

Imaging for assessment of treatment response in hepatocellular carcinoma: Current update

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Abstract

Morphologic methods such as the Response Evaluation Criteria in Solid Tumors (RECIST) are considered as the gold standard for response assessment in the management of cancer. However, with the increasing clinical use of antineoplastic cytostatic agents and locoregional interventional therapies in hepatocellular carcinoma (HCC), conventional morphologic methods are confronting limitations in response assessment. Thus, there is an increasing interest in new imaging methods for response assessment, which can evaluate tumor biology such as vascular physiology, fibrosis, necrosis, and metabolism. In this review, we discuss various novel imaging methods for response assessment and compare them with the conventional ones in HCC.

Key words: Computed tomography perfusion; diffusion weighted imaging; dynamic contrast-enhanced magnetic resonance imaging; hepatocellular carcinoma; positron emission tomography

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer-related mortality worldwide.^[1] Liver transplantation and resection are considered curative; however, most patients do not meet the selection criteria.^[2] Molecular targeted agents such as sorafenib have shown a survival benefit for advanced HCC.^[1,3-5] Locoregional therapies (LRTs) deliver toxic thermal/chemical/radioactive doses to tumors with minimal toxicity to the normal tissue. Among the various LRTs, transarterial chemoembolization (TACE) and yttrium-90 radioembolization are palliative, whereas thermal ablative methods provide results equivalent to surgical resection in early stage HCC.^[6-9]

Imaging plays an important role in the management of HCC, and the efficacy of treatment is usually monitored and assessed radiologically. Therapeutic response has been assessed by morphologic methods using various criteria such as the World Health Organization (WHO) criteria or the Response Evaluation Criteria in Solid Tumors (RECIST) in cancer treatment.^[10-12] These criteria are well established, and have been applied to response assessment of clinical trials in various kinds of tumors.^[13] However, these morphologic evaluations have confronting limitations, including the presence of tumors that cannot be measured, poor measurement reproducibility, and mass lesions of unknown activity that persist following therapy.^[12] Furthermore, with the increasing clinical use of molecular targeted agents in HCC, these criteria have confronting limitations in distinguishing viable tumor from necrotic or fibrotic tissue, and are not suitable to assess cellular death/apoptosis, because the new molecular targeted drugs act differently as compared to the traditional chemotherapeutic drugs and result in changes in blood flow (BF) of the tumor and cellular death without significant tumor shrinkage.

Faced with these limitations of morphologic tumor assessment criteria, new reliable markers including serum markers, metabolic and functional imaging markers based

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on computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) to assess response to targeted agents or LRTs are desired urgently.^[14-17] Imaging for tumor response assessment has evolved over the past few years as a result of advances in imaging modalities and the introduction of new functional imaging.^[18,19] In this review, we discuss the conventional and new imaging methods to assess tumor response in the management of HCC.

Morphologic response assessment

Clinical trials are mandatory in the evaluation of new tumor treatments. A common measure of the effect of an instituted therapy is the change of tumor size. In 1979, the WHO criteria established the concept of an overall assessment of tumor response by bidimensional lesion measurement, which is calculated by multiplying the maximum diameter by its longest perpendicular diameter, and determined the response to the therapy by evaluating the change from baseline while on treatment. Subsequently, RECIST criteria were introduced in 2000, updating the WHO criteria [Figure 1],^[10] and brought many advances and facilitated comparison of the results among clinical trials. After extensive experience and validation in several chemotherapeutic trials in solid tumors, it was revised as RECIST 1.1 in 2009.^[12] RECIST 1.1 is based on the measurement of a maximum of five target lesions, not exceeding two per organ; subsequently, the sum of the greatest diameters is recorded followed by a final classification.^[12] Morphologic response criteria are summarized in Table 1. However, RECIST 1.1 has some limitations as follows: (1) it assumes that all lesions

are spherical and that they decrease or increase in size uniformly; (2) necrosis is not taken into consideration in measuring the tumor size on the basis of RECIST, but recent LRTs or targeted therapies induce necrosis, which may indicate favorable tumor response;^[20,21] and (3) RECIST 1.1 does not define the standard phase of contrast material enhancement for measuring specific tumors. This criterion may be important if the lesion is best seen during either arterial or venous phase of enhancement.

