Review

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Established and novel imaging biomarkers for assessing response to therapy in hepatocellular carcinoma

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Summary

The management of hepatocellular carcinoma (HCC) is evolving because of recently introduced novel therapeutic approaches. There is growing recognition that optimal outcome requires choosing treatment tailored to suit each individual patient, necessitating an early and accurate assessment of tumor response to therapy. The established and adapted image biomarkers based on size for tumor burden measurement continues to be applied to HCC as size measurement can easily be used in any clinical practice. 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. Therefore the importance of image biomarkers such as tumor viability measurement, functional perfusion and diffusion imaging for response assessment is increasingly being recognized. Although promising, these imaging biomarkers have not gone through all the required steps of standardization and validation. In this review, we discuss various established, evolving and emerging imaging biomarkers and the criteria of response evaluation and their challenges in HCC.

Introduction

Hepatocellular carcinoma (HCC) is a highly prevalent disease worldwide. Most HCC patients present with advanced disease at the time of diagnosis and have poor prognosis [1]. HCC is the third most common cause of cancer-related death in the world, causing more than 500,000 deaths every year and representing a major health challenge with significant and increasing global impact [2]. Although surgical resection and liver transplantation are curative therapeutic options, they are indicated only in fewer than 20% patients due to advanced disease staging, poor hepatic function and limited organ availability [3]. Liver directed therapies (non-surgical locoregional treatment directed to HCC) are increasingly used as alternative options to surgery, especially in patients with unresectable disease. Although many novel targeted chemotherapy agents have been developed for clinical trials owing to significant progress in the understanding of the molecular pathogenesis of HCC over the past several years [4,5], the underlying mechanism of action of these new approaches is vastly different from the conventional chemotherapy and the expectations are unique for assessing the success of these therapies. In addition, given the high cost, toxicity as well as choices of treatment options, an early assessment of tumor response to treatment in advanced HCC is crucial to any individualize treatment paradigm.

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 [6–9]. 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, with the introduction of novel targeted agents, there has been a growing interest to monitor the therapeutic response at an early phase of treatment by measuring tumor viability and/or perfusion. Other advances in MR imaging such as diffusion weighted imaging (DWI) are also emerging as biomarkers of cellular integrity [10]. In addition, positron emission tomography (PET) can be used to investigate tumor metabolism [11]. With the availability of so many imaging techniques, it is challenging to determine the most appropriate image biomarker to serve as a surrogate end point of treatment response.

An ideal image biomarker should be non-invasive, objectively quantitative, reproducible, readily available, validated and easy for clinical application to meet the expectations of regulatory authorities such as the FDA for using imaging as a surrogate end point of treatment response. In this review, we discuss various established, evolving and emerging imaging biomarkers, the criteria of response evaluation, and their challenges in HCC.

Key Points

We discuss established and emerging imaging biomarkers applicable to hepatocellular carcinoma (HCC). This review also describes the criteria of HCC response evaluation and addresses the challenges for applying them. Information presented has potential for optimizing treatment tailored to the needs of each individual patient, permitting the early and accurate assessment of tumor response to therapy

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Review

Tumor burden measurement

Although improvement of clinical symptoms and survival are considered the ultimate proof of the effectiveness of therapy in HCC, surrogate end points, such as objective response or time to progression in phase II trials according to radiological tumor burden measurement, are increasingly used [12]. The tumor burden measurement to assess the *in vivo* effectiveness of an oncologic drug was initially performed using WHO criteria and subsequently RECIST was introduced and approved for clinical use in 2000 [8]. RECIST was primarily conceived to provide specific guidelines for tumor burden measurement. After extensive experience and validation in several chemotherapeutic trials in solid tumors including HCC (Table 1), it was revised in 2009 with the introduction of RECIST 1.1 [13–25].

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 $\geqslant$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 indeed quantitative, reproducible and simpler to apply and therefore meet the FDA's expectations for using imaging as a surrogate end point. However, over time the limitations of anatomic measurements in HCC became more evident [26,27]. 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 bidimensional measure (as described by the WHO criteria) of tumor enhancement in arterial phase of contrast-enhanced imaging studies to assess only viable target tumors [9]. 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) [28].

It has often been questioned whether the unidimensional measurements in RECIST accurately reflect total tumor burden. Moreover, for irregular and poorly defined target HCC lesions, considerable intra- and interobserver variability of unidimensional measurements has been found, which may lead to substantial differences in response assessment [29]. With the introduction of three-dimensional (3D) software tools on modern CT and MRI equipment, the reproducibility of volumetric measurements in response evaluation for HCC was investigated [29]. Monsky *et al.* confirmed that the tumor volumetry measurement is reproducible and superior to RECIST to predict long-term outcome [29]. The consistency of volume measurement was also confirmed in phantom experiments with a reported error of 1–5% [30].

However, the practical clinical value of tumor volume measurements remains controversial. Moreover, we do not know whether the recommended volume equivalents (73% tumor growth and 65% size diminution) converted from diameter thresholds (20% and 30%, respectively) can be effectively applied without sacrificing either reproducibility or sensitivity to tumor progression or partial response.

HCC viability measurement

Current targeted systemic agents and several directed therapies present particular challenges to response monitoring in clinical research. In a recent study on HCC treated with transarterial chemoembolization (TACE) or percutaneous ablation, RECIST-based tumor measurement has underestimated the extent of partial tumor response because of therapy-induced tumor necrosis [31]. As discussed earlier, EASL and AASLD have recommended bidimensional measurement of tumor viability (tumor enhancement in the arterial phase) and they subsequently adopted the modification in the RECIST criteria (mRECIST) [9,32,33]. Memon *et al.* reported that following chemoembolization, the EASL method was a more effective surrogate than the WHO approach in predicting clinical outcome and survival [12,33].

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

Table 1. Response in hepatocellular carcinoma and image biomarkers.

Treatment	Objective response (various criteria's)	Applied image biomarkers	Potential image biomarkers
Systemic therapy [13]	10% PR	RECIST	mRECIST/DWI
Locoregional therapy [21,24-25]	20~37% (PR), 53~60% (SD)	EASL/RECIST	3D/DWI/perfusion
Molecular targeted therapy			
Small-molecule kinase inhibitors			
Multitargeted: sorafenib [23]	2.2% (PR), 33.6% (SD)	RECIST	Perfusion/mRECIST
Multitargeted: sunitinib [14,17]	2.9% (PR), 50% (SD)	RECIST	Perfusion/mRECIST
EGFR/HER1: erlotinib [18]	8% (PR), 43% (SD)	RECIST	Perfusion/mRECIST
Monoclonal antibodies			
Anti-VEGF: bevacizumab [15,20]	10~13% (PR), 27~40% (SD)	RECIST	Perfusion/mRECIST
Anti-EGFR: cetuximab [16,19]	0% (PR), 17% (SD)	RECIST	Perfusion/mRECIST

HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; CR, complete response; PR, partial response; SD, stable disease; VEGFR, vascular endothelial growth factor receptor; VEGF, vascular endothelial cell growth factor; EGFR/HER1, epidermal growth factor receptor/human epidermal growth factor receptor 1; EGFR, epidermal growth factor receptor; mRECIST, modified response evaluation criteria in solid tumors; 3D, three dimensional tumor volumetric measurement; EASL, European Association for the Study of the Liver; DWI, diffusion weighted imaging.