대한영상의학회지

Detection of Recurrent/Residual Hepatocellular Carcinoma: Single-Center Retrospective Comparative Study Between Parenchymal Blood Volume Mapping Using Cone Beam CT and Multiphase Dynamic CT
재발 또는 잔여 간세포암의 발견에서 콘빔 단층촬영을 이용한 실질혈류량 지도와 다중검출 전산화단층촬영의 비교: 단일 기관 후향적 연구

Na Rae Kim, MD[1], Ji Dae Kim, MD[2]*, Hyun Young Han, MD[1], Hee Jin Kim, MD[1]

[1]Department of Radiology, Eulji University Hospital, Eulji University, Daejeon, Korea
[2]Department of Radiology, Anyang Sam Hospital, Anyang, Korea

Purpose: To evaluate the usefulness of cone beam computed tomography (CT)-based parenchymal blood volume (PBV) mapping for the detection of marginal recurrence or residual hepatocellular carcinoma, after transcatheter arterial chemoembolization (TACE), and to compare it with multiphase dynamic CT (MDCT).
Materials and Methods: From March 2015 to October 2016, 26 patients with 49 iodized nodules who underwent TACE and a pre-interventional MDCT scan were enrolled in our study. We evaluated the diagnostic efficacies of PBV mapping using cone beam CT and MDCT in the detection of marginal recurrences or viable tumors.
Results: The sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of PBV mapping and MDCT were 100%, 96.7%, 94.7%, and 100%, and 77.9%, 93.5%, 87.5%, and 87.8%, respectively. The overall sensitivity for identifying local marginal recurrence was higher for PBV mapping than for MDCT ($p < 0.005$). The performances of PBV mapping and MDCT in the diagnosis of local marginal recurrence were significantly different ($p = 0.037$, McNemar test).
Conclusion: Compared with MDCT, PBV mapping can significantly increase the detection of marginal recurrence or residual tumor after TACE because it is free of beam-hardening artifact. PBV mapping should be considered as a feasible modality-related tool for patients who have undergone chemoembolization.

INTRODUCTION

Transcatheter arterial chemoembolization (TACE) is currently one of the most widely performed methodologies for curative and palliative treatment of hepatic malignancies (1-3). Although conventional TACE has been shown to be an efficient therapeutic modality and has led to improved survival rates, it remains unsatisfactory due to the high recurrence rate (4, 5). Therefore, the early detection of viable or recurrent tumor after chemoembolization is necessary to improve the long term out-comes and patient's prognosis (4, 6).

Several imaging modalities have been used for follow-up after chemoembolization, including computed tomography (CT), contrast-enhanced ultrasonography, and magnetic resonance imaging (MRI); these have been compared for their utility in evaluation of the therapeutic effects and detection of recurrences (5, 7). Recently, hepatocyte-specific MR contrast agents such as gadoxetic acid-enhanced MRI and the inclusion of diffusion-weighted imaging have made it possible to diagnose even small hepatocellular carcinomas (HCCs) (8). Although MRI may be

considered the optimal imaging modality because it has higher sensitivity and specificity than CT, CT still remains the "workhorse," because of its lower cost and higher availability (7, 9). However, CT has problem with the interpretation of local marginal recurrences after chemoembolization, because of beam hardening artifact due to iodized oil (9).

Recently, parenchymal blood volume (PBV) mapping using cone beam CT was introduced into the angiography suite. Cone beam CT can generate a three-dimensional data set, real time fluoroscopy, digital subtraction angiography (DSA), and tomographic images, and can achieve superior spatial resolution compared to conventional CT (10, 11). PBV mapping using cone beam CT provides information on tumor angiogenesis and allows functional analysis with the results expressed in color and free from beam hardening artifacts; this can be advantageous for the detection of marginal recurrence after TACE (1, 5).

Thus, the purpose of this study was to evaluate the feasibility of PBV mapping using cone beam CT as a follow up modality after TACE, and to compare it with multiphase dynamic CT (MDCT) in the detection of local marginal recurrence.