Quantification of volumetric change can be a more accurate measure of the actual tumor size change than uni- or bidimensional measurements because volumetric analyses compensate for actual tumor shape rather than assuming it to be a sphere, an ellipsoid, or a cube. Welsh *et al.*^[22] reported that volumetric analysis might be the preferred method to detect tumor progression, showing that RECIST might overestimate tumor burden compared to volumetric analysis. Sohaib *et al.*^[23] demonstrated the accuracy and reproducibility of CT volumetric measurements in their phantom study. However, the optimal volumetric response evaluation criteria have not been defined. Volumetric analysis can be time consuming and laborious because volumetric analysis still relies on manual trace of tumor margins. In the future, a computerized tumor segmentation method with high reproducibility and reliability may allow for automatic lesion contouring and volumetric calculation.

Tumor viability and density assessment

Generally, targeted therapy agents induce reduction in tumor vascularization, provocation of necrotic area and sometimes cavitation in solid tumors, and these features have been reported in various targeted therapies of HCC.^[3,24-27] Furthermore, all LRTs attempt to induce necrosis of the tumor, which may delay tumor shrinkage during the early post-treatment period. Given these limitations of morphologic response criteria, the European Association for the Study of Liver (EASL) proposed new response criteria in 2000 to take into account tumor necrosis induced by treatment.^[28] Accordingly, necrosis is defined as non-enhanced areas on contrast-enhanced (CE)

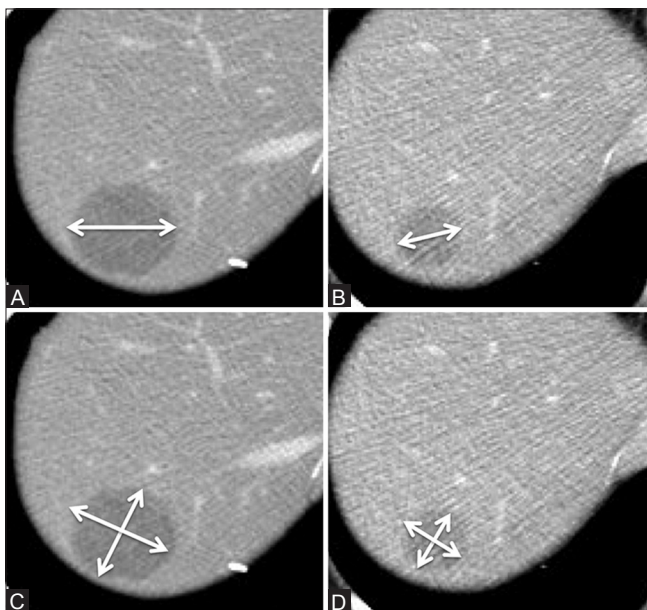


Figure 1 (A-D): According to RECIST, this patient was categorized as partial response [from (A) to (B), 33% reduction in tumor diameter], while WHO criteria categorized this patient as stable disease [from (C) to (D), 43% reduction in tumor area]

Table 1: Morphologic response criteria

Response category	WHO	RECIST 1.1
CR	Disappearance of all lesions	Disappearance of all lesions and pathologic lymph nodes
PR	≥50% decrease in sum of the area (longest diameters multiplied by longest perpendicular diameters)	≥30% decrease in the sum of longest diameters of targeted lesions
SD	Neither PR nor PD	Neither PR nor PD
PD	>25% increase in sum of the area	>20% increase in the sum of longest diameters and ≥5 mm absolute increase in the sum of longest diameters

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, WHO: World Health Organization, RECIST: Response evaluation criteria in solid tumors

