Review

Imaging Modalities for Assessment of Treatment Response to Nonsurgical Hepatocellular Carcinoma Therapy: Contrast-Enhanced US, CT, and MRI

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Abstract

Tumor response and time to progression have been considered pivotal for surrogate assessment of treatment efficacy for patients with hepatocellular carcinoma (HCC). Recent advancements in imaging modalities such as contrast-enhanced ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are playing an important role in assessing the therapeutic effects of HCC treatments. According to some HCC clinical guidelines, post-therapeutic evaluation of HCC patients is based exclusively on contrast-enhanced dynamic imaging criteria. The recommended techniques are contrast-enhanced CT or contrast-enhanced MRI. Contrast-enhanced US is employed more in the positive diagnosis of HCC than in post-therapeutic monitoring. Although contrast enhancement is an important finding on imaging, enhancement does not necessarily depict the same phenomenon across modalities. We need to become well acquainted with the characteristics of each modality, including not only contrast-enhanced CT and MRI but also contrast-enhanced US. Many nonsurgical treatment options are now available for unresectable HCC, and accurate assessment of tumor response is essential to achieve favorable outcomes. For the assessment of successful radiofrequency ablation (RFA), the achievement of a sufficient ablation margin as well the absence of tumor vascular enhancement is essential. To evaluate the response to transcatheter arterial chemoembolization (TACE), enhanced tumor shrinkage is relied on as a measure of antitumor activity. Here, we give an overview of the current status of imaging assessment of HCC response to nonsurgical treatments including RFA and TACE.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third most frequent cause of cancer deaths. Surgical resection is regarded as a standard treatment for HCC patients [1]; however, the majority of HCC patients are not suitable for curative resection at the time of diagnosis because of large tumor size, multifocal disease, vascular involvement, extrahepatic spread, or poor liver function, among others [2–7]. Therefore, various nonsurgical treatment options have been developed in the effort to provide for patients with unresectable HCC. Local ablative techniques are increasingly used for minimally invasive treatment, and radiofrequency ablation (RFA) is currently performed widely due to its ease of use, safety, and effectiveness for managing unresectable HCC in patients with cirrhosis [8–14]. Transcatheter arterial chemoembolization (TACE) is the current standard of care for patients presenting with multinodular HCC with relatively preserved liver function, no cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread [15–21].

Monitoring tumor response to therapy is imperative for the clinical management of cancer patients, and accurate assessment of tumor response is essential for favorable outcomes. For HCC patients, imaging techniques such as contrast-enhanced US, CT, and MRI are used to diagnose HCC [22, 23] and to assess therapeutic effects [24–26]. However, these techniques employ different principles to generate images, and the types and doses of contrast agents are also different. Although contrast enhancement is an important finding on imaging, enhancement does not necessarily depict the same phenomenon across modalities. We therefore need to be familiar with the findings for each modality to evaluate the success of treatment, detect residual or recurrent tumors, and diagnose new lesions. In this review, we focus our discussion on the imaging assessment of HCC response to nonsurgical treatment including RFA and TACE.

Response Evaluation Criteria

The endpoint in cancer research is overall survival. Nonetheless, tumor response and time to progression have been considered pivotal for surrogate assessments of efficacy. In 2000, the European Association for the Study of the Liver (EASL) recommended measuring the change in the area of tumor enhancement on contrast-enhanced imaging as the optimal method to assess treatment response [27]. Introduced in 2008 as an amendment of the Response Evaluation Criteria in Solid Tumors (RECIST), the modified RECIST (mRECIST) [28] and the Response Evaluation Criteria in Cancer of the Liver (RECICL) [29] focus on the viable (enhanced on dynamic studies) tumoral components to assess the response of HCC to locoregional or antiangiogenic treatment. mRECIST, which is based on the unidimensional measurement of the enhanced portions of target tumors, is simple and easy to apply in clinical practice. According to some HCC clinical guidelines, post-therapeutic evaluation of HCC patients is based exclusively on contrast-enhanced dynamic imaging criteria. The recommended techniques are contrast-enhanced CT or contrast-enhanced MRI. However, there are cases (e.g., infiltrative tumors, heterogeneous necrosis) and situations (e.g., after ablation) in which the mRECIST criteria are difficult or impossible to apply [30]. Other imaging techniques such as angiography, contrast-enhanced US, and positron emission tomography-CT are considered to be controversial. It is worth mentioning that their roles have been explored more in the positive diagnosis of HCC than in post-therapeutic monitoring.