MATERIALS AND METHODS

Patients

This retrospective cohort study was approved by our Institutional Review Board (EMC 2018-06-008). We included 31 patients who had undergone TACE between March 2015 and October 2016. The inclusion criteria were 1) at least 18 years-of-age, 2) an interval between TACE procedures exceeding 1 month, 3) an interval between the pre-interventional follow-up CT and TACE of less than 1 month, and 4) received TACE in combination with pre interventional cone beam CT with PBV mapping.

We excluded patients, who had no previous TACE procedures ($n = 1$), received other anticancer treatment, including drug-eluted-microspheres TACE (DEM-TACE) ($n = 1$) and failed to obtain PBV mapping due to motion artifact ($n = 3$). Finally, 26 patients with 49 iodized nodules were included in this study.

The baseline characteristics of the 26 patients are presented in Table 1. All patients had preserved underlying liver function (Child-Pugh class A diseases). The mean interval between the pre-interventional follow-up CT and chemoembolization was

19 days (range, 1−30 days).

Multidetector CT

All patients underwent multiphasic CT before TACE. The CT

Table 1. Baseline Characteristics of the Patients with Hepatocellular Carcinomas

Demographics	Value
Patients (*n*)	26
Iodized nodules evaluated (*n*)	49
Age (years)	65.38 (44−79)
Sex	
Male	17
Female	9
Etiology	
HBV	15
HCV	6
Alcohol	5
Other	0
Child-Pugh class	
A	26
Serum tests	
Basal AFP (ng/mL)	52.77
Albumin (g/dL)	3.88
INR	1.16
Bilirubin (mg/dL)	0.97
Interval between last CT and TACE (day)	19 (1−30)

Values are number or mean (range).
AFP = alpha fetoprotein, CT = computed tomography, HBV = hepatitis B virus, HCV = hepatitis C virus, INR = international normalized ratio

Table 2. Diagnostic Performance of CT and PBV Mapping

Performance Measure	CT	PBV Mapping	*p*–Value
Sensitivity (%)	77.9	100	0.004
Specificity (%)	93.5	96.7	0.317
PPV (%)	87.5	94.7	
NPV (%)	87.8	100	

CT = computed tomography, NPV = negative predictive value, PBV = parenchymal blood volume, PPV = positive predictive value

Table 3. Comparisons between CT and PBV Mapping for Detection of Marginal Recurrence

	HCC (True +)	HCC (True −)
CT		
Positive	14	2
Negative	4	29
PBV mapping		
Positive	18	1
Negative	0	30

CT = computed tomography, HCC = hepatocellular carcinomas, PBV = parenchymal blood volume

was performed by using a 128-row CT scanner (SOMATOM Definition AS; Siemens, Erlangen, Germany) with the following scan parameters: detector configuration = 128 × 0.6, tube voltage = 120 kVp, gantry rotation time = 0.3 seconds, pitch = 0.6, slice thickness = 3 mm.

All patients received 1.5 mL/kg body weight of Iohexol 350 (Iobrix 350; Taejoon Pharmaceuticals Co. Ltd, Seoul, Korea), intravenously by using a dual-chamber mechanical power injector (Stellant; Medrad Inc., Indianola, PA, USA) at a rate of 3 mL/s through an 18-gauge intravenous catheter inserted into an

antecubital vein. The scan delay before initiation of arterial-phase imaging was determined by means of bolus tracking with automated scan triggering (CARE Bolus; Siemens). Arterial-phase scanning began automatically 10 seconds after a trigger threshold of 100 Hounsfield unit was reached in the abdominal aorta.

