

RAPID COMMUNICATION

Computed tomography perfusion in evaluating the therapeutic effect of transarterial chemoembolization for hepatocellular carcinoma

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Abstract

AIM: To prospectively assess the changes in parameters of computed tomography (CT) perfusion pre- and post-transarterial chemoembolization (TACE) of hepatocellular carcinoma (HCC) in different treatment response groups, and to correlate the changes with various responses of HCC to TACE.

METHODS: Thirty-nine HCC patients underwent CT perfusion examinations pre-(1 d before TACE) and post-treatment (4 wk after TACE). The response evaluation criteria for solid tumors (RECIST) were referred to when treatment responses were distributed. Wilcoxon-signed ranks test was used to compare the differences in CT perfusion parameters pre- and post-TACE for different response groups.

RESULTS: Only one case had treatment response to CR and the CT perfusion maps of post-treatment lesion displayed complete absence of signals. In the PR treatment response group, hepatic artery perfusion (HAP), hepatic arterial fracture (HAF) and hepatic blood volume (HBV) of viable tumors post-TACE were reduced compared with pre-TACE ($P = 0.001$, 0.030 and 0.001 , respectively). In the SD group, all CT perfusion parameters were not significantly different pre- and post-TACE. In the PD group, HAP, HAF, portal vein perfusion (PVP) and hepatic blood flow (HBF) of

viable tumors post-TACE were significantly increased compared with pre-TACE ($P = 0.005$, 0.012 , 0.035 and 0.005 , respectively).

CONCLUSION: Changes in CT perfusion parameters of viable tumors are correlated with different responses of HCC to TACE. Therefore, CT perfusion imaging is a feasible technique for monitoring response of HCC to TACE.

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Key words: Hepatocellular carcinoma; Computed tomography; Transarterial chemoembolization; Digital subtraction arteriography; Region of interest

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INTRODUCTION

Transarterial chemoembolization (TACE) has been widely accepted as a choice of treatment for advanced hepatocellular carcinoma (HCC) and shows promising results^[1-3]. The therapeutic efficacy of TACE has been evaluated by various imaging modalities. Digital subtraction angiography (DSA) is probably the most sensitive and effective imaging modality^[4,5]. However, angiography is an invasive procedure and its routine use in evaluation of therapeutic effectiveness needs justification^[5]. CT examination after TACE has been widely used to assess the efficacy of TACE^[6], but its limitation is that a quantitative evaluation cannot be provided and an incomplete lipiodol accumulation may disturb the assessment of viable tumors on contrast-enhanced CT imaging^[7].

Alternatively, CT perfusion imaging is a non-invasive technique for assessment of tissue perfusion in locally

advanced HCC^[8-10]. The response to TACE may be evaluated by comparing the difference in perfusion parameters pre- and post-treatment^[11,12].

To our knowledge, there are few reports on the application of this technique in evaluating the efficacy of TACE based on the quantitative analysis of perfusion parameters. In this study, we prospectively assessed the changes in perfusion parameters of viable tumors after TACE for different treatment response groups, and correlated the changes in CT perfusion parameters to different responses of tumors to TACE.

MATERIALS AND METHODS

Patients

Thirty-nine consecutive patients (28 men and 11 women; age range, 36-82 years; mean, 60.1 years) with histopathologically proven HCC (fine needle aspiration) referred to our center for TACE from September 2007 to June 2008 were included in the study. The average size of HCC was 6.1 ± 3.3 cm, ranging 2.5-16.5 cm. All patients underwent CT perfusion examinations pre-(1 d before TACE) and post-treatment (4 wk after TACE).

CT perfusion imaging technique

CT perfusion was performed with a 64-row multi-detector CT scanner (VCT 64 slices; GE Medical Systems). For initial localization of the tumor, a CT scan of the abdomen was performed without contrast medium during a breath hold at the end of expiration. After tumor localization, a 4-cm tumor region was selected independently for the dynamic study of the tumor maximal diameter. A dynamic study of the selected area was performed in a single breath hold at a static supine position. A total of 40-50 mL of non-iodinated contrast medium (Iohexol300, 300 mg of iodine per milliliter) was injected at a rate of 4 mL/s through an 18-gauge intravenous cannula. The following CT parameters were used to acquire dynamic data: 1-second gantry rotation time, 120 kV, 80 mA, acquisition in 264 transverse mode (64 sections per gantry rotation), and 5-mm reconstructed section thickness. The examination was repeated in all patients using the same technique before and 4 wk after TACE.

