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REVIEW

Evaluation and Prediction of Treatment Response for Hepatocellular Carcinoma

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The incidence of hepatocellular carcinoma (HCC) is still on the rise in North America and Europe and is the second leading cause of cancer-related mortality. The treatment of HCC varies, with surgery and locoregional therapy (LRT) such as radiofrequency ablation and transcatheter arterial chemoembolization, and radiation therapy being the primary treatment. Currently, systemic therapy with molecular-targeted agents and immune checkpoint inhibitors (ICIs) is becoming a major treatment option for the unresectable HCC. As the HCC after LRT or systemic therapy often remains unchanged in size and shows loss of contrast effect in contrast-enhanced CT or MRI, the response evaluation criteria in solid tumors (RECIST) and World Health Organization criteria, which are usually used to evaluate the treatment response of solid tumors, are not appropriate for HCC. The modified RECIST (mRECIST) and the European Association for the Study of the Liver (EASL) criteria were developed for HCC, with a focus on viable lesions. The latest 2018 edition of the Liver Imaging Reporting and Data System (LI-RADS) also includes a section on the evaluation of treatment response. The cancer microenvironment influences the therapeutic efficacy of ICIs. Several studies have examined the utility of gadoxetic acid-enhanced MRI for predicting the pathological and molecular genetic patterns of HCC. In the future, it may be possible to stratify prognosis and predict treatment response prior to systemic therapy by using pre-treatment imaging findings.

Keywords: *hepatocellular carcinoma, locoregional therapy, magnetic resonance imaging, systemic therapy, treatment response*

Introduction

There are approximately 500000 patients with hepatocellular carcinoma (HCC) worldwide, which is the sixth most common cancer and the second leading cause of cancer-related mortality.[1,2] Currently, in North America and Europe, mortality from HCC is increasing rapidly, and HCC is still one of the most challenging health problems. The Barcelona Clinic Liver Cancer (BCLC) staging system is widely applied to stage the HCC and is recommended by the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines.[3] The BCLC staging system has been revised repeatedly, where the HCC is classified into five stages (very early, early, intermediate, advanced, and terminal) according to the degree of progression (size and number of intrahepatic lesions, presence of vascular invasion, and presence of extrahepatic lesions), liver function, and general condition.

Surgical treatment is indicated only in the very early and early stages, while HCC is often diagnosed in the intermediate or more advanced stages and is often treated with locoregional therapies (LRTs) such as transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) or systemic therapy. Complete response (CR) after LRT significantly increases the patient survival; however, the presence of residual tumor requires additional treatment.[4] Accurate assessment of the response to treatment is extremely important. Clinical studies have shown that an accurate assessment of the objective response after LRT is important in defining prognosis and considering re-treatment.[5,6] This review describes the conventional criteria for treatment response after LRT and introduces imaging findings related to molecular targeted agents and immune checkpoint inhibitors (ICIs), which have become the new standard of care for patients with HCC.

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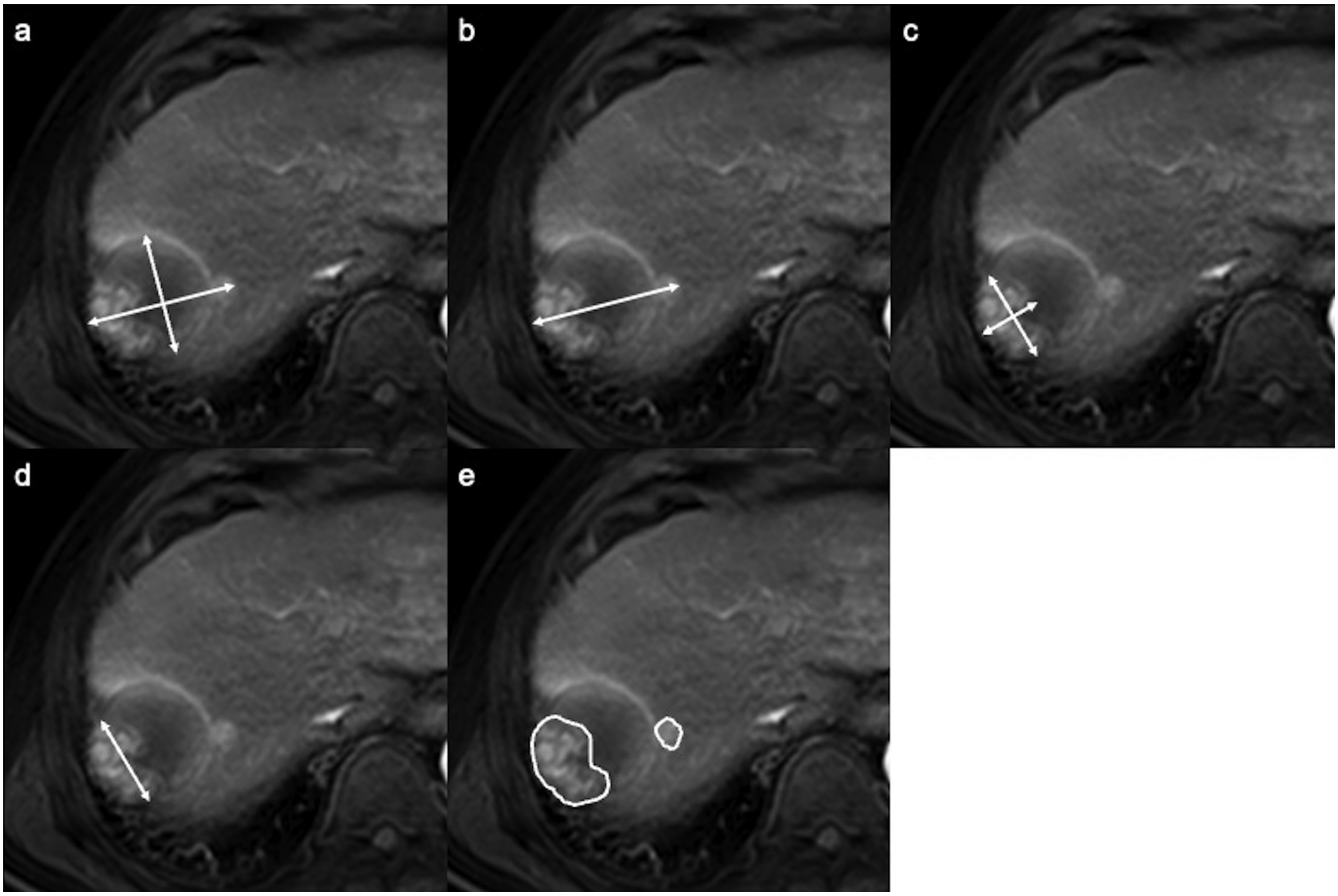