PBV Mapping Using Cone Beam CT

The cone beam CT-based PBV mapping was performed using a dedicated workstation (Artis Q ceiling VD10; Siemens) in an interventional procedure room, before the TACE procedure.
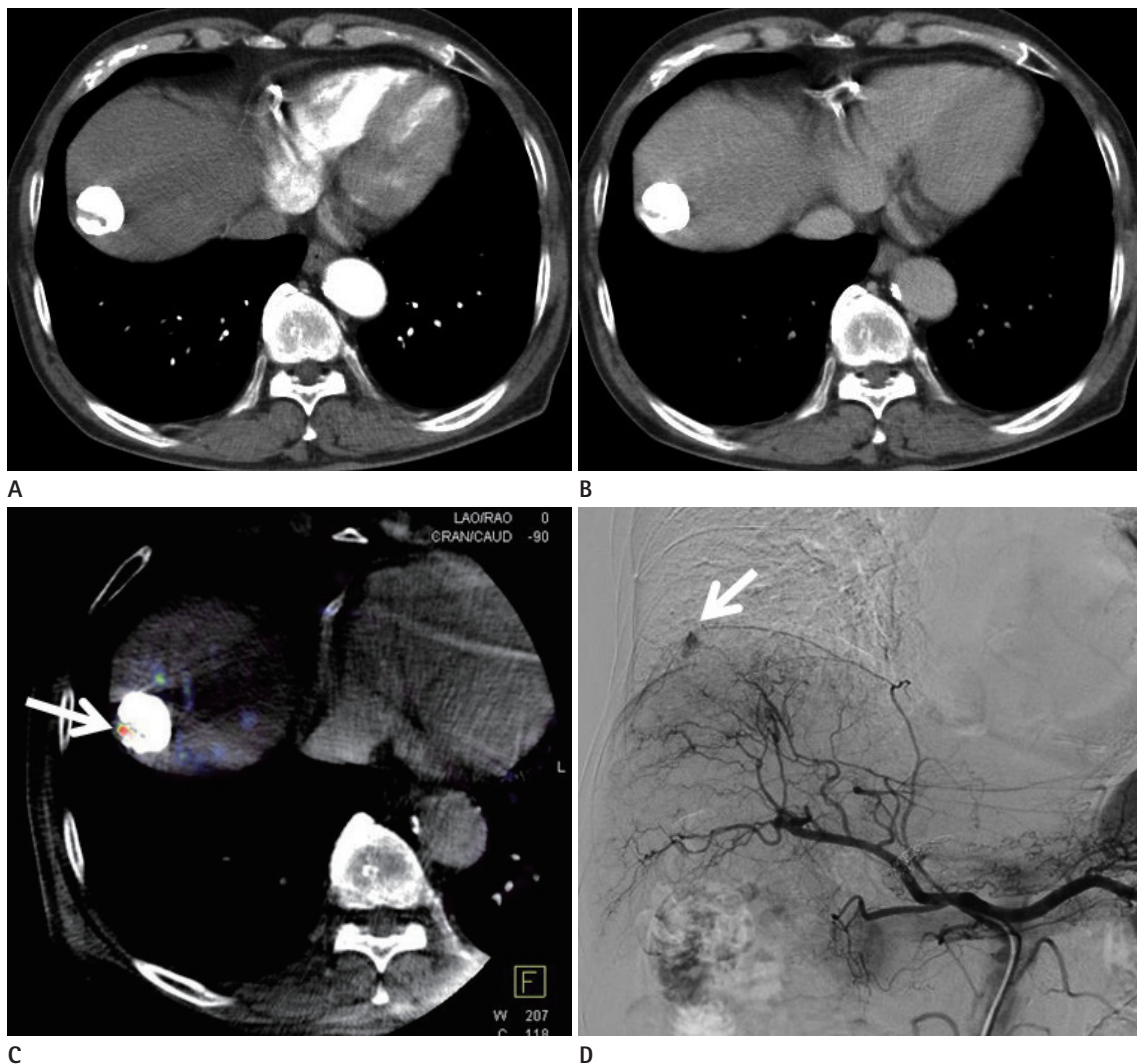

Fig. 1. A 71-year-old male patient who had undergone a single transarterialchemoembolization treatment.
A. Axial image of the arterial-phase CT scan show a tiny defect at the margin of the iodized oil-containing nodule at S8 of the liver, although no significant enhancing portion was seen.
B. Axial images of the delay-phase CT scan show a tiny defect at the margin of the iodized oil-containing nodule at S8 of the liver, although no significant wash-out portion was seen.
C. Parenchymal blood volume mapping using cone beam CT shows increased blood flow (arrow).
D. Selective arteriogram demonstrating an enhancing residual marginal tumor (arrow).
CT = computed tomography

The acquisition consisted of two rotations during a single breath hold. After an initial rotation of 6 seconds for the mask run, contrast injection was started immediately, with the C-arm rotating back and running a second rotation (fill run) that took 12 seconds. Using a power injector, a nonionic contrast medium (Pamiray® 300; Dongkook Pharmaceutical, Seoul, Korea) was intra-arterially injected with a microcatheter at a rate of 4 mL/s.