Imaging data processing

After image acquisition, the data were transferred to an image processing workstation (Advantage Windows 4.3; GE Medical Systems) and analyzed using CT Perfusion 3.0 (GE Medical Systems). For derivation of the functional maps of perfusion parameters, a reference arterial input curve was obtained by placing a region of interest (ROI) in the aorta (range, 10-15 mm²) manually, and a reference input curve of portal vein was obtained by placing a ROI in the portal vein (range, 8-12 mm²) manually. A ROI for tumor was hand drawn in a selected section in which the lesion demonstrated the maximal diameter.

The parameters generated by the software included

hepatic blood flow (HBF), hepatic blood volume (HBV), mean transit time (MTT), and permeability-surface area product (PS), hepatic arterial fraction (HAF), hepatic artery perfusion (HAP), and portal vein perfusion (PVP).

TACE technique

All TACE procedures were performed by one experienced interventional radiologist. Diagnostic arteriogram of the common, right or left hepatic artery was obtained in all patients prior to TACE. For solitary lesions in liver, TACE with superselective catheterization of the feeding hepatic artery branch was performed. Chemoembolization was performed at the common hepatic artery for multiple lesions involving both lobes of liver. After a combined chemotherapy with an average dose of epirubicin (60 mg), hydroxycamptothecin (20 mg), and fluorouracil (750 mg), an average dose of lipiodol (6 mL) with epirubicin (10 mg) mixture and/or gelfoam particles were used in our study. The total volume of emulsion was judged by the tumor size and achievement of stagnant arterial flow. Follow-up hepatic angiograms were performed in the latter sessions, 4-5 wk and 8-9 wk following the first TACE. Additional chemoembolization would be given at the same session setting if there was evidence of residual hypervascularity in hepatic arteriograms.

Statistical analysis

DSA has been recognized as the gold standard for detection of viable hepatic tumors^[5,7]. Therefore, in this study, DSA was used as the assessment method for measuring target lesions responsive to TACE. The first angiogram and follow-up angiograms in the latter sessions 4-5 wk and 8-9 wk following the first TACE were compared. The following response evaluation criteria [complete response (CR): disappearance of all target lesions; partial response (PR): at least a 30% decrease in the sum of the longest diameters (LD) of target lesions; progressive disease (PD): at least a 20% increase in the sum of the LD of target lesions; stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD]^[13] for solid tumors (RECIST) were referred to when it was necessary to assess the therapeutic effect after TACE.

All data were expressed as mean \pm SD, and statistical analysis was performed with SPSS 11.0. Wilcoxon-signed ranks test (nonparametric test) of variance was used to compare the differences in CT perfusion parameters pre- and post-TACE for different treatment response groups. $P < 0.05$ was considered statistically significant.

RESULTS

In all patients of our study cohort, only one patient who underwent a period of TACE and CT perfusion examinations pre- and post-treatment had treatment response to CR. His CT perfusion imaging of post-treatment lesion displayed complete absence of blood

