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Re: Baseline and Early MR Apparent Diffusion Coefficient Quantification as a Predictor of Response of Unresectable Hepatocellular Carcinoma to Doxorubicin Drug-Eluting Bead Chemoembolization

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Editor

We read with great interest the work by Kokabi et al (1) regarding the role of apparent diffusion coefficient (ADC) as a predictor of response after doxorubicin drug-eluting bead chemoembolization in patients with unresectable hepatocellular carcinoma (HCC). Evaluation of treated HCC is still a clinical challenge for radiologists and clinicians.

Recently, repeated transarterial chemoembolization with degradable starch microspheres (DSMs) was proposed to provide transient occlusion of small arteries (2). Prediction and early assessment of tumor response after locoregional or systemic therapy is essential for making therapeutic decisions. In our center, beginning in December 2013, we used DSM chemoembolization in patients with unresectable HCC and observed that repeated DSM chemoembolization was a safe and effective treatment.

Our institutional review board approved this study, and all patients gave written informed consent. Like Kokabi et al (1), we performed diffusion-weighted imaging (DWI) for prediction and early assessment of treatment response. DSM chemoembolization was performed in 20 patients, and we compared the DWI findings with those of computed tomography (CT). All treated patients were scanned by CT and diffusion-weighted magnetic resonance (MR) imaging before the beginning of repeated DSM chemoembolization (ie, baseline, time 0). The time between these two initial studies did not exceed 1 week. DWI was performed by axial-triggered free-breathing echo-planar diffusion-weighted multi-b imaging (eight b-values ranging from 0 to 750 s/mm²). DWI was then repeated within 15 days after every DSM chemoembolization treatment. CT was then performed within 30 days after each treatment. Tumor response was evaluated per modified Response Evaluation Criteria In Solid Tumors. As described by Kokabi et al (1), we defined objective response (OR) as complete response (CR) or partial response (PR). Conversely, nonresponse was

noted in targeted lesions with stable disease (SD) or progressive disease. To evaluate early response to treatment, ADC values were then calculated at baseline and within 15 days after every treatment.

Two radiologists measured mean ADC values of HCC lesions drawing in consensus a region of interest (ROI) over all HCC lesions by copying ROIs from diffusion images into ADC maps. ADC values were measured on pretreatment and posttreatment images, and values were recorded in a lesion-by-lesion analysis that included 48 lesions. Lesions with CR did not undergo subsequent treatments or MR imaging evaluation. The mean ADC value at baseline was $0.92 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.09$ for all lesions. After one treatment, CT classified seven of 48 lesions as showing CR, 23 as showing PR, and 18 as showing SD; as a result, 30 lesions were considered as having shown OR and 18 as having shown no response. Mean ADC values of CR, PR, and SD groups were $1.39 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.19$, $1.25 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.13$, and $1.10 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.12$, respectively, with a statistically significant difference between the CR group and SD group. ADC values in the CR and PR groups were significantly higher than those found at time 0.

The area under the receiver operating characteristic (ROC) curve for prediction of OR to DSM chemoembolization based on ADC values was 0.85 (95% confidence interval [CI], 0.732–0.972), with a sensitivity of 80% (95% CI, 61.43%–92.29%) and specificity of 77.78% (95% CI, 52.36%–93.59%) using an ADC value $> 1.18 \times 10^{-3} \text{ mm}^2/\text{s}$ (Fig). Like Kokabi et al (1), we observed a significant increase in ADC value in lesions in the OR group compared with nonresponding lesions after the first cycle of DSM chemoembolization. Indeed, the authors reported an AUC of 0.94 with a sensitivity of 91% and specificity of 87% (1).

Recently, Mannelli et al (3) demonstrated excellent performance of ADC for prediction of complete tumor necrosis after chemoembolization with Lipiodol (Guerbet, Roissy, France), with an area under the curve (AUC) of 0.85, sensitivity of 75%, and specificity of 88% with ADC, and no significant difference between ADC and contrast-enhanced imaging. Based on the study of Mannelli et al (3), the present data show a good correlation between postchemoembolization ADC values and necrosis on the basis of imaging. We also carried out DWI evaluation after sequential repeated DSM chemoembolization procedures. Excluding lesions with CR after each treatment, the AUC for prediction of OR to two DSM chemoembolization procedures based on ADC values was 0.87, with a sensitivity of 82.76% and specificity of 61.54% using an ADC value $> 1.27 \times 10^{-3} \text{ mm}^2/\text{s}$. Moreover after three treatments, using an ADC value of $1.37 \times 10^{-3} \text{ mm}^2/\text{s}$, the AUC was 0.91, with a sensitivity of 83.3% and specificity of 75%. We observed a decreased specificity of ADC values (from 77.78% to 61.54% after two treatments), and this reduction could be related to necrosis in the lesions. Postchemoembolization ADC values had an acceptable sensitivity but limited specificity for predicting response. Therefore, it will be interesting to predict and assess tumor response prospectively by using a multiparametric imaging approach integrating DWI and contrast-enhanced imaging or possibly perfusion-weighted imaging.

Contrary to Kokabi et al (1), we used axial-triggered free-breathing echo-planar multi-b DWI (eight b-values ranging from 0 to 750 s/mm^2), and obtained good quality images. The

possible disadvantage of a free-breathing versus a breath-hold sequence is the duration of the examination. Respiratory-triggered diffusion-weighted MR imaging has also been shown to improve liver detection compared with the breath-hold diffusion-weighted MR imaging technique. Using our protocol, with few morphologic sequences and free-breathing DWI, the entire examinations had a mean duration of approximately 12 minutes and were well tolerated by patients.

To determine ADC values, we drew an ROI on the entire lesion, including, eventually, both necrotic and vital portions of the lesions. Filipe et al (4) did not show significant difference between ROIs of different characteristics and claimed that any ROI greater than 1 cm can provide accurate ADC measurements in homogenous lesions.

In conclusion, we found that trends of early ADC increase could be a good indicator of a responding lesion after DSM chemoembolization. Therefore, DWI could be used as an option for short-term follow-up of patients with HCC following chemoembolization and could be considered as an imaging biomarker in these patients.

References

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Figure.

(a) ROC analysis demonstrates that, using an ADC value $> 1.18 \times 10^{-3} \text{ mm}^2/\text{s}$, the AUC for prediction of OR of lesions to the first DSM chemoembolization procedure is 0.85 (95% CI, 0.732–0.972), with a sensitivity of 80% (95% CI, 61.43%–92.29%) and specificity of 77.78% (95% CI, 52.36%–93.59%). (b) Box plots illustrate median (line inside the box), interquartile range (box), and minimum and maximum values (lines extending above and below the box, respectively) of ADC for OR in lesions after sequential treatment. Significant differences are observed between ADC values recorded before treatment and after the first session of DSM chemoembolization ($P = .001$). However, no significant differences are highlighted after second and third treatments. This decrease could be related to the presence of cellular necrosis inside the lesions. (c,d) ROC analysis shows a decrease in specificity of ADC values (from 77.78% to 61.54%). The AUC for prediction of OR in lesions treated with two DSM chemoembolization procedures is 0.87, with a sensitivity of 82.76% and specificity of 61.54% using an ADC value $> 1.27 \times 10^{-3} \text{ mm}^2/\text{s}$. After three DSM chemoembolization procedures, using an ADC value of $1.37 \times 10^{-3} \text{ mm}^2/\text{s}$, the AUC is 0.91, with a sensitivity of 83.3% and specificity of 75%.