The following parameters were used for the acquisitions: acquisition time 5 seconds, 90 kV, 512 × 512 matrix, projection to a 30 × 40 cm flat panel size, 200° total angle, 0.8°/frame, 248 frames in total, detector entrance dose 0.36 μGy/frame. PBV post-processing was performed on a separate workstation (Syngo X Workplace VC10; Siemens).

We followed a previously described post-processing work flow (12). The mask and fill run were reconstructed and subtracted, with motion between the two runs being corrected by a non-rigid registration algorithm. The value of the arterial input function was calculated from an automated histogram analysis of the vessel. The arterial input value was then applied as a scaling factor. In a final step, a smoothing filter was applied to re-
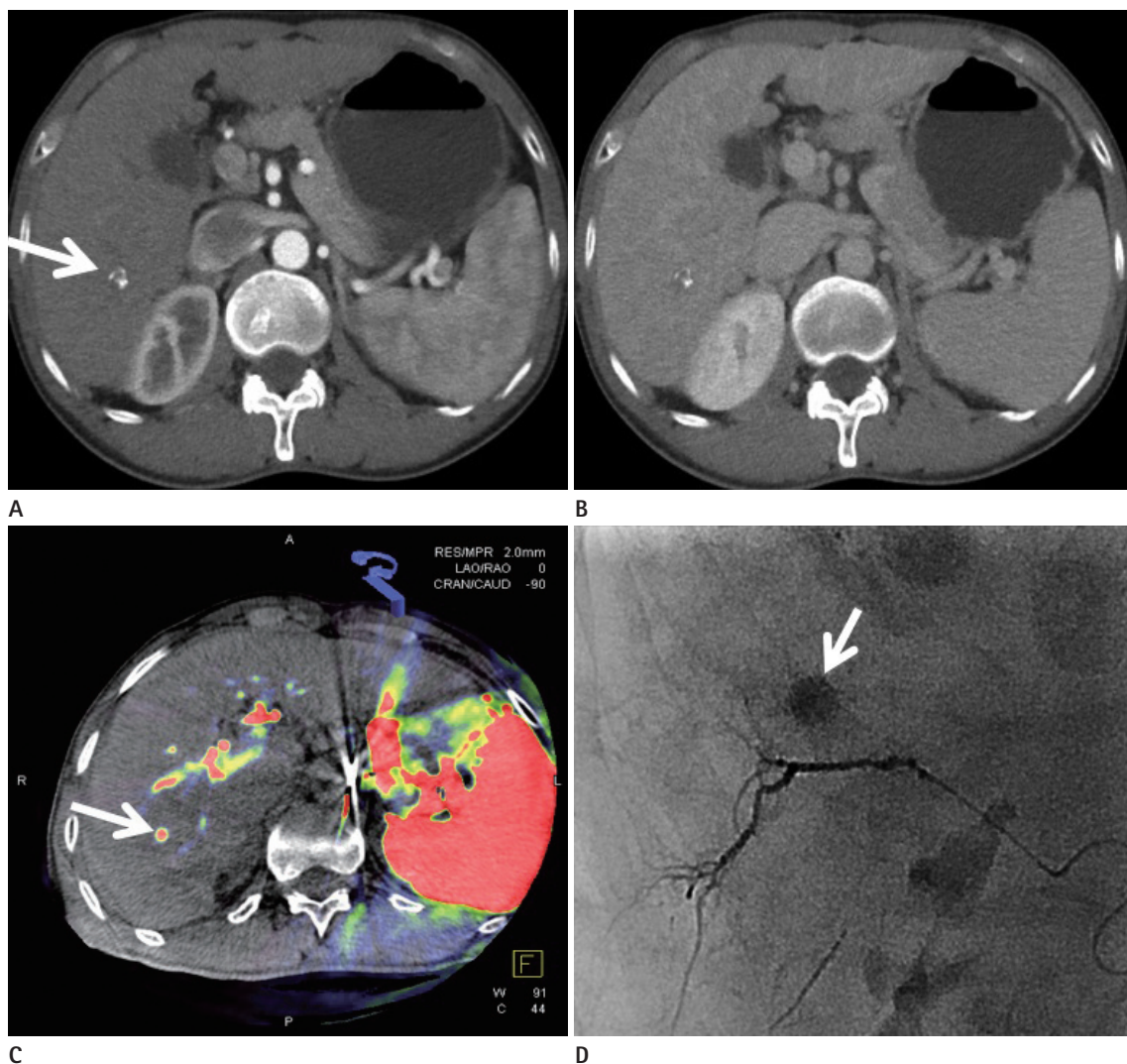