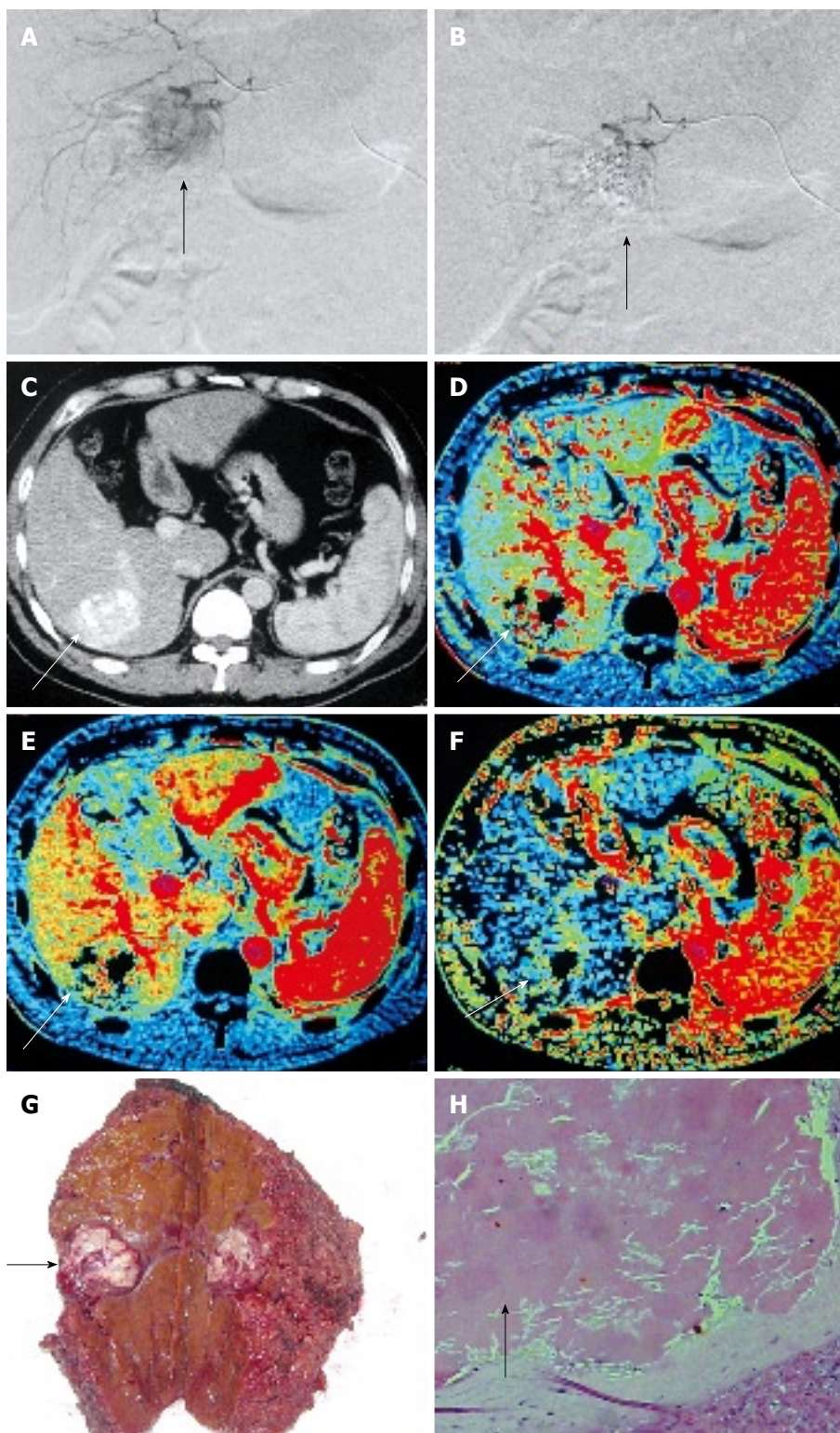


Figure 1 Images obtained in a patient with HCC verified with treatment response of PR. **A:** Pre-TACE angiography showing a tumor with a diameter of 3.5 cm in the right lobe of liver (arrow); **B:** Post-TACE angiography showing a viable region of tumor that was reduced by more than 50% compared with pre-TACE (arrow); **C:** CT image 4 wk after TACE showing an incomplete lipiodol accumulation in the viable tumor region (arrow); **D:** HBF map of post-TACE CT perfusion showing a significant decrease of HBF in the viable tumor (arrow) compared with pre-TACE; **E:** Post-TACE HBV map showing a significant decrease of HBV in the viable tumor (arrow) compared with pre-TACE; **F:** Post-TACE HAF map showing a significant decrease of HAF in the viable tumor (arrow); **G:** Small necrotic lesions observed (arrow) after two periods of TACE treatment (arrow); **H:** Pathological slides (HE staining, × 40) showing lipiodol embolism in the small vascular cavity (arrow).

perfusion on CT perfusion maps. Therefore, in the CR group, the perfusion parameters of post-treatment tumor could not be generated.

In remaining 38 HCC patients, response to treatment was observed in the PR group ($n = 14$), SD group ($n = 14$), and PD group ($n = 10$).

In the PR treatment response group, some perfusion parameters (HAP, HAF, and HBV) of HCC post-TACE were significantly reduced compared with pre-TACE (Figure 1) and significantly different pre- and post-

TACE ($P = 0.001, 0.030$ and 0.001 , respectively), while no significant difference was observed in other perfusion parameters (HBF, MTT, PS, and PVP) pre- and post-TACE (Table 1).

In the SD treatment response group, no significant difference was found in all CT perfusion parameters pre- and post-TACE (Table 1).

In the PD treatment response group, some CT perfusion parameters (HAP, HAF, PVP, and HBF) of HCC post-TACE were significantly increased compared

