Commentary

Novel imaging biomarkers of response to transcatheter arterial chemoembolization in hepatocellular carcinoma patients

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer death worldwide (1). Most patients present with intermediate or advanced disease that is not amenable to curative treatment, and the median survival in this group is 6-8 months (2). Several studies and well-designed randomized trials have shown a positive effect of transcatheter arterial chemoembolization (TACE) on patient outcome and survival (3-8). As nicely described in the present article from Wáng *et al*., assessment of tumor response is of extreme importance in patients undergoing locoregional treatments of liver cancer (9). Early assessment of the effectiveness of TACE and monitoring of tumor response are paramount to the identification of treatment failure, guidance of future therapy, and determination of the interval for repeat treatment. Wáng *et al*. confirm in this article that imaging evaluation of HCC response to therapy is generally and widely performed with cross-sectional imaging [computed tomography (CT) and magnetic resonance imaging (MRI)] by using the modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria and the European Association for the Study of the Liver (EASL) criteria which have been introduced in the past decade (9). It is interesting to note that these criteria are not based on experimental or observational studies, but are proposed as revised versions of World Health Organization (WHO) and RECIST criteria (10-13). Initial reports showed that they were better than the latter for assessment of response, and both have been shown to be independent prognostic factors (14-19). Nevertheless, these criteria have been shown to have several limitations, mainly the lack of standardization, and there are concerns about applicability and reproducibility that have been raised. Indeed, they may be difficult to use, especially in heterogeneous lesions, and their use is dependent on operator experience. Although recent guidelines have acknowledged the potential value of these new criteria, they are not considered robust enough to replace older morphological criteria in trials (18). As a result, since they were first introduced, numerous studies have been published to better define the type and optimal number of target lesions, the ideal imaging technique, and the follow-up schedule. At present most teams perform one-dimensional mRECIST or two-dimensional EASL measurement of the enhanced portion of a maximum of two target lesions (18,19). Nevertheless, very recent data have suggested that three-dimensional (3D) evaluation of the whole tumor burden using specific software, functional imaging or cone-beam CT (CBCT) imaging may be of interest as novel imaging biomarkers to predict future tumor response to TACE in HCC patients (10,20-27).

Three-dimensional (3D) evaluation

The anatomic imaging biomarkers assume that tumors are spherical before and after treatment (28). In both RECIST and mRECIST, a 30% decrease in diameter of tumor, defined as the threshold for partial response, is presumed to correspond to a 65% decrease in tumor volume. Similarly, a 20% increase in diameter of viable tumor, which defines the threshold for defining disease progression, corresponds to an approximately 73% increase in spherical volume. These cut points are rather arbitrary and may not be applicable to all therapies. Furthermore, both RECIST and modified

RECIST measurements are only estimates of the tumor volume and are prone to inter-observer measurement variability. In a retrospective study of 45 HCCs, diameter based on 3D measurements was significantly different than diameter based on conventional bidimensional (2D) measurements (29). Volumetric evaluation of HCC and its necrotic component eliminates this limitation and, when available, offers the most comprehensive anatomic evaluation for determining treatment response (30). Voxel-by-voxel volumetric analysis of tumor density and necrosis has been shown to be more reproducible than 2D analysis (29,31). Volumetric quantification is particularly helpful in cases in which necrosis is heterogeneously distributed in HCC and cannot be assessed using modified RECIST. Volumetric evaluation of HCC and its degree of necrosis is a very promising tool because it is more accurate and reproducible than the currently used 2D measurement. However, volumetric measurement is not easily feasible in the routine clinical setting and is still not included in tumor response criteria.

Functional imaging

Functional imaging, unlike anatomic imaging, provides information on tumor viability, cellularity, vascularity, and metabolism (32-34). These changes can be detected earlier than anatomic changes and are more applicable in assessing treatment response after TACE.