CT/MR within the treated tumor. In 2008, the American Association for the Study of Liver Disease (AASLD) proposed the modified RECIST (mRECIST) criteria, which conceptualized viable tumor measurements. The major change is the definition of the target lesion, which is no longer the whole lesion but only the contrast-enhanced portion of the hepatic lesion on the arterial phase image [Figure 2].^[29,30] Previous reports demonstrated that EASL or mRECIST had better overall response rate than conventional morphologic criteria such as RECIST and WHO.^[21,31,32] In addition, these criteria have shown a better correlation with survival. Gillmore *et al.*^[20] reported that responses measured by EASL and mRECIST after 2-3 months of TACE were independently associated with survival, whereas RECIST 1.1 had no significant association with survival. In a recent retrospective study of HCC patients treated with sorafenib, patients categorized as responders according to mRECIST had a longer overall survival (OS) than the non-responders.^[33] Similarly, Shim *et al.*^[34] reported that responses measured by mRECIST and EASL were independent predictors for OS following TACE. Prajapati *et al.*^[32] reported significant associations of mRECIST and EASL with survival, and also suggested that the response based on mRECIST showed a better correlation with survival than that based on EASL. Therefore, response evaluation based on the enhancement

may enable more accurate response assessment in terms of survival.

The tumor density analysis on CECT can be used as an additional method for response assessment.^[35] On treating gastrointestinal stromal tumor (GIST) with imatinib mesylate, there was a decrease in density of the tumor, which was measured by drawing a region of interest (ROI) circumscribing the boundary of the tumor on the portal venous phase, while no change was observed in tumor size.^[35,36] In GIST, a reduction in tumor Hounsfield Units (HU) greater than 15% was associated with better progression-free survival (PFS; Choi criteria).^[37] In a recent study of HCC, Faivre *et al.*^[38] demonstrated that the tumor response measured by Choi criteria was more sensitive than that measured by RECIST in detecting patients with longer time to progression after sunitinib therapy [Figure 3]. Criteria for tumor viability and density analysis are summarized in Table 2.

Diffusion-weighted imaging for response assessment

Motion of water molecules in tissue can be assessed by applying diffusion-weighting gradients to T2-weighted sequences. Various tissue types have unique diffusion characteristics, which are measured as the apparent diffusion coefficient (ADC) by the diffusion-weighted imaging (DWI)

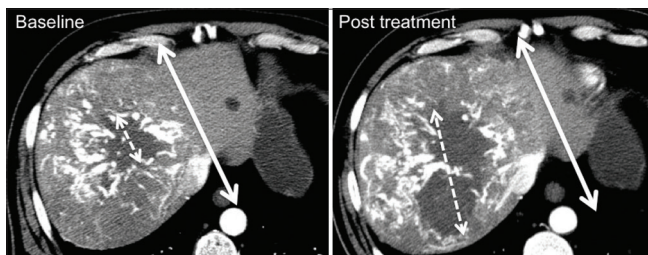


Figure 2: Arterial phase CECT of a 72-year-old man with HCC. The area of central necrosis increased after a tyrosine kinase inhibitor therapy (dashed line), while the change in tumor size was not obvious (solid line)

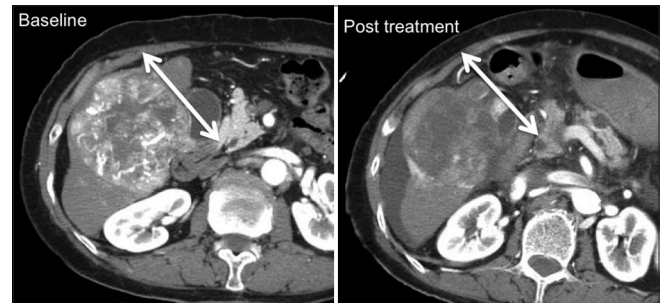


Figure 3: Portal-phase CECT of a 73-year-old woman with HCC. Tumor density changed obviously after antiangiogenic therapy

Table 2: Summary of response criteria based on tumor viability and density

EASL	mRECIST	Choi criteria
CR		
Disappearance of intratumoral arterial enhancement	Disappearance of all lesions and pathologic lymph nodes	Disappearance of all lesions
PR		
≥50% decrease in the sum of the arterial enhancing areas (longest diameters multiplied by longest perpendicular diameters)	≥30% decrease in the sum of diameters of enhancing target lesions	≥10% decrease in the longest diameter of target lesion or ≥15% decrease in attenuation (HU)
SD		
Neither PR nor PD	Neither PR nor PD	Neither PR nor PD
PD		
≥25% increase in the size of the arterial enhancing areas or development of a new lesion	≥20% increase in the sum of diameters of viable target lesions recorded since treatment started or development of new lesions	≥10% increase in the longest diameter of target lesion without PR criteria or development of new lesions