Fig. 1 Current tumor response classification systems are used to report tumor response after treatment. A 77-year-old male with alcohol-related hepatocellular carcinoma who underwent TACE. The WHO criteria (**a**, arrows) and RECIST (**b**, arrow) are size-based classification systems, and enhancement is not considered. Enhancement-based classification systems include the EASL criteria (**c**, arrows) and mRECIST (**d**, arrow). The LR-TR evaluates each viable lesion (**e**, circles). EASL, European Association for the Study of the Liver; LR-TR, Liver Imaging Reporting and Data System Treatment Response; mRECIST, modified RECIST; RECIST, response evaluation criteria in solid tumors; TACE, transcatheter arterial chemoembolization; WHO, World Health Organization.

Response Evaluation Criteria of HCC (Fig. 1)

The response evaluation criteria in solid tumors (RECIST) and World Health Organization criteria have been conventionally used to determine the treatment response in HCC, as in other solid tumors.[7,8] However, these criteria only evaluate the tumor size. Approximately 60% of HCCs are advanced at diagnosis in Europe and North America, and TACE or systemic therapy is indicated.[9] These therapies often allow tumor necrosis as a therapeutic effect, and the arterial phase hyperenhancement (APHE) is reduced, while the size of the lesion remains unchanged. In addition, despite improvements in survival, these therapies often fail to induce tumor regression, making the evaluation of tumor size alone insufficient.[10] Additionally, patients with HCC suffer from chronic liver disease or cirrhosis, which may cause extrahepatic symptoms including reactive lymphadenopathy and ascites. These symptoms can be misdiagnosed as the progression of HCC based on the RECIST. The EASL and American Association for the Study of Liver Diseases proposed an evaluation method for only viable lesions in 2000 and 2006, respectively.[11,12] Based on these issues, Lencioni et al. proposed modified RECIST (mRECIST), which has now become the international standard for determining treatment response.[13]

mRECIST and EASL Criteria

According to the change in the diameter of the viable lesion that can be evaluated on contrast-enhanced CT or MRI, the mRECIST and EASL criteria have defined four response categories: CR, partial response (PR), stable disease (SD), and progressive disease (PD).[11,13] Both the mRECIST and EASL criteria have comprehensively evaluated all the measurable lesions in each patient. Recommendations for the evaluation of vascular invasion, lymph node involvement, ascites, and new lesions were also included. In the mRECIST, a viable lesion is defined by the contrast effect of the arterial phase,

whereas in EASL criteria, the contrast effect of the portal vein phase can also be applied. There is a slight difference in the categorization threshold, as mRECIST evaluates viable lesions in one dimension while EASL criteria in two.

Several meta-analyses have used the mRECIST or EASL criteria for evaluation after LRT and systemic therapy and showed a significant relationship with survival rate.[6,14,15] Vincenzi et al. have shown a very good concordance between the mRECIST and EASL criteria in patients with HCC after LRT and reported that the objective response by these criteria was a possible surrogate for overall survival.[6] The objective response according to mRECIST was also reported to have a strong prognostic value in terms of overall survival in HCC patients treated with molecular targeted agents and ICIs.[14,15] The EASL guideline recommends mRECIST for evaluation after LRT, and mRECIST or RECIST for evaluation after systemic therapy.[16]

LI-RADS Treatment Response (LR-TR)

The Liver Imaging Reporting and Data System (LI-RADS) is the diagnostic algorithm proposed by The American College of Radiology.[17] The LI-RADS was first published in 2012 and has been revised repeatedly, with the 2018 edition being the latest. The LI-RADS is a comprehensive data system that standardizes the imaging findings of HCC, covering lesion management and treatment response features. As the LRT for HCC generally targets specific lesions and often involves multiple treatments over a long period in the same patient, the treatment response varies by lesion. While the above-mentioned algorithms (mRECIST and EASL criteria) determine the treatment response by patient, the LR-TR focuses on each lesion. The LR-TR classifies treatment responses after LRT into four categories: LR-TR non-evaluable, LR-TR non-viable, LR-TR equivocal, and LR-TR viable. The LR-TR viable includes nodular, mass-like, or irregular thickening inside or outside the lesion, APHE or washout appearance, or contrast effects similar to pre-treatment. No contrast effect or treatment-specific contrast effect was assigned as LR-TR non-viable. It is classified as LR-TR equivocal when it is not applicable to LR-TR viable or non-viable. Compared with the mRECIST and EASL criteria, LR-TR is characterized in that a washout appearance is an evidence for determining a viable lesion, and that size measurement is not necessarily required for the evaluation.

Several meta-analyses have reported a favorable correlation between prognosis and treatment response evaluation using the LR-TR after LRT.[18,19] Shropshire et al. adapted LR-TR for the evaluation after bland transcatheter arterial embolization (TAE) and reported that the tumor size reduction and loss of APHE were associated with viability, and that the washout appearance might not contribute to the assessment of treatment response.[20] On the other hand, a meta-analysis comparing the diagnostic performance of each parameter reported that APHE, washout appearance, and enhancement similar to pre-treatment, in that order, performed well.[19] Several reports have shown that the application of LI-RADS ancillary features (hepatobiliary phase [HBP] or transitional phase hypointensity, restricted diffusion, and intermediate T2-weighted imaging hyperintensity) to the LR-TR algorithm resulted in a higher accuracy for tumor viability in patients with HCC, compared with the evaluation using the conventional contrast-enhanced CT or MRI.[21,22] The criteria introduced in this paper are currently recommended for evaluating the treatment response after LRT or radiation therapy, and a careful adaptation is required for patients undergoing systemic therapy.