Imaging Assessment of Tumor Response

Radiofrequency Ablation

Among the risk factors for recurrence, tumor size, portal vein invasion, and intrahepatic metastasis are generally considered the major causes of intrahepatic HCC recurrence after treatment. Several studies have addressed the relationship between micrometastases/microvascular invasion of HCC cells and tumor size. Okusaka et al. reported that 19% of HCC nodules of 3.0 cm or less in diameter had satellite lesions that were not detected [31]. The reported frequency of microvascular invasion in patients with an HCC tumor of 2–3 cm is in the range of approximately 20–30% [31–33]. Consequently, effective treatment is indicated not only by the absence of HCC tumor enhancement, but also by the safety margin. Nakashima et al. revealed that 59.1% of small HCC ≤3.0 cm in diameter had micrometastases within 5 mm of each micrometastatic lesion and its primary HCC [32]. For the RFA procedure to be considered technically successful, the tumor and at least a 5-mm safety margin must be included in the ablation zone [34]. The local recurrence rate differs markedly depending on whether a 5-mm safety margin is secured. Kudo et al. reported that the local recurrence rate was 2.6% in HCC patients with a ≥5-mm safety margin at 2 years after RFA, whereas it was 20.8% in HCC patients without such a safety margin (p=0.01) [35].

Recurrence of tumors in the treated area or elsewhere is defined as reappearance of vascular enhancement. The ideal imaging interval is unknown, but initially a 3–4 month interval is commonly used to monitor HCC lesions after RFA therapy.

Computed Tomography

Contrast-enhanced CT is widely used for the evaluation of treatment response. Tissue contrast enhancement on CT depends on the blood flow, capillary permeability, rate of diffusion, and the extravascular extracellular space volume. In clinical practice, evaluation of the absence of tumor enhancement and the safety margin is based on a visual comparison of the pre- and post-RFA CT images by referring to specific landmarks such as hepatic vessels and the liver surface [35–37]. In addition, the safety margin has one more important role as security in avoiding the limitations of CT assessment due to partial volume effects.

Hyperemia in tissue surrounding the ablated lesion can represent an inflammatory reaction resulting from thermal injury. Peripheral rim enhancement resulting from reactive hyperemia is usually uniform in thickness and envelops the ablated lesion, whereas residual HCC demonstrates focal and irregular peripheral enhancement [38, 39].

Compared with RFA alone, the combination of RFA and TACE markedly increased the extent of induced coagulation of RFA [40]. Conventional Lipiodol-TACE offers another potential advantage for assessment of a subsequent RFA procedure. Lipiodol (Lipiodol Ultra-Fluide, Laboratoire Guerbet, Aulnay-Sous-Bois, France) is an oily contrast medium used in radiography. The ablative margin can be shown as the boundary between the high-density area of Lipiodol accumulation in HCC and the enhanced area of surrounding normal liver parenchyma. Therefore, the safety margin can be easily evaluated only by post-RFA dynamic CT images in HCC patients treated by RFA combined with TACE [41].

Ultrasound

US contrast mediums consist of gas-cored microbubbles that are encapsulated by a shell constructed of a lipid monolayer or cross-linked albumin. Contrast-enhanced echo signals contain significant energy components at higher harmonics from inside blood vessels. Contrast harmonic imaging can depict signals from microbubbles with a very slow flow and is a useful tool for depicting small residual HCCs or local recurrence of HCC [42–46]. Vilana et al. reported that the sensitivities for detection of residual tumors 1 day after RFA were 27% and 20% on contrast-enhanced US using SonoVue and contrast-enhanced CT, respectively [43].

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Meanwhile, a double-contrast US technique using Sonazoid reinjection has been developed on the basis of two specific characteristics of Sonazoid: arterial flow images and Kupffer images in the post-vascular phase [47, 48]. Residual HCC can demonstrate a focal defect during the Kupffer phase and show hypervascular enhancement by the reinjection of Sonazoid. However, it is difficult to identify the safety margin on US in some cases. Zhou et al. found that contrast-enhanced US could not evaluate the safety margin in 34.8% of HCC nodules because the tumor boundary could not be identified clearly by US after RFA [49].