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, EASL: European Association for the Study of Liver, mRESIST: Modified response evaluation criteria in solid tumors

performed with a different gradient duration and amplitude (b-values). Because the movement of water molecules in the body tissues is restricted by various factors including cells, macromolecules, and fibers in tissue compartments, DWI can be exploited in clinical practice for indirect assessment of tissue properties such as cellularity, gland formation, perfusion, fibrosis, and cell death.^[39,40] DWI has the potential to be an effective biomarker for monitoring the response to the treatment, and this potential in the management of cancer patients has been already discussed in a consensus meeting and a publication.^[41]

Several studies have reported that the ADC value of HCC significantly increased after TACE.^[42-44] A previous study reported that high baseline ADC value in HCC was associated with poor response to TACE, and that responding lesions showed a significant increase in ADC values than the non-responding ones after 48 h of TACE.^[45] The results of antiangiogenic agents such as multitargeted tyrosine kinase inhibitors are controversial.^[46-48] Schraml *et al.*^[46] reported that on treating HCC with sorafenib, the tumor ADC initially decreased after 2-4 weeks of therapy and was followed by an increase after 10 weeks of the therapy. But, Lewin *et al.*^[47] reported that the tumor ADC did not significantly change after sunitinib therapy. In HCC treated with sunitinib, significant increase in tumor ADC was observed after 2 weeks of the therapy with no change in tumor size, based on RECIST and mRECIST [Figure 4].^[48]

DWI can be a desirable imaging biomarker because it needs no radiation exposure and no contrast material. However, there are several limitations. Various factors including magnetic field strength, technical factors (e.g. b-value

selection) and the ROI setting may affect accurate ADC assessment.^[49,50] Furthermore, in the abdomen, the strong influence of motion due to breathing and vascular pulsation often results in image artifacts, which may lead to inaccurate ADC calculation.^[51] Optimal time frame for precise response evaluation needs to be further studied.

Assessment of tumor vascular physiology

Because most of the targeted agents inhibit angiogenesis to control tumor progression, tissue perfusion analysis is a highly promising method to assess treatment response. In recent years, perfusion analysis has already been readily incorporated into the existing CT and MRI protocols, and most scanners are now equipped with sophisticated hardware platforms coupled with user-friendly software packages.^[52]

In dynamic contrast-enhanced (DCE) CT, the temporal changes in attenuation following intravenous contrast material administration can be analyzed using the mathematical kinetic models such as compartmental or deconvolution analysis for contrast material exchange.^[53,54] The common perfusion parameters of CT perfusion (CTP) are BF (flow rate through vasculature in a tissue), blood volume (BV, volume of flowing blood within a vasculature in a tissue), mean transit time (MTT, time taken to travel from artery to vein), and permeability surface area product (PS, total flux from plasma to interstitial space).^[24,25,54] Chen *et al.*^[55] demonstrated that in HCC treated with TACE, changes in CTP parameters of tumors were correlated with different responses of HCC to TACE. According to their findings, tumors of responders showed significant reduction in hepatic arterial perfusion and BV, while those of non-responders did not show significant changes. Yang *et al.*^[56] reported that the values of hepatic arterial perfusion, total liver perfusion, and hepatic arterial perfusion index in tumors significantly decreased 4 weeks after TACE in comparison to those before TACE. Previous studies reported reduction in BF or BV after 10-12 days of antiangiogenic therapy without any significant change in tumor size based on RECIST [Figure 5].^[24,25] Moreover, baseline CTP values have a potential to be a predictive biomarker for survival after antiangiogenic therapy.^[25] Jiang *et al.*^[25] demonstrated that HCC with higher baseline MTT correlated with favorable clinical outcome. A recent paper of CTP reported that the heterogeneity of tumor BF showed a good correlation with OS in HCC patients treated with an antiangiogenic agent.^[57]

