Study of the Liver; GI: gastro-intestinal; HCC: hepatocellular carcinoma; MR: magnetic resonance; mRECIST: modified response evaluation criteria in solid tumors; PD: progressive disease; PET: positron emission tomography; PR: partial response; RECIST: response evaluation criteria in solid tumors; RFA: radiofrequency ablation; SD: stable disease; TACE: trans-arterial chemoembolization; WHO: World Health Organization
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Imaging Criteria for Response Evaluation

Traditionally, therapeutic response has been assessed by serial tumor burden measurements according to Response Evaluation Criteria in Solid Tumors (RECIST), World Health Organization (WHO) criteria, or European Association for the Study of the Liver (EASL) criteria.[4,7] RECIST was primarily conceived to provide specific guidelines for tumor burden measurement. RECIST was adapted for HCC and as per its guidelines, a target lesion should meet all the following criteria:

- the lesion can be classified as measurable lesion (i.e., the longest diameter ≥1 cm);
- is suitable for repeat measurement;
- shows intratumoral enhancement on contrast-enhanced CT or MRI; and
- the lesion has not been previously treated with local–regional therapy.

It is mandated that only lesions with discernible margins and those showing arterial enhancement are selected as target lesions. The tumor measurements as defined by RECIST are quantitative, reproducible and simpler to apply and therefore meet the requirements of using imaging as a surrogate end point.

However, over time the limitations of anatomic measurements in HCC became more evident.[7] RECIST criteria were designed primarily for evaluation of cytotoxic agents.[3] They did not address measures of antitumor activity other than tumor shrinkage. Many HCC treatments act by induction of tumor necrosis or reduction in vascularity, which is not necessarily accompanied by tumor shrinkage in spite of response. Hence, to assess viable tumor contrast uptake in arterial phase has to be assessed using dynamic CT or MRI studies. Therefore expert groups convened by the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) introduced the concept of including bi-dimensional measure (as described by the WHO criteria) of tumor enhancement in arterial phase of contrast-enhanced imaging studies to assess only viable target tumors.[4] The tumor viability measurement guidelines have recently been amended to include the measurement of only the longest diameter of the enhancing tumors to formally amend RECIST to modified RECIST (mRECIST) (Table 1).[8] Viable tumor should be

Table 1 Response Assessment by Modified RECIST (adapted from Lencioni et al[8]).

	Terminology	Description
Target lesions	**Complete response (CR)**	Disappearance of any intratumoral arterial enhancement in all target lesions
	Partial response (PR)	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
	Stable disease (SD)	Any cases that do not qualify for either PR or PD
	Progressive disease (PD)	An increase of at least 20% in the sum of the diameters of viable (enhancement in the arterial phase) target lesions recorded since treatment started
Non-target lesions	**Complete response (CR)**	Disappearance of any intratumoral arterial enhancement in all non-target lesions
	Stable disease (SD) or incomplete response (IR)	Persistence of intratumoral arterial enhancement in one or more non-target lesions
	Progressive disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Additional recommendations	**New lesion**	A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1-cm interval growth.
	Pleural effusion or ascites	Cytopathological confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD
	Lymph nodes in the porta hepatis	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is at least 2 cm
	Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group

Abbreviations: HCC, hepatocellular carcinoma; mRECIST, modified response evaluation criteria in solid tumors.

defined as uptake of contrast agent in the arterial phase. Consequently, a modification of the RECIST criteria (mRECIST criteria) has been adopted.[8] This proposal is based on the fact that diameter of the target lesions with *viable* tumor should guide all measurements.

The mRECIST follows the cut-off percentages for response assessment similar to those laid down in RECIST to defines four response categories as: complete response (CR) (100% decrease in amount of enhancing tissue in target lesions), partial response (PR) (>30% decrease in the sum of diameters of viable target lesions, taking as reference the baseline sum of the diameters of enhancing tissue in target lesions), progressive disease (PD) (>20% in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable target lesions recorded since treatment started) and SD (neither PR nor PD).[7,8] The mRECIST criteria also include guidelines regarding evaluation of vascular invasion, lymph nodes, effusions and new lesions.

In a study comparing tumor response by RECIST and mRECIST criteria in patients treated with sorafenib for HCC, the investigators Edeline et al[9] retrospectively analyzed 53 patients who received sorafenib for advanced HCC. Patients underwent a 4-phase CT scan before treatment and repeatedly thereafter. CT scans were analyzed using RECIST and mRECIST. The study validated mRECIST and the authors also concluded that for patients with HCC, mRECIST should be used for the standard assessment of treatment efficacy, particularly in patients who are receiving antiangiogenic drugs.[9] The mRECIST criteria are now used in ongoing prospective phase II and III studies with new drugs or locoregional treatments. Thus, although these mRECIST criteria need further prospective validation, it is recommended in daily clinical practice to consider not only tumor diameters but also lesion viability in therapy decision-making.