Fig. 2. A 54-year-old male patient who had undergone a single transarterial chemoembolization treatment.
A. Axial images of the arterial-phase CT scan show defect within the iodized nodule at S6 of the liver, but no definite enhancing viable tumor focus was visible (arrow).
B. Axial images of the delay-phase CT scan show defect within the iodized nodule at S6 of the liver, but no definite wash-out portion is seen.
C. Parenchymal blood volume mapping using cone beam CT shows an area of increased blood flow (arrow).
D. After selective chemoembolization to a branch of the S6 artery, the viable tumor is confirmed by uptake of dense iodized oil (arrow).
CT = computed tomography

duce pixel noise. The PBV was then visualized with a color map.

Procedure of TACE

All transarterial chemoembolization procedures were performed by an interventional radiologist with more than 5 years of experience. After the cone beam CT, superselective chemoembolization was performed by injecting a mixture of iodized oil (Lipiodol; Andre Guerbet, Aulnay-Sous-Bois, France) and doxorubicin hydrochloride (Adriamycin; Kyowa Hakko, Tokyo, Japan) until stasis was achieved. Gelatin sponge particles (Cali-Gel®; Alicon Pharm SCI&TEC Co., Ltd., Hangzhou, China) were used for embolization, if required. Finally, completion angiography from the common hepatic artery was performed.

Data Analysis

The CT images were interpreted independently by two hepatobiliary radiologists with more than 5 years of experience in abdominal imaging. Assessment of marginal recurrence on CT was based on the following criteria: 1) a newly developed arterial enhancing lesion at the margin of a previous iodized nodule, 2) a focal defect within an iodized nodule with enhancement seen on the arterial phase.

The PBV maps were evaluated by one interventionist and one resident. Assessment of marginal recurrence on the PBV map was considered if a lesion had higher blood flow (colored to represent express blood flow) than that of the normal liver tissue. The confirmation of a viable margin or recurred tumor was considered according to a dense accumulation of oil during
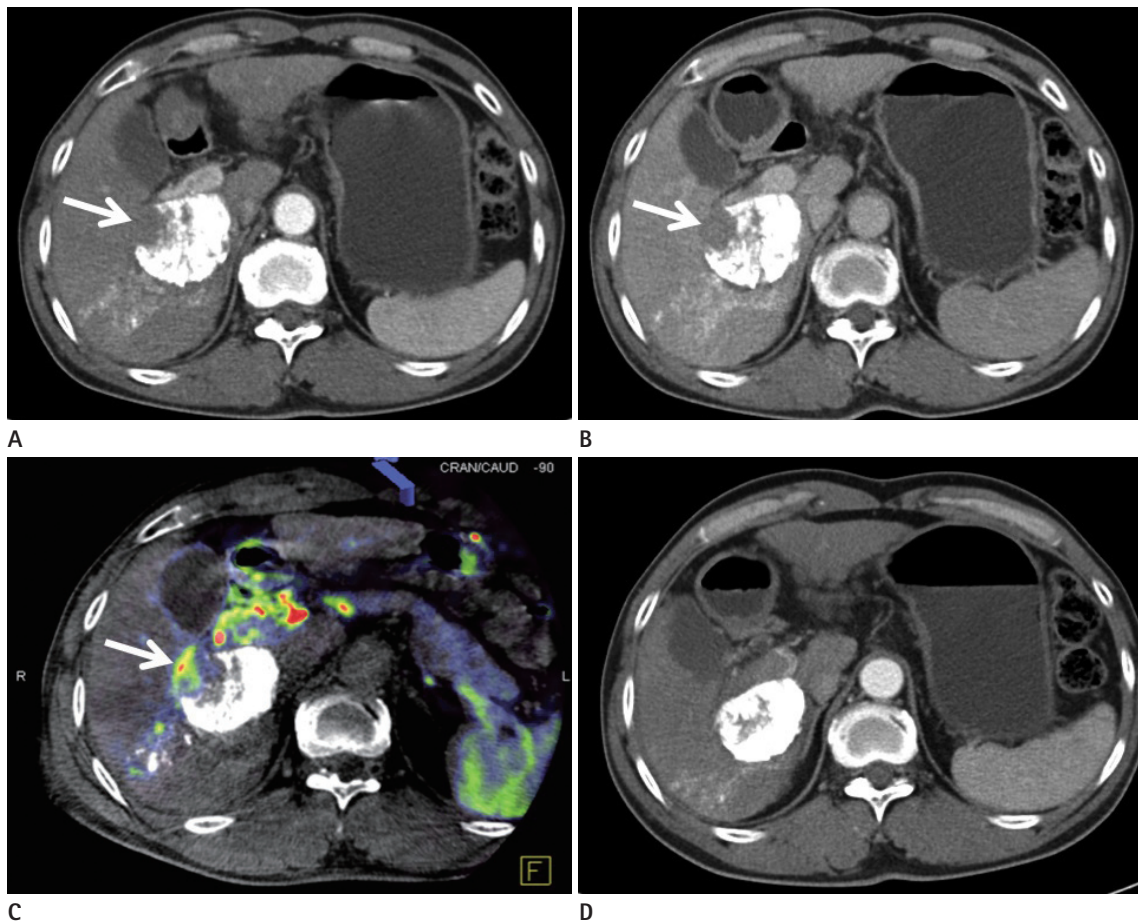