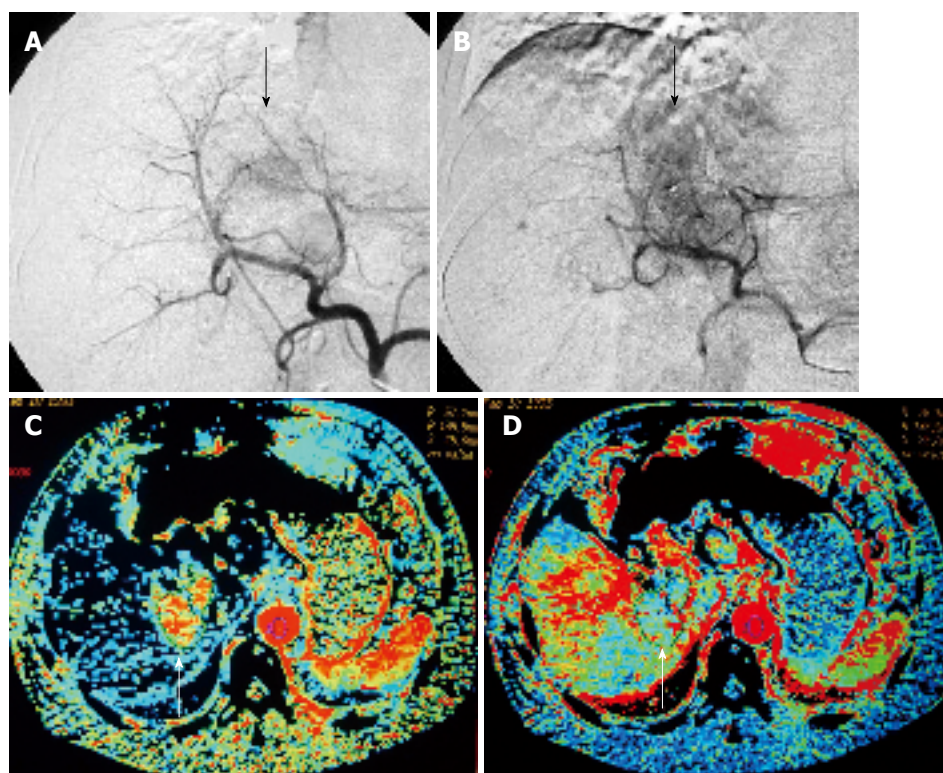


Figure 2 Images obtained from a patient with HCC with treatment response of PD group. **A:** Pre-TACE angiography showing a tumor in the left lobe of liver (arrow); **B:** Post-TACE angiography showing an increased viable tumor region by more than 25% (arrow) compared with pre-TACE; **C:** HAF map of post-TACE CT perfusion showing significantly increased HAF in the viable tumor (arrow) compared with pre-TACE; **D:** Post-TACE HBF map showing increased HBF in the viable tumor (arrow) compared with pre-TACE.

Table 1 Perfusion parameters in PR and SD group (mean ± SD)

n = 14	PR			SD		
	Pre-treatment	Post-treatment	P value	Pre-treatment	Post-treatment	P value
HBV (mL/min per 100 mL)	294.594 ± 162.104	203.941 ± 147.717	0.096	133.277 ± 111.124	205.580 ± 217.101	0.054
HBV (mL/100 mL)	37.569 ± 19.818	19.252 ± 11.847	0.001	19.399 ± 17.515	21.558 ± 21.085	0.220
MIT (s)	10.385 ± 4.747	10.687 ± 2.132	0.637	14.097 ± 4.276	12.235 ± 4.276	0.421
PS (mL/min per 100 mL)	20.066 ± 19.398	19.997 ± 22.516	0.638	27.357 ± 21.960	22.504 ± 18.439	0.310
HAF (%)	63.671 ± 20.218	38.154 ± 22.357	0.030	42.343 ± 14.025	33.793 ± 18.575	0.248
HAP (mL/min/100 mL)	201.857 ± 145.608	57.266 ± 33.537	0.001	62.621 ± 65.274	78.230 ± 76.442	0.172
PVP (mL/min/100 mL)	92.590 ± 69.771	146.681 ± 144.414	0.330	70.664 ± 50.880	127.349 ± 167.413	0.054

Table 2 Perfusion parameters in PD group (mean ± SD)

PD (n = 10)	Pre-treatment	Post-treatment	P value
HBV (mL/min per 100 mL)	178.508 ± 63.650	263.828 ± 91.731	0.005
HBV (mL/100 mL)	28.101 ± 26.862	29.978 ± 9.261	0.385
MIT (S)	9.336 ± 2.517	10.001 ± 2.457	0.798
PS (mL/min/100 mL)	33.103 ± 3.784	26.384 ± 10.544	0.092
HAF (%)	45.856 ± 41.332	69.628 ± 30.126	0.012
HAP (mL/min per 100 mL)	32.686 ± 7.145	94.200 ± 55.928	0.005
PVP (mL/min per 100 mL)	19.820 ± 5.546	33.480 ± 8.765	0.035

to pre-TACE (Figure 2) and their difference showed a statistical significance ($P = 0.005, 0.012, 0.035$ and 0.005 , respectively), while no significant difference was found in other perfusion parameters (HBV, MIT, and PS) pre- and post-TACE (Table 2).