Similarly, DCE-MRI also enables quantification of tumor vascular physiology. The common DCE-MRI parameters are vascular permeability (K_{trans}) and reverse reflux rate constant between extracellular space and plasma (K_{ep}) and the fractional extravascular, extracellular space (V_e).^[26,48,58-60] Several studies have demonstrated the value of DCE-MRI derived parameters for monitoring

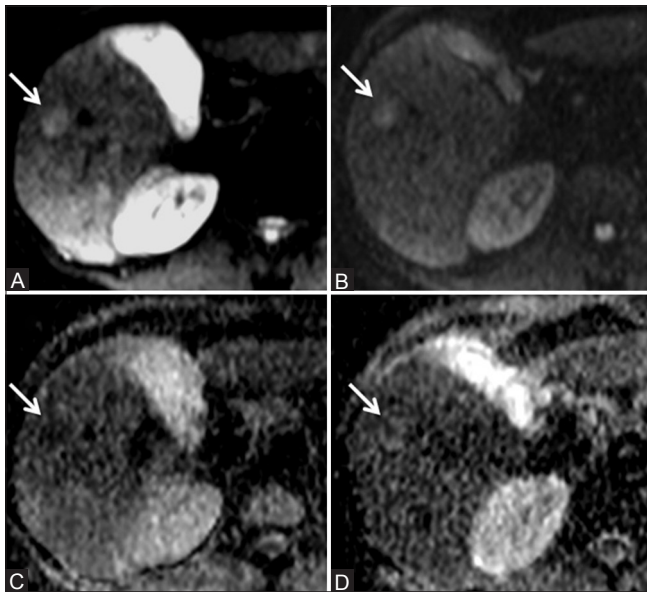


Figure 4 (A-D): DWI at baseline (A) and post-treatment (B), and ADC maps at baseline (C) and post-treatment (D) of a 68-year-old man with HCC (arrows). ADC showed 55.1% increase after 2 weeks of tyrosine kinase inhibitor therapy

antiangiogenic therapies in various solid tumors.^[26,48,58-60] In advanced HCC, DCE-MRI demonstrated reduction in Ktrans during antiangiogenic treatment and the change of Ktrans during treatment was related to better PFS and OS in clinical trials of tyrosine kinase inhibitors [Figure 6].^[26,48,60,61] In a phase I study of pazopanib, patients who had either a partial response or stable disease showed significant reduction in Ktrans.^[61] In a study of HCC patients treated with sorafenib and metronomic tegafur/uracil, reduction in Ktrans on day 14 was found to be an independent predictor for PFS and OS.^[60] In a phase II study of sunitinib, higher baseline Ktrans and larger drop in Ve correlated with longer PFS.^[48]

CTP may be superior to DCE-MRI in accessibility and availability.^[62,63] However, CTP essentially implies two major drawbacks: High radiation exposure and limited coverage of the anatomy. Thus, several efforts are being made with low-dose scanning techniques.^[54] It is still unclear which scanning protocol or mathematical model is optimal for abdominal organs. The definitions of the tumor ROI and the acquisition time also need further investigation in terms of reproducibility and reliability.^[64,65] On the contrary, DCE-MRI has the advantage in spatial resolution and soft-tissue contrast without ionizing radiation. However, it is still expensive and technically challenging, and requires longer image acquisition times in comparison to CT.^[62,63] DCE-MRI also lacks consensus on the standard protocol or the response evaluation criteria. However, given the importance of vascularization in cancer progression, perfusion technique can be a potentially powerful imaging biomarker to predict or detect early tumor response to the treatment.