Fig. 3. A 48-year-old male patient who had undergone a single transarterial chemoembolization treatment.
A, B. Axial images of the arterial and delayed phase CT scan images show large defects within the iodized nodule, but no definite enhancing viable tumor focus is visible (arrows).
C. Parenchymal blood volume mapping using cone beam CT shows an area of increased blood flow (arrow).
D. After transarterial chemoembolization, the follow up CT shows lipiodol uptake at a previously defective area that was confirmed as viable tumor.
CT = computed tomography

chemoembolization and/or positive lipiodol uptake on CT after TACE.

The sensitivity, specificity, positive and negative predictive values for the detection of marginal recurrence or viable tumor were calculated for each imaging modality.

The statistical significances of differences between CT and PBV map results were assessed using McNemar's test. All statistical analyses were performed using SPSS software (version 20.0; IBM Corp., Armonk, NY, USA).

RESULTS

Of the two modalities, PBV mapping had higher sensitivity, specificity, and positive and negative predictive values than CT for the detection of marginal recurrence of HCC. The sensitivity and negative predictive value of PBV mapping were 100%. Sensitivity showed statistically significant differences between the two modalities ($p < 0.005$) (Table 2).

In the 4 tumors with incorrect negative MDCT results, the PBV mapping accurately depicted the tumors (Table 3, Figs. 1–3). The McNemar's test showed a statistically significant difference for detection of marginal recurrence between the two modalities ($p = 0.037$).