DISCUSSION

CT perfusion is a feasible, reproducible technique for assessing tissue perfusion in locally advanced HCC^[14].

Measures of tumor perfusion have been correlated with angiogenesis and microvessel density within the tumor^[14,15]. It is logical to speculate that high perfusion values indirectly suggest a high rate of angiogenesis and microvessel density within the tumor.

However, to our knowledge, there are few studies on the role of CT perfusion in evaluating the therapeutic efficacy of TACE, although Tsushima *et al*^[11] presented their data on CT perfusion and demonstrated decreased values of HAP and HAF in viable tumors post-treatment compared with pre-treatment, which are consistent with our findings.

In our study, the number of cases collected allowed us to divide them into different treatment response groups for observation. In the CR group, CT perfusion imaging of post-TACE lesion displayed complete absence of signal on the CT perfusion maps. We observed significant differences in some CT perfusion parameters of viable tumors pre- and post-TACE in the treatment response PR and PD groups. In the PR group of HCC, after TACE treatment, the change in perfusion parameters

was consistent with previous findings^[11,16]. The decreased HBV and HBF within liver tumors indicate the reduction of vascular capacity and microvessel density, which are due to the lipiodol embolism (Figure 1G and H). Kan *et al*^[6] reported that post-embolization MTT is elongated in intrahepatic lesions of a rat model, while post-embolization PS is significantly decreased. However, we did not find any significant difference in values of MTT and PS pre- and post-treatment, which may be due to the difference in observational time windows, in which the microvascular function within tumors dynamically changes. In the SD group, the perfusion parameters remained unchanged pre- and post-TACE treatment, suggesting a perfusion recovery within the tumor after treatment. In the PD group, HBF, HAF, and HAP were increased after treatment, reflecting the increased angiogenesis and microvessel density within the liver tumor. The value of PVP was further increased in HCC of the PD group after treatment, suggesting involvement of hepatic portal vein during tumor advancement. In our study, the value of HBV was not further increased during tumor advancement, suggesting that the vascular capacity within the tumor mass has reached its limit and thus, cannot further expand. Further histological research is needed to prove this speculation.

In addition, many CT perfusion analyses were performed using a single arterial input^[8,9,15], but the liver has a dual arterial-portal blood supply, and the tumor and portal vein could not be consistently included. In our study, 64-rows multi-detector CT was introduced to offer a greater coverage (up to 4 cm), thus overcoming this limitation by including both the tumor and portal vein in dual-input analysis. The introduction of multi-detector CT has stimulated further interest in perfusion CT techniques and their future implementation in clinical practice^[14].

We believe that comparison of the results from different CT perfusion studies has to be made cautiously, as the values measured are dependent on mathematic model and pharmacokinetics of the contrast medium used. Thus, application of different models to the same data may well yield different perfusion values. It should be emphasized that our results were specific to the method of analysis and the software employed in this study.

The limitations of our study are as follows. The grouping of patients did not involve factors such as differentiation of HCC, cirrhosis, invasion of portal vein, dosage of chemotherapeutant and lipiodol, and use of gelfoam particles, all of which could influence the therapeutic response of HCC to TACE and change the CT perfusion parameters after TACE. Because the determinants for therapeutic response of HCC to TACE are complicated and numerous, this study did not take into account these determinants of therapeutic response to TACE, but rather it only correlated the changes in CT perfusion parameters with different treatment responses to TACE.

In conclusion, CT perfusion imaging can be used in the assessment of perfusion changes resulting from TACE therapy. Post-treatment changes in perfusion

parameters are correlated with different therapeutic efficacies for HCC. Thus, CT perfusion imaging is a feasible and non-invasive technique for monitoring treatment response to TACE.

COMMENTS

Background

Computed tomography (CT) perfusion imaging is a non-invasive and non-invasive technique for assessing tissue perfusion in locally advanced HCC.

Research frontiers

CT perfusion scan for patients with HCC allows assessment of perfusion changes due to transarterial chemoembolization (TACE). There are few reports on the application of this technique in evaluating the efficacy of TACE based on the quantitative analysis of perfusion parameters.

Innovations and breakthroughs

In this study, changes in parameters of CT perfusion pre- and post-TACE were observed in different treatment response groups.

Applications

CT perfusion imaging, a feasible and non-invasive technique, can be used for monitoring treatment response to TACE.

Peer review

This study reported the changes of CT perfusion parameters in different treatment response groups and provides a useful imaging modality for monitoring treatment response to HCC.

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