Imaging Findings and Treatment Response after LRT (Figs. 2 and 3)

Treatment-specific imaging findings are observed after LRT and must be distinguished from recurrence. Although contrast-enhanced CT or contrast-enhanced MRI is usually recommended to evaluate the response after LRT, contrast-enhanced ultrasound is also useful because of its high temporal resolution, making it possible to observe the blood perfusion of HCC in real time.[23,24] Compared to CT and MRI, contrast-enhanced ultrasound has the advantage of a lower risk of complications from the contrast material. Kong et al. showed a good correlation between contrast-enhanced ultrasound and CT in assessing the cauterization range after RFA.[25] Kudo et al. reported that contrast-enhanced ultrasound evaluated residual lesions more accurately than contrast-enhanced CT.[26] CT is the first choice for evaluating the response to treatment after TACE with lipiodol, and a homogeneous accumulation in the lesion is the standard of technical success.[27] Several studies have reported that the degree of lipiodol accumulation in HCC strongly correlates with tumor necrosis.[28,29] However, in CT, the strong beam hardening from lipiodol leads to difficulty in assessing APHE and the washout appearance of viable lesions. The dual-energy CT, which uses two different energies for imaging, can create an iodine map by extracting the iodine contrast distribution from contrast-enhanced CT.[30] Lee et al. reported that using dual-energy CT to evaluate APHE after lipiodol TACE showed a reduced rate of uncertain diagnosis and increased the inter-observer reliability compared to conventional single-energy CT.[31] After conventional lipiodol TACE, the beam-hardening artifact leads to underestimation of the viable lesion, and the contrast-enhanced MRI is advantageous compared to CT.[32] It was reported that the evaluation using gadoxetic acid-enhanced MRI was unaffected by lipiodol and showed a high inter-observer reliability when applying LR-TR.[33] On the other hand, Kloeckner et al. showed that there was no significant difference in diagnostic performance for evaluating viable lesions between contrast-enhanced CT and MRI after TACE with drug-eluting beads.[32] Gadoxetic acid-enhanced MRI is also useful in distinguishing viable lesions from arterioportal shunts after RFA. The typical imaging findings of CR

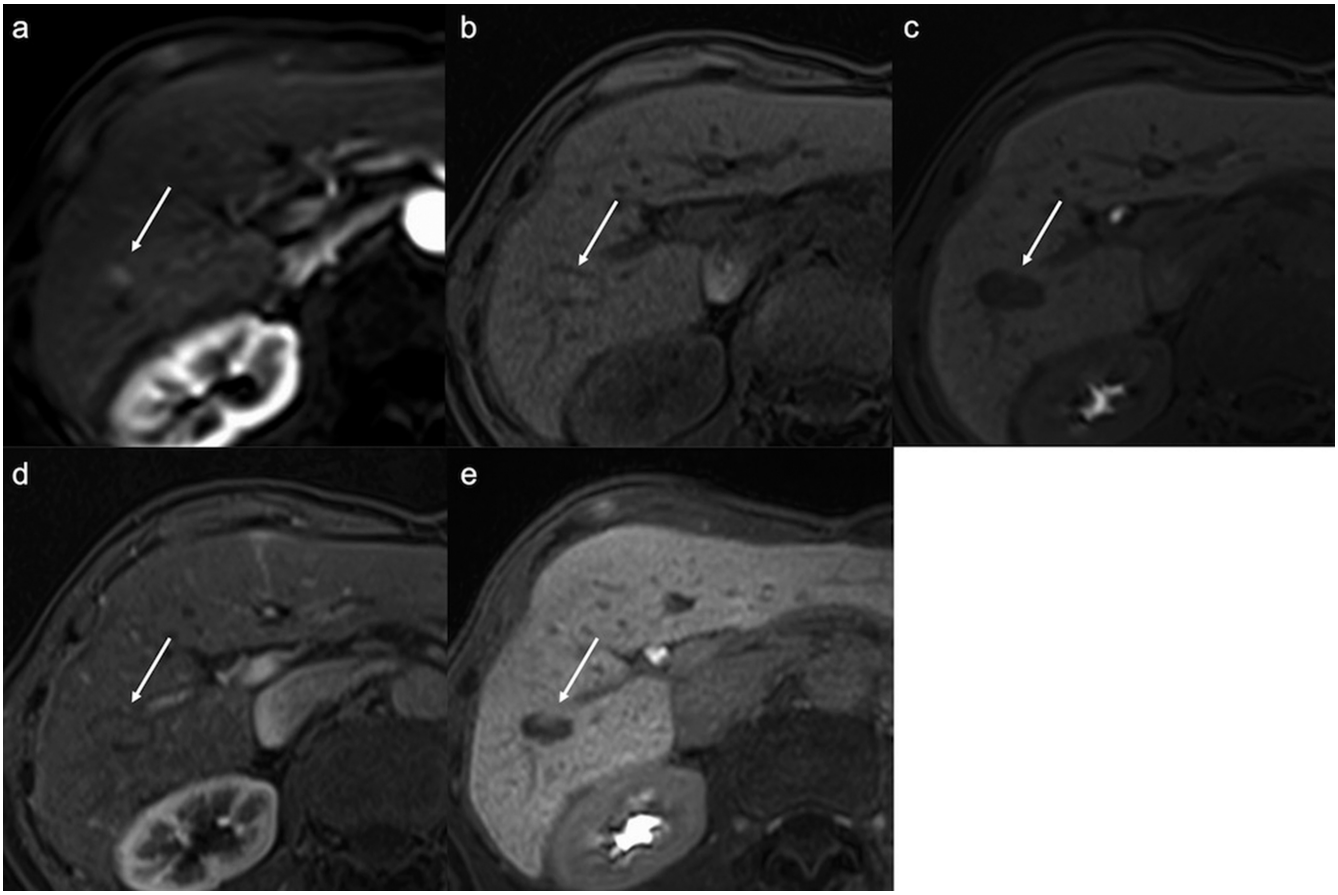

Fig. 2 A 72-year-old male patient with hepatocellular carcinoma who underwent RFA. Pre-treatment gadoxetic-acid-enhanced MRI showed the hypervascular tumor in the segment Ⅵ (**a**, arrow). Five months after RFA, the tumor showed hyperintensity on the pre-contrast T1 weighted image (**b**, arrow), a hypointense area on hepatobiliary phase surrounded the tumor (**c**, arrow), and the arterial phase hyperenhancement disappeared (**d**, arrow), consistent with complete response according to mRECIST. One year after the treatment, the size of the hypointense area in the hepatobiliary phase decreased (**e**, arrow). mRECIST, modified response evaluation criteria in solid tumors; RFA, radiofrequency ablation.