Diffusion-weighted imaging (DWI)

DWI has recently shown potential for HCC detection compared to or combined to contrast-enhanced T1-weighted imaging (35,36). DWI is also increasingly used to evaluate tumor response to locoregional therapy (37). There are several reports about the use of DWI to evaluate HCC response to TACE (23,25,38). These studies have shown differences in apparent diffusion coefficient (ADC) values between viable and necrotic portions of HCCs after treatment and measurable differences before and after treatment. In a prospective study, Kamel *et al*. (25) observed an increase in tumor ADC value that was significant 1-2 weeks after initial TACE, borderline significant 3 weeks after therapy, and insignificant 24 h and 4 weeks after therapy. They also showed that the maximum difference in tumor enhancement was present 1-2 weeks after TACE. Thus, they recommend the use of contrast-enhanced T1-weighted imaging and DWI 1-2 weeks after TACE. In an explant correlation study, investigators observed that ADC had a significant correlation with tumor necrosis assessed with histopathology (39). For prediction of complete tumor necrosis after TACE, an area under the curve (AUC) of 0.85 was observed for ADC compared with an AUC of 0.82-0.89 for image subtraction, without significant difference between the two techniques (39). The use of DWI in combination with conventional MRI shows promising results in increasing the sensitivity for detecting viable tumor (38). Diffusion restriction (hyperintensity on imaging performed with high b values and low ADC values) suggests viable tumor components (39). However, a study showed lower performance of DWI compared with contrast-enhanced imaging, with lower sensitivity for detection of local HCC recurrence (60.7% *vs*. 82%, respectively) (40). Regarding the use of pretreatment ADC as a marker of response to TACE, the data are limited, and two studies published to date report conflicting results (41,42). In a prospective study by Yuan *et al*. (41), non-responding HCCs had a significantly higher pretreatment ADC than HCCs that responded. On the other hand, a recently published retrospective study showed that HCCs with poor or incomplete response to TACE had significantly lower pretreatment ADC and lower post-TACE ADC values than HCCs with good or complete response (42). Both studies showed an increase in ADC in HCC with good response compared with HCC with poor response (41,42). Given the conflicting results from these two studies, the value of pre-TACE ADC in predicting response should be verified in a large prospective study. The limitations of DWI relate to image quality, with possible echo-planar imaging-related artifacts, and to limited knowledge on ADC reproducibility in liver tumors (43-45). In other words, despite promising results, DWI cannot still replace contrast-enhanced T1-weighted imaging and subtraction for assessment of HCC response. The role of baseline ADC and early changes in ADC values as markers of tumor response and time to tumor progression should be determined in a large prospective study.

Perfusion imaging

Dynamic contrast-enhanced MRI (DCE-MRI) (46) and perfusion CT (47) involve the use of contrast agents with high-temporal-resolution imaging to capture changes in MR signal intensity or CT attenuation as a function of time. These changes are used to quantify tissue and tumor vascular characteristics. Perfusion CT has the advantage of

a direct linear relation between enhancement change and iodine concentration, whereas the relationship between MR signal intensity and gadolinium concentration is not necessarily linear depending on the dose of contrast injected, sequence parameters, and concentration reached in the target tissue. Although linearity can be assumed in DCE-MRI at certain concentrations, it is preferable to determine gadolinium concentration using unenhanced baseline T1 measurement. In contrast, perfusion CT is limited by the risk of radiation exposure, especially when follow-up studies are needed, and the lack of multipara-metric imaging. Multipara-metric imaging is possible only with MRI in which DCE-MRI can be combined with DWI. Recent studies using perfusion CT or DCE-MRI have shown potential for quantifying perfusion of malignant liver lesions and for monitoring treatment response to antiangiogenic drugs in HCC (48-51). Antiangiogenic agents are thought to induce an antipermeability effect while TACE reduces tumor blood volume (52). These effects result in a significant decrease in hepatic arterial fraction and perfusion in tumors effectively treated by TACE. In conclusion, as with DWI, it will be interesting to determine the role of pretreatment and early changes in tumor perfusion parameters as predictors of subsequent response to therapy and time to tumor progression. In addition, clinical utility, reproducibility, accuracy, proper modeling, and validation of perfusion CT and MRI techniques must be established.