One tumor identified on PBV mapping showed no enhancement on arterial phase on MDCT and no lipiodol uptake on TACE. This lesion remained untreated but at 6 months, lesion showed strong arterial enhancement with delayed washout and increased in size on MDCT. And proved to be a recurrent tumor on TACE (Fig. 4).
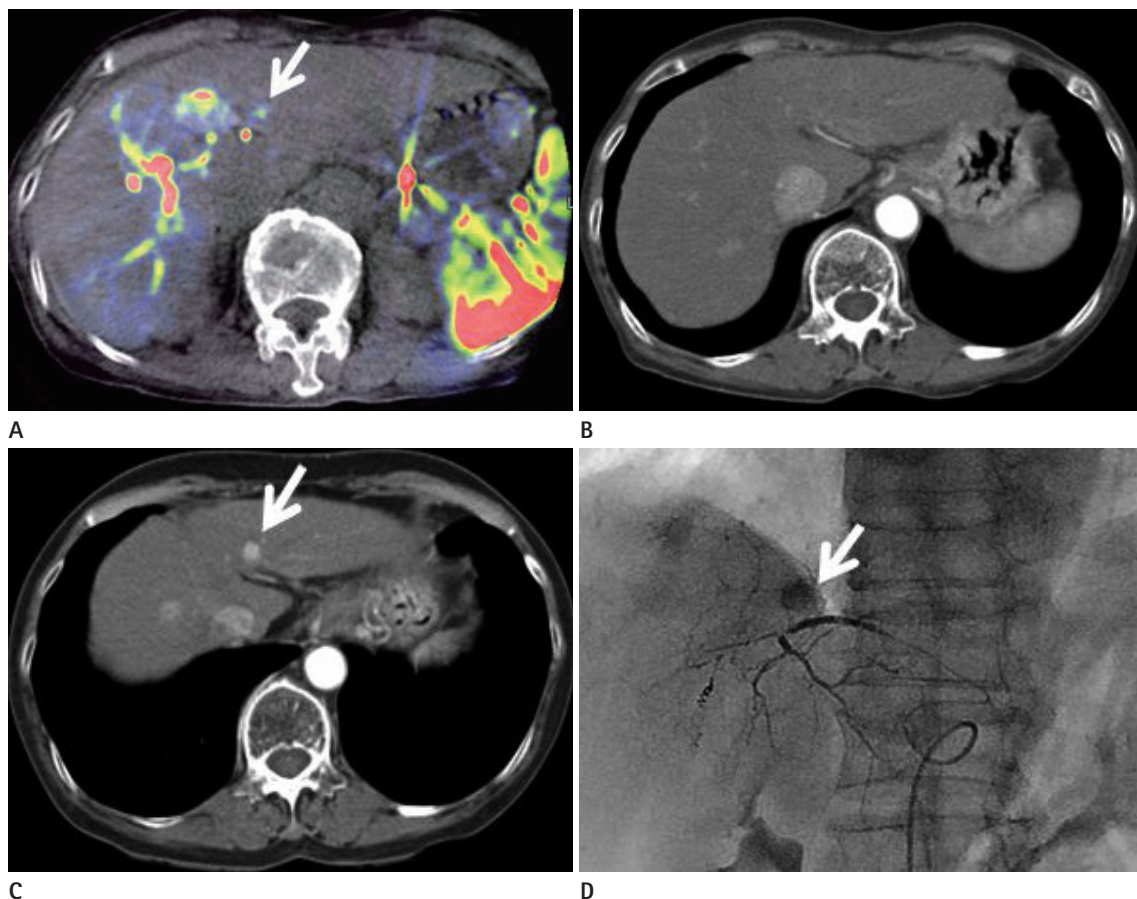

Fig. 4. A 65-year-old female patient who had undergone fourth transarterial chemoembolization treatment.
A. Parenchymal blood volume mapping using cone beam CT shows an area of increased blood flow (arrow).
B. Axial images of the arterial phase CT scan image show no arterial enhancement.
C. 6 months later, arterial phase CT scan image show arterial enhancement (arrow).
D. After selective chemoembolization to a branch of the S3 artery, the viable tumor is confirmed by uptake of dense iodized oil (arrow).
CT = computed tomography

DISCUSSION

In this study, PBV mapping using cone beam CT was successfully used to distinguish marginal recurrences after TACE. It was also shown to be more successful in the diagnosis of local marginal recurrence than MDCT ($p = 0.037$), with detection of some newly developed HCCs that were not apparent on CT. PBV mapping also showed higher sensitivity, specificity, and positive and negative predictive values. We also showed statistically significant differences in sensitivity and diagnostic accuracy between the two modalities.

One of the important features of HCC is an increase in arterial vascularization (13). CT and MRI may be inadequate for detecting such changes in tumor vascularity (14), and CT has limitations due to beam hardening artifacts. Perfusion CT provides acceptable image quality and has been reported as being a useful tool for the assessment of liver tumor vascularity (15) and the monitoring and prediction of treatment responses to early antiangiogenic treatments (16, 17).