lesions after RFA are thin and smooth rim enhancements around the lesion.[34] Imaging findings of the residual tumor include irregular, nodular, and focal enhancement, washout appearance, restricted diffusion, and hypointensity on the HBP of gadoxetic acid-enhanced MRI. In the evaluation of viable lesions and local recurrent lesions after RFA, gadoxetic acid-enhanced MRI had a significantly higher diagnostic performance than contrast-enhanced CT.[35,36]

Evaluation of Treatment Response after Molecular Targeted Therapies (Fig. 4)

Molecular targeted therapies are available for HCC, as is the case for other cancers. Sorafenib was first approved in 2007 as a systemic therapy for advanced HCC.[37,38] In 2017, regorafenib was established as the second treatment for sorafenib-ineffective patients.[39] Lenvatinib has been established as an alternative tyrosine kinase inhibitor-based first-line treatment.[40] Cabozantinib and ramucirumab are currently approved as second-line treatment.[41,42] These medications are unlikely to cause tumor shrinkage, even in cases of CR and PR, and it is important to evaluate the intratumoral hemodynamics. It has been reported that the objective response based on the above-mentioned criteria (mRECIST, EASL criteria, and LR-TR) is valuable in predicting patient outcomes after systemic therapy.[43,44] The EASL guideline recommends mRECIST or RECIST for evaluation following systemic therapy.[16]

In addition, a quantitative evaluation of the decrease in intratumoral perfusion is expected to provide more accuracy in evaluating the treatment response. The Choi criteria were initially developed for gastrointestinal stromal tumors and have also been studied for other hypervascular tumors including HCC.[43,45,46] The Choi criteria are characterized by its quantitative assessment of intratumoral perfusion, involving changes in CT value as well as tumor size. Gavanier et al. reported that the objective response defined by Choi criteria was significantly correlated with a prolonged