Magnetic Resonance Imaging

MRI (conventional T1-weighted image (WI), T2WI, and dynamic contrast-enhanced imaging) for tumor response assessment following liver thermal ablation is considered the most accurate method for the early detection of residual/recurrent tumors. MRI evaluation of the absence of tumor enhancement and the safety margin is also based on a visual comparison of the pre- and post-RFA images by referring to specific landmarks of the liver. A hyperintense zone on non-enhanced T1WI within 2 days after RFA reflects the extent of the ablated region [50]. Functional imaging including diffusion-weighted MRI has the ability to provide unique insights into molecular water distribution within a tumor, and therefore indicate tumor viability at a cellular level [51]. Viable tumors after RFA appeared as hyperintense, and necrotic regions were recognized as hypointense areas on diffusion-weighted MRI. Kele et al. found that ablation site recurrences showed significantly lower apparent diffusion coefficient values than the ablation zone and normal liver parenchyma (1.02×10^3 mm^2/s vs. 1.31×10^3 mm^2/s) [52]. Hepatocyte-specific MRI contrast agents were developed for the detection and characterization of focal liver lesions, and gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is a contrast agent with the combined properties of a conventional non-specific extracellular contrast agent and a hepatocyte-specific contrast agent. Hepatocyte-phase images help to distinguish vascular pseudolesions (e.g., those caused by arterioportal shunting, portal venule obstruction, nonportal splanchnic veins, or rib compression) from hypervascular tumors [53]. Makino et al. reported that Gd-EOB-DTPA-enhanced MRI enabled treatment evaluation in a significantly larger number of HCCs than CT did (86/92 [93.5%] vs. 62/92 [67.4%], p<0.05) [54].

TACE

Conventional TACE (c-TACE), involving administration of an anticancer agent-in-oil emulsion followed by embolic agents, is a popular technique, and Lipiodol accumulation in HCCs after TACE can be regarded as representing a necrotic area. Recently, drug-eluting beads (DEB) have provided an attractive alternative to iodized oil-based regimens [55]. Both c-TACE and DEB-TACE can induce direct tumor necrosis and demonstrate anticancer efficacy. Enhanced tumor shrinkage is relied on as a measure of antitumor activity. However, tumor response is not paralleled by a reduction in overall tumor load but rather by a reduction in viable tumor [29]. Therefore, response assessment of TACE is recommended; this can be achieved by performing contrast-enhanced imaging 1 month after initial treatment and at least every 3 months during follow-up [29].

Computed Tomography

CT is also commonly used as the standard imaging technique for evaluating the therapeutic response to TACE. Dense, uniform retention of Lipiodol in the tumor is a reliable surrogate marker for complete or near-complete tumor necrosis, and the pattern and distribution of Lipiodol in the tumor are useful for assessing the therapeutic effects of c-TACE (fig. 1). However, small vague areas of hypervascularity that represent arterial–portal shunts, commonly seen in patients with HCC, are a frequent cause of "pseudolesions" on CT, again

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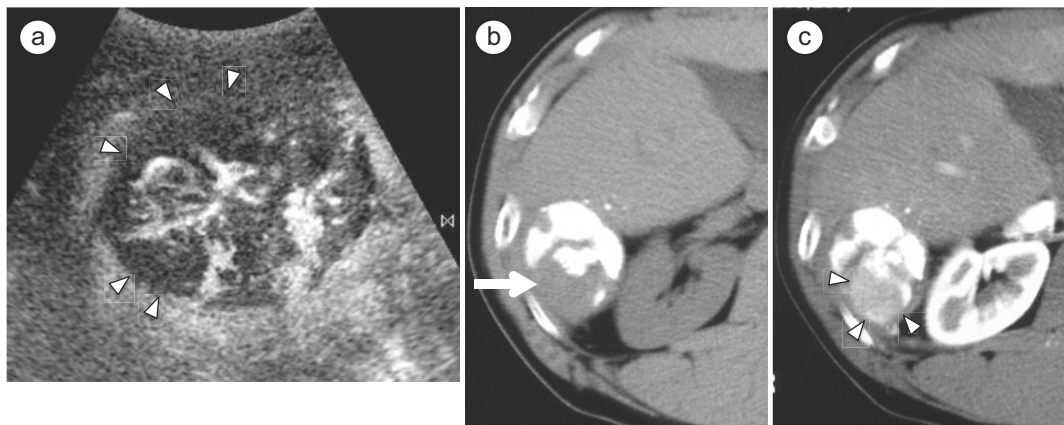Minami et al.: Treatment Response Assessment of Nonsurgical HCC Therapy

Fig. 1. A 64-year-old man with a 4-cm HCC in segment 6 that was treated with c-TACE. **a** Contrast-enhanced US obtained 5 days after chemoembolization shows blood flow and avascular areas (*arrowheads*) in tumor during the arterial phase. **b** Plain CT scan obtained 1 week after treatment clearly shows defect of iodized oil accumulation (*arrow*) in tumor. **c** Arterial phase dynamic CT scan obtained at same time as Fig. 1b clearly shows a partially enhancing area (*arrowheads*) corresponding to an area lacking Lipiodol accumulation.

limiting specificity. In addition, beam-hardening artifacts from the iodized oil can make it difficult to visualize marginal recurrences as well as residual viable tumor.