The timing of initial treatment response evaluation should depend on treatment: Following resection, ablation or TACE the initial response evaluation should be done at 4 weeks. The initial response evaluation following liver transplantation should be done at 3 months. Patients with more advanced stages of HCC who are treated with TACE or systemic agents (e.g. sorafenib) are evaluated clinically for signs of liver decompensation and for tumor progression by dynamic CT or MRI every 2 months to guide therapy decisions.

Role of Tumor Markers in Response Evaluation

New imaging techniques offer better ways of measuring response to treatment and remain central to the formal assessment of response in clinical trials and routine clinical practice. Increasing tumor size is consistently associated with progressive disease. However, there is evidence that the designation 'partial response', as determined by conventional imaging techniques, may not always accurately reflect the degree of treatment-induced tumor necrosis.[10] Thus, responses classified as partial on imaging grounds have, in some cases, been shown to be complete pathological responses after surgical resection, implying that residual tumor and necrotic/fibrotic tumor remnants cannot always be accurately distinguished by imaging. In this situation, serum tumor markers (such as AFP or DCP levels) may be helpful particularly in the case of not easily measurable disease and may be useful in measuring the true degree of response. While radiological imaging is likely to remain the main method of assessing response in phase II trials of drugs for the treatment of liver cancer, it may in some instances be useful to apply additional parameters such as AFP level.[10] However, AFP level should not be used as the only determinant for treatment decision.

In a recent study by Sherman,[11] patients with HCC who were treated with chemoembolization or radioembolization were studied for the AFP response and is correlation with imaging response according to WHO criteria. Following parameters were studied: radiologic response, time-to-progression (TTP), progression-free survival (PFS), and overall survival (OS). AFP response was defined as more than 50% decrease in AFP from baseline. Eighty-one patients (65%) showed AFP response. AFP response was seen in 26 (55%) of 47 and 55 (70%) of 78 of patients treated with chemoembolization and radioembolization, respectively (P = 0.12). WHO response was seen in 41 (53%) of 77 and 10 (24%) of 42 of AFP responders and nonresponders, respectively (P = 0.002). The hazard ratio (HR) for TTP in AFP nonresponders compared with responders was 2.8 (95% CI, 1.5–5.1). The HR for PFS was 4.2 (95% CI, 2.4–7.2) in AFP nonresponders compared with responders. The HR for OS in AFP nonresponders compared with responders was 5.5 (95% CI, 3.1–9.9) and 2.7 (95% CI, 1.6–4.6) on univariate and multivariate analyses, respectively. The author supported the use of AFP response after locoregional therapy as an ancillary method of assessing tumor response and survival, as well as an early objective screening tool for progression by imaging.[11]

Serum tumor markers may be helpful for treatment response evaluation or follow-up when:

- the level was high at diagnosis, and
- the level decreased after treatment but rises again especially in none or difficult to measure lesions.

However tumor markers cannot replace imaging modalities.

FOLLOW-UP AFTER TREATMENT FOR HEPATOCELLULAR CARCINOMA

Follow-up After Curative Treatment

After the initial response evaluation at 4 weeks, the further follow-up of patients who underwent resection or RFA

should consist of the clinical evaluation of liver decompensation and the early detection of recurrence by dynamic CT or MRI studies every 3 months the first 2 years and surveillance every 6 months later on.[12] In case of tumor recurrence after curative treatments, re-assessment of the patient should be done using the BCLC staging system and re-treatment should be planned accordingly. Patients with recurrence following radical therapies may still be candidates for curative therapies.

The risk of tumor recurrence after liver transplantation for HCC is 8–20%.[13,14] HCC recurrence is usually seen within the first 2 years after liver transplantation, and is associated with a median survival of less than 1 year from the time of diagnosis.[15] The adoption of post-transplant surveillance criteria has led to the detection of early recurrence, with a possibility of cure with ablation therapies in up to a third of cases.[14,16] Following the initial response assessment at 3 months, the surveillance for recurrence should be done every 6 months.

Follow-up After Palliative Treatment

After the initial response at 4 weeks following TACE, the further follow-up of these patients should consist of clinical evaluation for liver decompensation and dynamic CT or MRI for tumor progression every 3 months to guide therapy decisions. For patients on sorafenib the clinical evaluation should be done every 2–3 months.

Serum tumor markers (such as AFP levels or DCP) may be helpful for treatment response evaluation or follow-up when the level was high at diagnosis, and the level decreased after treatment but rises again especially in none or difficult to measure lesions. However tumor markers cannot replace imaging modalities.

CONCLUSIONS

With the growing recognition that the treatment for HCC be tailored to suit the needs of each individual patient, an early and accurate assessment of tumor response to therapy is mandatory. An ideal imaging modality should be able to detect an immediate response to any therapeutic regimen in one examination. Since liver directed therapies and newer targeted drugs induce biologic changes much earlier than size-based alterations in tumor burden, reliance on tumor viability for response assessment has increased. The new mRECIST criteria are recommended in daily clinical practice for response evaluation as they incorporate not only tumor diameters but also lesion viability and thus help in therapy decision making.

CONFLICTS OF INTEREST

All authors have none to declare.

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