Cone-beam CT (CBCT) imaging

Assessing treatment success during TACE is critically important as it affects treatment endpoints and consequently tumor response, local progression-free, and overall survival (53,54). The objective of post-treatment CBCT is to provide immediate assessment of tumor coverage and offer the possibility to change catheter positioning to ensure complete treatment of tumor burden and even predict tumor response (11,18,26). Incomplete tumor treatment negatively impacts survival (55,56). The imaging characteristics of different chemo-embolic agents differ substantially, thus requiring different post-treatment CBCT techniques. Lipiodol is a radiopaque contrast agent, which has also been used as a biomarker for HCC (55). Lipiodol deposition in the tumor is a prognostic factor affecting local recurrence of HCC and may be determined directly during the procedure using unenhanced CBCT, which offers equivalent lipiodol detection accuracy to unenhanced MDCT imaging (55-58). Drug-eluting beads (DEB), commonly loaded with doxorubicin, are radiolucent and so are mixed with contrast agent during delivery. These beads occlude tumor-feeding arteries from where the chemotherapy diffuses locally into the tumor (59). Assessment of DEB-TACE therefore requires the visualization of tumor-feeding vessel devascularization or tumor contrast agent saturation features on CBCT images (26,60,61). The value of immediate post-procedural CBCT scanning has been explored in several studies.

Lipiodol-CBCT (Lip-CBCT)

Lip-CBCT is a technique used to assess the lipiodol deposition into the tumor after drug delivery. This technique involves the acquisition of a CBCT scan without contrast medium injection immediately after conventional TACE treatment. Incomplete deposition of lipiodol into the tumor may be indicative of extrahepatic supply or incomplete delivery (62). Lip-CBCT imaging provides immediate feedback to the operator with lipiodol conspicuity equivalent to unenhanced multidetector CT and is predictive of tumor response when compared with 1-month follow-up multiphasic multidetector CT or contrast-enhanced MR imaging (57,58,62). The use of Lip-CBCT helps to achieve complete iodized oil filling of tumor(s) and therefore improves therapeutic effects by optimizing the embolization endpoint (62). Intra-procedural Lip-CBCT depicts HCC with 100% sensitivity compared with preprocedural diagnostic imaging (54,55).

Drug-eluting bead-CBCT (DEB-CBCT)

DEB-CBCT is a technique that involves a single non-contrast-enhanced CBCT scan after DEB-TACE to assess treatment success by visually estimating the degree of marginal contrast material saturation of the entire tumor volume, which is used as a surrogate for the beads deposition location and can help in determining the embolization endpoint. With DEB-CBCT, the positive predictive value of tumor response for marginal contrast agent saturation above 75% on DEB-CBCT images is 85% (60).

Dual-phase-CBCT (DP-CBCT)

The aim of DP-CBCT after DEB-TACE is to assess treatment success by displaying the changes in contrast enhancement of the target tumor(s) on both phases owing to tumor feeding vessel devascularization. The same protocol of the DP-CBCT technique as described

elsewhere is used also after treatment ensuring that the same microcatheter positioning and contrast agent injection protocols are used (26,27). DP-CBCT helps to assess the lack of contrast agent uptake in the tumor whereas DEB-CBCT depicts the contrast agent uptake of the tumor margins, in both cases indicating successful tumor coverage with DEB-TACE. DP-CBCT has also shown to be predictive of tumor response according to the EASL and the RECIST guidelines at 1-month follow-up contrast-enhanced MR imaging. Limited tumor enhancement changes on DP-CBCT images after DEB-TACE may suggest to the operator either the need for retreatment or to search for additional feeding arteries. Commonly, the post-DEB-TACE DP-CBCT technique displays an arterial tumor enhancement and tumor-feeding arteries on the first scan (arterial phase, 3-15-second acquisition delay), and then parenchymal tumor enhancement on the second (parenchymal phase, 28-second acquisition delay).

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Footnote

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