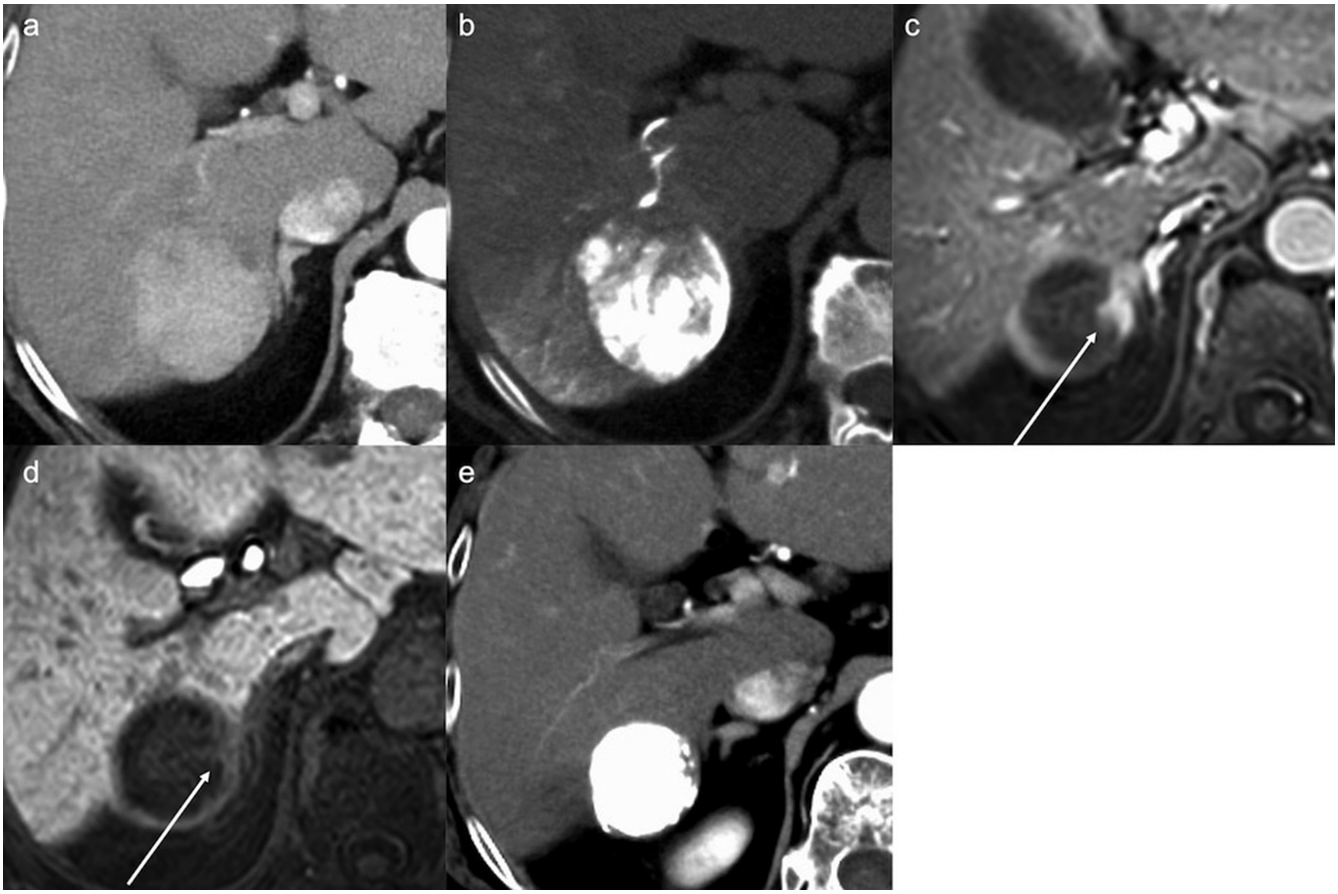

Fig. 3 A residual lesion of a hepatocellular carcinoma after TACE with lipiodol in a 71-year-old female with hepatitis B virus-related cirrhosis. A pre-treatment CT image obtained during the arterial phase showed a hyperenhanced lesion in the segment Ⅶ (**a**). After lipiodol TACE, the unenhanced CT image showed the lesion presenting with heterogenous lipiodol retention (**b**). Two months after the treatment, gadoxetic acid-enhanced MRI showed the viable lesion (consistent with partial response according to mRECIST) (**c** and **d**, arrow), unaffected by lipiodol, while the arterial phase hyperenhancement is difficult to detect in CT because of the beam hardening artifact (**e**). mRECIST, modified response evaluation criteria in solid tumors; TACE, transcatheter arterial chemoembolization.

overall survival, compared with the other criteria, in patients of advanced HCC treated with sorafenib.[47] Evaluation in a single-axial plane is highly dependent on the observer, which makes it difficult to deal with the complex tumor shapes and changes common in HCC. HCC is frequently supplied by multiple vessels, and the residual lesions are heterogeneously distributed. The quantitative EASL technique based on 3D enhancement, which was developed to correct such inaccuracies, provided a better prediction of prognosis after LRT than the 1D technique.[48,49] The objective response derived from the quantitative EASL technique has also been reported to correlate well with the overall survival after sorafenib administration.[50] Lenvatinib, currently the first-line agent for unresectable HCC, inhibits angiogenesis by interrupting the vascular endothelial growth factor and fibroblast growth factor pathway.[51]

As lenvatinib strongly decreases the blood perfusion early after administration, several studies have used the contrast-enhanced ultrasound with high temporal resolution to assess the tumor hemodynamics and early response to treatment.[52–54] Dynamic contrast-enhanced MRI under free-breathing using a stack-of-stars technique was developed as a method to evaluate the blood perfusion over time, and may be applied in the future to evaluate the early therapeutic effect of HCC after lenvatinib administration.[55,56]

Evaluation of Treatment Response after ICI (Fig. 5)

A phase III trial in patients with unresectable HCC demonstrated that atezolizumab plus bevacizumab significantly prolonged the overall survival and progression-free survival compared with sorafenib.[57] The American Association for the Study of Liver Diseases and European Society for Medical Oncology made atezolizumab plus bevacizumab the first-line treatment for unresectable HCC.[58,59] Other currently approved agents include nivolumab, pembrolizumab, and nivolumab plus ipilimumab.[60–62]

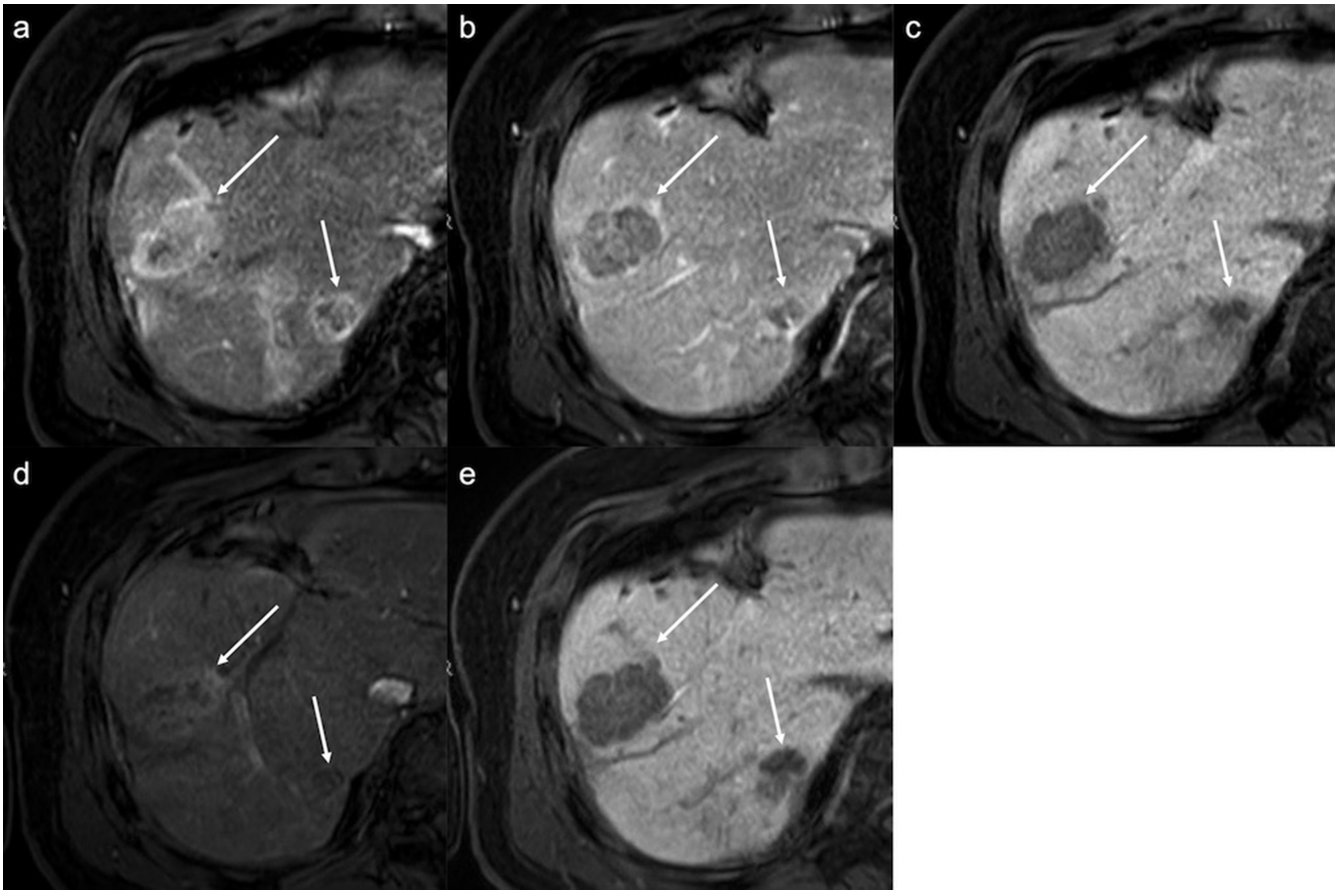

Fig. 4 MR images from a 78-year-old male of multiple hepatocellular carcinomas treated with lenvatinib. The target lesion showed hyperenhancement in the arterial phase (**a**, arrows), and hypointensity in portal venous and hepatobiliary phases (**b** and **c**, arrows). Two months after the initiation of lenvatinib, the arterial phase hyperenhancement of these tumors decreased (**d**, arrows), but unchanged in size (**e**, arrows).