In patients treated with DEB-TACE, viable tumor is defined according to the uptake of contrast in the arterial phase of dynamic CT. The density, expressed in Hounsfield units (HU), is measured at CT examination both before and after treatment. The absence of significant differences of density between the phases is defined as indicating the presence of coagulative necrosis [56, 57].

Ultrasound

Contrast-enhanced US offers not only a very high sensitivity to contrast agents but also a high spatial resolution (fig. 1). Unlike CT imaging, contrast-enhanced US imaging is not influenced by Lipiodol retention. Xia et al. reported that the detection rates of positive enhancement with contrast-enhanced US and dynamic CT 1 week after TACE were 25 (58.1%) of 43 lesions and 17 (39.5%) of 43 lesions, respectively [58]. Contrast-enhanced US was significantly more sensitive than dynamic CT in depicting the residual tumor blood supply to HCCs 1 week after TACE (p<0.01; chi-squared test). Use of contrast-enhanced US permits the proper and early selection of patients who would benefit from additional focal therapy after TACE, as well as helping to guide focal ablation to the viable portion of HCC [59, 60]. However, contrast-enhanced US has technical limitations imposed by body habitus and the difficulty involved in accessing lesions near the hemidiaphragm. Additionally, contrast-enhanced US examinations used to be performed on a solitary mass or on a dominant mass in patients with multiple lesions.

Magnetic Resonance Imaging

Lipiodol causes variable signal intensity changes on unenhanced MRI, and is difficult to detect accurately. Recently, diffusion-weighted MRI is increasingly used in addition to conventional unenhanced and enhanced MRI. Diffusion-weighted MRI is known to have limitations such as a relatively low signal-to-noise ratio. However, it may offer additional value in evaluation and follow-up because diffusion-weighted MRI can provide information about molecular tissue characteristics [52].

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Gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) is the most commonly used MRI contrast agent. It has an extracellular distribution and behaves similarly to the iodinated contrast agents used in CT. The presence of gadolinium can strongly influence the relaxation properties of nearby protons, leading to changes in tissue contrast. Consequently, enhanced areas in the embolization site on gadolinium-enhanced MRI presumably represent viable tumor [61, 62] but could also result from posttreatment granulation tissue [63]. Goshima et al. reported that sensitivity for the detection of local HCC recurrence after TACE was higher on gadolinium-enhanced MR imaging (82%) than on diffusion-weighted MR imaging (60.7%) for two readers, in combination and separately (p<0.05) [64].

Adverse Reactions

Kobayashi et al. reported in their large-scale study that the prevalence of all adverse reactions to nonionic contrast media was 2% and that of severe reactions was 0.1% [65]. The vast majority of these reactions were mild, including rash/hives, itching, nausea with or without vomiting, cough, or lump in the throat, among others.

The total incidence of adverse reactions to contrast agents in MRI ranges between 2% and 4%. Most frequent are minor, general reactions such as nausea, emesis, hives, and headache and local reactions such as skin irritation, itching, and coolness.

It should be noted that gadolinium chelates administered to patients with acute renal failure or severe chronic kidney disease can result in a syndrome of nephrogenic systemic fibrosis. Therefore, use of these contrast media is no longer recommended in these patients.

The adverse reaction rate of US contrast agents seems to be relatively low compared with the contrast agents used in CT or MRI. The incidence of contrast agent complications ranges from 0.014% to 0.077% [66]. The most frequently reported adverse events are diarrhea, headache, albuminuria, and rash.

Conclusion

Accurate assessment of tumor response with imaging modalities is essential for favorable outcomes. For successful RFA, the achievement of a sufficient ablation margin as well the absence of tumor vascular enhancement is essential. For TACE response evaluation, enhanced tumor shrinkage is relied on as a measure of antitumor activity. We need to become well acquainted with the characteristics of each modality, including contrast-enhanced US, CT, and MRI, and careful comparison of imaging before/after therapy is critical for HCC patients treated with RFA or TACE.

Disclosure Statement

The authors declare that no conflict of interest exists.

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