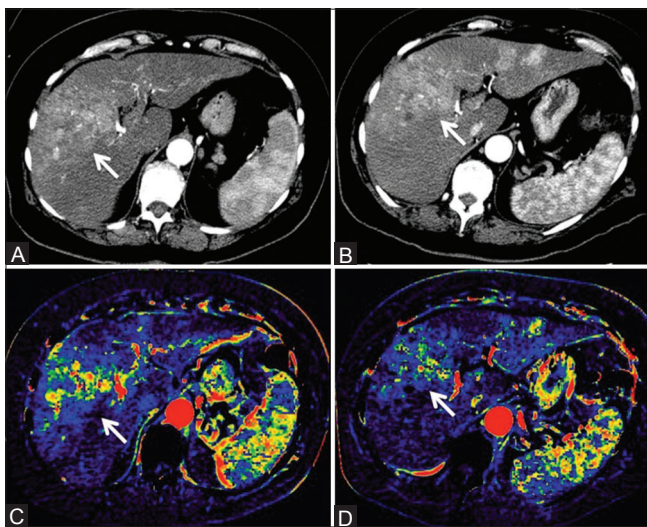


Figure 5 (A-D): CECT images ((A) Baseline, (B) Post-treatment) and perfusion (blood volume) maps ((C) Baseline, (D) Post-treatment) of a 73-year-old woman with HCC. CTP demonstrated perfusion changes (-34% in blood volume) without significant changes in size and density after 2 weeks of antiangiogenic treatment

Metabolic assessment

In PET, various kinds of tracers including ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG),^[66-70] ¹¹C-acetate (¹¹C-Act),^[71-74] ¹¹C- or ¹⁸F-F-choline (¹¹C-Cho, ¹⁸F-F-Cho)^[75] and ¹⁸F-fluorothymidine (¹⁸F-FLT)^[76] enable quantitative measurement of various biological features such as metabolism, lipogenesis, cellular membrane turnover, and proliferation. It is, therefore, possible to noninvasively obtain information on a number of different biological properties of HCC. Integrated PET/CT and PET/MRI instruments have the potential for providing unique biological information in a single patient examination.

¹⁸F-FDG is the most widely available tracer, and ¹⁸F-FDG PET can assess the glucose metabolism in tumor. In HCC treated with TACE, an increase of ¹⁸F-FDG uptake in HCC was significantly associated with tumor burden and could provide effective information on the prognosis of the treatment response.^[77] In addition, ¹⁸F-FDG uptake after TACE might be a favorable marker to assess tumor viability after TACE.^[73,78] Similar findings have been reported in detecting local tumor progression following radiofrequency ablation of HCC.^[79] Kim *et al.*^[80] reported that in HCC patients treated with chemoradiation therapy, low ¹⁸F-FDG uptake was associated with longer PFS and OS and that the high ¹⁸F-FDG uptake group was more likely to have extrahepatic metastasis within 6 months. However, because the expression of glucose-6-phosphatase enabling ¹⁸F-FDG to accumulate in tumor cells varies widely in HCC, ¹⁸F-FDG PET shows poor sensitivity for detection of HCC, ranging from 50 to 55%.^[81-85] Thus, the role of ¹⁸F-FDG PET in assessing treatment response is still limited in HCC, and further investigations are needed. HCC-specific tracers may be the key in the future.

Conclusion

Morphologic assessment, which has served as the gold standard for a long time, is confronting limitations. However, recent advances in imaging modalities and the introduction of new functional imaging pave the way to assess tumor response based on tumor biology *in vivo*.

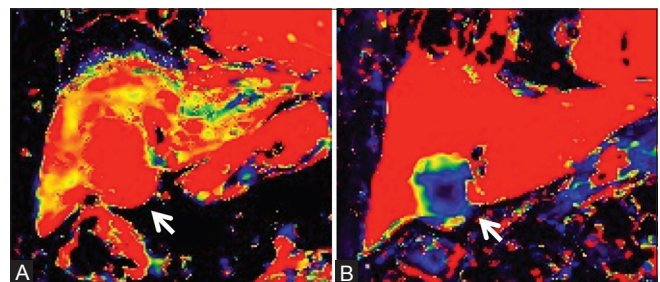


Figure 6 (A and B): Ktrans maps of a 69-year-old man with HCC at baseline (A) and at 2 weeks after tyrosine kinase inhibitor therapy (B). Ktrans of the tumor showed 79.8% reduction after the therapy, while the change in tumor size was not obvious

As antiangiogenic therapy and LRTs have become the standard of care for HCC patients, such functional imaging techniques for response assessment are of paramount importance. In this review, we suggest that the evaluation of tumor response should include not only the morphologic change but also functional changes such as enhancement, density, perfusion, diffusion, and metabolism. Functional imaging will serve as a biomarker for response assessment of HCC, and radiologists must become familiar with these new techniques.

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