With a variety of systemic treatment options available, the response to an agent must be accurately evaluated radiologically in the early stages, and when the response is poor, the patient must be treated with another agent before the general condition worsens. In evaluating the treatment response after the administration of ICIs, the criteria for targeting viable lesions were also applied. However, because of the strong antitumor effect of ICIs, tumor shrinkage can be expected, and an evaluation with RECIST is being focused on again. In practice, RECIST has been applied in phase III clinical trials of ICIs for HCC.[57] Although pseudo-progression occurs in 5%–10% of cases during immunotherapy for other solid tumors, it has rarely been reported in HCC. Immune-based RECIST was proposed as an evaluation criterion that reflected the possibility of pseudo-progression and may be used in the future for HCC.[63,64]

Prediction of Systemic Therapy Using Gadoxetic Acid-enhanced MRI

The immune microenvironment around tumors is considered important for the efficacy of ICIs, and activated lymphocytes have a significant impact on therapeutic efficacy. Recently, several studies have evaluated the immune microenvironment using imaging examinations such as gadoxetic acid-enhanced MRI. Although HCC usually shows hypointensity on the HBP of gadoxetic acid-enhanced MRI, some HCCs (12%–22%) show isointensity or hyperintensity.[65–67] It has been suggested that OATP1B3, one of the transporters expressed in hepatocytes, is strongly expressed in this type of HCC and is primarily responsible for the uptake of gadoxetic acid. In recent years, genome analysis of several tumors, including HCC, has been advancing, and it is known that the frequency of gene mutations such as p53 and CTNNB1 (encoding β-catenin) is high in HCC.[68,69] Sekine et al. reported that the expression of SLCO1B3 (encoding OATP1B3) was associated with CTNNB1 mutasions, which caused the intratumoral cholestasis.[70] Several studies showed HCC with a mutation in the Wnt/β-catenin signaling pathway elevated the expression of OATP1B3 and showed isointensity or hyperintensity on HBP (Fig. 6).[71,72] Molecular profiling of HCC showed that in patients with advanced HCC with Wnt/β-catenin mutation, the ICI treatment resulted in lower disease control and

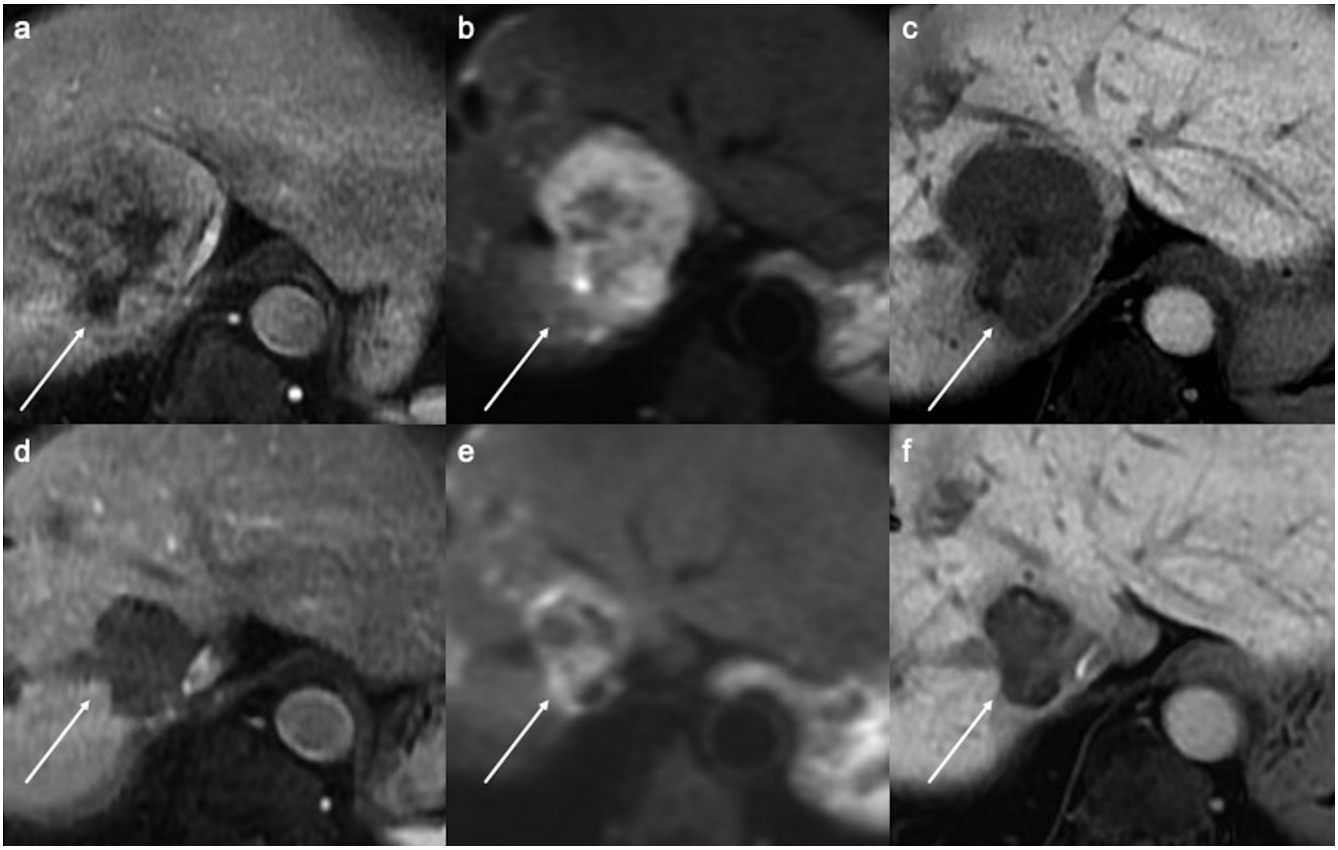

Fig. 5 MR images from a 70-year-old female of hepatocellular carcinoma with extrahepatic spread (lymph node metastasis) treated with atezolizumab plus bevacizumab. The hepatic lesion showed the arterial phase hyperenhancement (**a**, arrow), restricted diffusion (**b**, arrow), and hypointensity in hepatobiliary phase (**c**, arrow) before the treatment. After 5 cycles of atezolizumab plus bevacizumab, the lesion became hypovascular and decreased in size, consistent with partial response according to RECIST (**d**–**f**, arrow). RECIST, response evaluation criteria in solid tumors.

shorter median overall survival than in HCC without the mutation.[73] A possible cause of this is the influence of the cancer microenvironment.[74]

In the basic mechanism of tumor immunity, antigen-presenting cells, such as dendritic cells that detect tumor antigens, stimulate the lymphocytes in lymph nodes. Activated cytotoxic T lymphocytes attack the tumor. However, tumors and surrounding macrophages express an immune checkpoint called PD-L1 and avoid attacks by cytotoxic T lymphocytes. This phenomenon is known as immune escape. The ICIs promote the antitumor immune system of cytotoxic T cells attacking tumor cells by inhibiting the expression of immune checkpoints. The ICIs block immune checkpoints expressed in tumors, causing cytotoxic T cells to attack the tumor cells. As a result of this mechanism, the ICIs are thought to be more effective in tumors with high lymphocyte counts and expression of immune checkpoints but less effective in immune-cold tumors with low lymphocyte counts. It has been reported that approximately 50% of common HCCs and 80%–90% of Wnt/β-catenin mutant HCCs are in an immune-cold environment.[75] Wnt/β-catenin mutant HCCs were reported to show downregulation of immune-related genes.[76,77]

HCCs with upregulated OATP1B3 expression, which are hyperintense on HBP, often include Wnt/β-catenin mutations, and the immune-cold tumor microenvironment is assumed to weaken the efficacy of ICIs. Aoki et al. suggested that advanced HCC with isointensity or hyperintensity on HBP had a low response rate to ICIs.[78] In addition to Wnt/β-catenin mutations, other subtypes of HCC are known to be immune-cold, and the macrotrabecular-massive (MTM) subtype and vessel-encapsulating tumor clusters (VETC) are subtypes of HCC that have been recently focused on because of their poor prognosis. Kurebayashi et al. reported that the majority of HCCs presenting with these patterns were immune-cold, which is an immuno-subtype characterized by low lymphocytic infiltration.[79] Imaging findings of MTM and VETC patterns have been reported to include intratumoral hemorrhage, necrosis, size larger than 5 cm on contrast-enhanced CT, intratumoral artery, AP peritumoral enhancement,

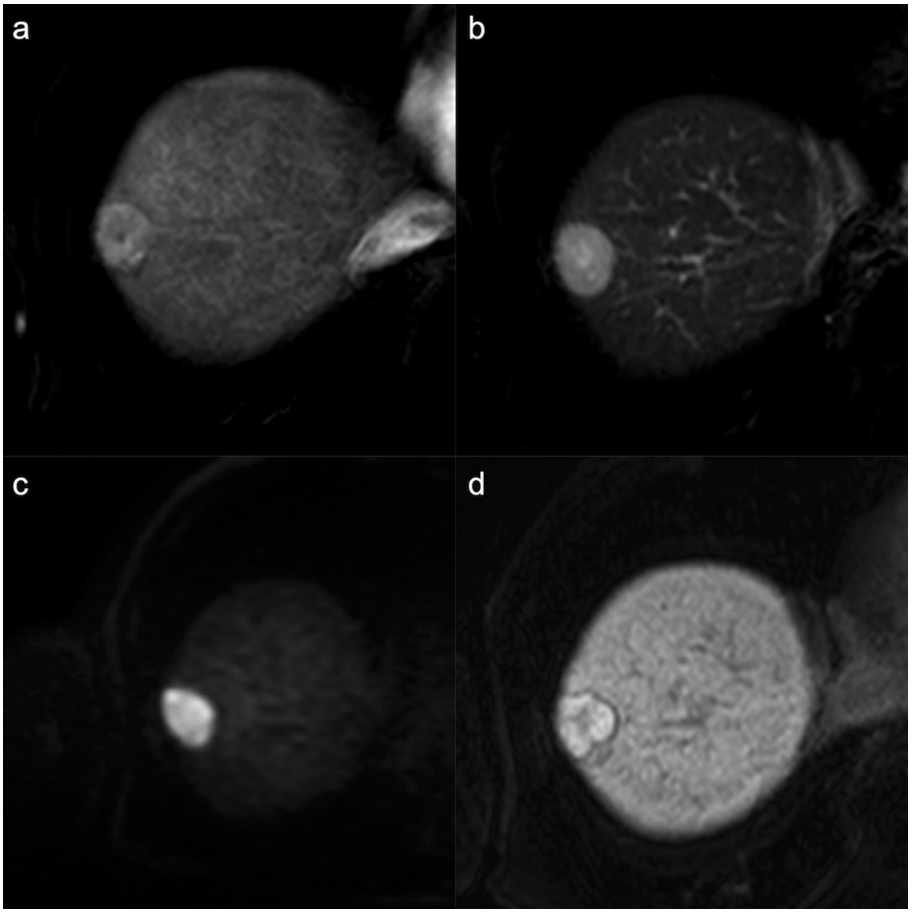

Fig. 6 MR images from a 76-year-old male of alcohol-related hepatocellular carcinoma with β-catenin mutation. The nodule in the segment VIII shows hyperenhancement on the arterial phase (**a**), hyperintensity on T2 weighted imaging (**b**) and diffusion weighted imaging (**c**), and hyperintensity on the hepatobiliary phase (**d**). The nodule includes the tumor capsule (**a** and **d**).

non-smooth tumor margin, and peritumoral hypointensity on HBP on gadoxetic acid-enhanced MRI.[80,81] Thus, HCC with these characteristic imaging findings may be immune-cold and resistant to ICIs. Further research that focuses on these patterns is required. In contrast, Murai et al. reported that the MRI might make it possible to predict immune-hot HCCs with a high expression of immune checkpoints.[82] This study stratified the non-viral HCC by ribonucleic acid (RNA) sequencing using surgical specimens and showed that steatotic HCC was in an immune-hot (inflamed) but immune-exhausted microenvironment characterized by T cell exhaustion, M2 macrophage and cancer-associated fibroblast infiltration, high PD-L1 expression, and transforming growth factor (TGF)-β signaling activation. Theoretically, an immune-hot and immune-exhausted microenvironment is a favorable indication for ICIs. Patients with steatotic HCC, confirmed by chemical-shift MR imaging, had significantly longer progression free survival compared with patients with non-steatotic HCC after treatment with atezolizumab plus bevacizumab. Steatotic HCC, with fat detected on MRI, may be diagnosed non-invasively as a group expected to respond to ICIs (Fig. 7).

On the other hand, there are studies that compared the response rates for lenvatinib in the two groups, isointensity or hyperintensity and hypointensity on HBP, and both studies showed no difference between the two groups.[83,84] A study using genomic analysis also suggested that lenvatinib did not reduce the response of HCC patients with β-catenin mutations.[85] Although many of the previous studies have focused on the prediction of the response to single-agent ICI treatment, Sasaki et al. reported the usefulness of pre-treatment gadoxetic acid-enhanced MRI to predict the response to lenvatinib and atezolizumab plus bevacizumab.[86] In the lenvatinib group, there was no significant difference in progression-free survival between hyperintense and hypointense HCC; however, in the atezolizumab plus bevacizumab group, progression-free survival was significantly shorter in hyperintense HCC, similar to previous studies. It was considered that lenvatinib did not reduce the treatment response to HCC with β-catenin mutations because there is a correlation between Wnt/β-catenin signaling and fibroblast growth factor receptor 4 expression, and lenvatinib is highly responsive to receptor expression.[85–87] In addition, lenvatinib treatment response was reported to be independent of tumor differentiation, and it is expected to be effective for various types of HCCs.[88]

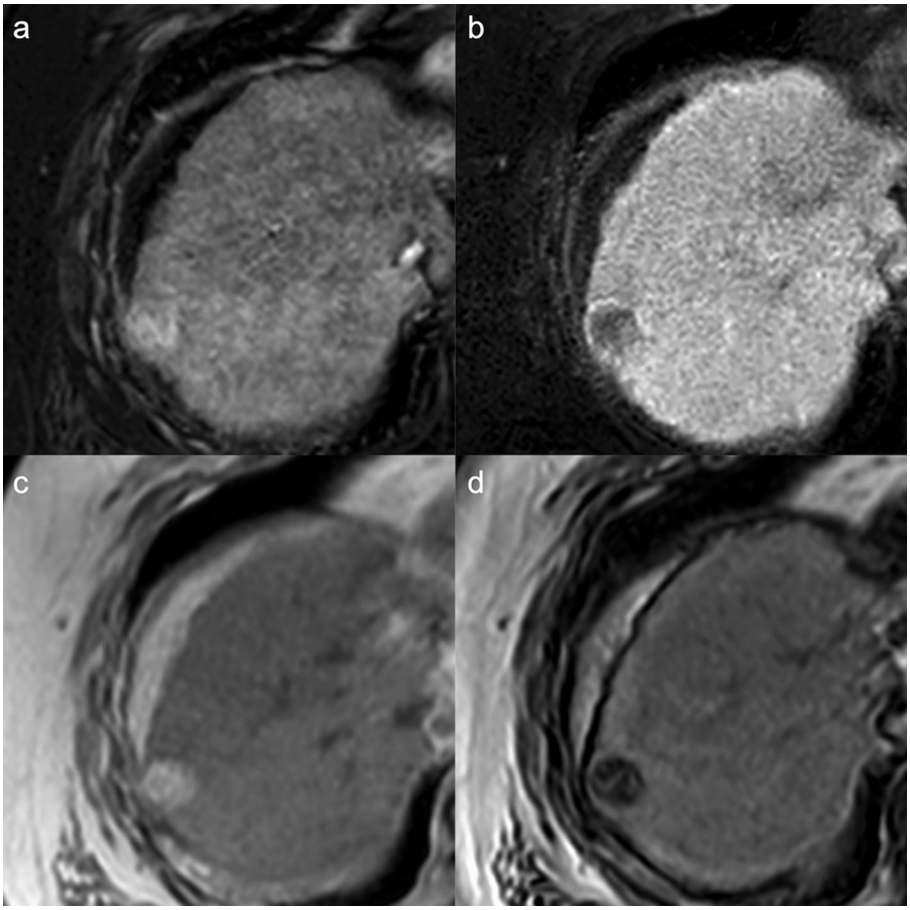

Fig. 7 MR images from a 70-year-old male of non-alcoholic steatohepatitis-related steatotic hepatocellular carcinoma. The nodule in the segment VIII shows hyperenhancement on the arterial phase (**a**), hypointensity on the portal venous phase (not shown), transitional phase (not shown), and hepatobiliary phases (**b**). In-phase T1-weighted gradient-echo MR image (**c**) shows a well-defined hyperintense and the opposed-phase T1-weighted gradient-echo MR image (**d**) reveals a drop in the signal intensity, which indicates the presence of fat.

Conclusion

In this article, we have reviewed the conventional treatment response criteria and post-treatment imaging findings for HCC. We have also presented molecular or radiological studies on systemic therapies, which are currently the major treatments for HCC. Although further research is needed, it may be possible to predict the response of HCC to systemic treatment and select an agent based on pre-treatment imaging findings

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Conflicts of Interest

The authors declare no conflicts of interest directly relevant to the content of this article.

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