Blood volume imaging with cone beam CT can also display similar features to perfusion CT, and has been shown to correlate very highly with it (18).

PBV mapping using cone beam CT has the disadvantage of having motion artifact and high radiation dose, caused by long rotation time, but it has more advantages.

Cone beam CT can enable direct monitoring, and can supply additional information from DSA imaging; this could impact decision making during chemoembolization through the improved detection of tumors (19). Lucatelli et al. (20) reported that cone beam CT showed a greater diagnostic performance compared with MDCT in the detection of hypervascular nodules that were subsequently diagnosed to be HCCs.

There were several limitations to this study. First, this study was performed at a single academic medical center and all patients were classified as Child-Pugh class A; this may have created a selection bias. Second, imaging findings considered as recurrences or viable tumors were not confirmed by histopathology, and accurate correlations of imaging and histopathologic findings were not made; this could have led to overestimation of recurrence. Third, compared with CT perfusion, which can provide various perfusion parameters such as arterial liver perfusion, portal venous perfusion and hepatic perfusion index, only blood volume can be assessed with PBV mapping using cone beam CT. Fourth, the PBV mapping using cone beam CT was performed an average of 19 days after the CT. This interval could have led to the development of HCC lesions in between acquisitions. Last, PBV mapping needs femoral artery puncture which is invasive procedure, this could be limitation on its use for diagnostic purpose.

In conclusion, our study demonstrates that PBV mapping using cone beam CT is a feasible modality-related tool for patients who have previously undergone chemoembolization, with it being more reliable than conventional CT for the detection of marginal recurrence.

REFERENCES

1. Vogl TJ, Schaefer P, Lehnert T, Nour-Eldin NE, Ackermann H, Mbalisike E, et al. Intraprocedural blood volume measurement using C-arm CT as a predictor for treatment response of malignant liver tumours undergoing repetitive transarterial chemoembolization (TACE). *Eur Radiol* 2016; 26:755-763

2. Yu JS. Hepatocellular carcinoma after transcatheter arterial chemoembolization: difficulties on imaging follow-up. *Korean J Radiol* 2005;6:134-135

3. Kim SH, Lee WJ, Lim HK, Lim JH. Prediction of viable tumor in hepatocellular carcinoma treated with transcatheter arterial chemoembolization: usefulness of attenuation value measurement at quadruple-phase helical computed tomography. *J Comput Assist Tomogr* 2007;31:198-203

4. Choi SJ, Kim J, Seo J, Kim HS, Lee JM, Park H. Parametric response mapping of dynamic CT for predicting intrahepatic recurrence of hepatocellular carcinoma after conventional transcatheter arterial chemoembolization. *Eur Radiol* 2016; 26:225-234

5. Choi SH, Chung JW, Kim HC, Baek JH, Park CM, Jun S, et al. The role of perfusion CT as a follow-up modality after transcatheter arterial chemoembolization: an experimental study in a rabbit model. *Invest Radiol* 2010;45:427-436

6. Lee JK, Chung YH, Song BC, Shin JW, Choi WB, Yang SH, et al. Recurrences of hepatocellular carcinoma following initial remission by transcatheter arterial chemoembolization. *J Gastroenterol Hepatol* 2002;17:52-58

7. Kubota K, Hisa N, Nishikawa T, Fujiwara Y, Murata Y, Itoh S, et al. Evaluation of hepatocellular carcinoma after treatment with transcatheter arterial chemoembolization: comparison of Lipiodol-CT, power Doppler sonography, and dynamic MRI. *Abdom Imaging* 2001;26:184-190

8. Choi JW, Kim HC, Lee JH, Yu SJ, Cho EJ, Kim MU, et al. Cone beam CT-guided chemoembolization of probable hepatocellular carcinomas smaller than 1 cm in patients at high risk of hepatocellular carcinoma. *J Vasc Interv Radiol* 2017;28:795-803.e1

9. Hunt SJ, Yu W, Weintraub J, Prince MR, Kothary N. Radiologic monitoring of hepatocellular carcinoma tumor viability after transhepatic arterial chemoembolization: estimating the accuracy of contrast-enhanced cross-sectional imaging with histopathologic correlation. *J Vasc Interv Radiol* 2009;20:30-38

10. Kim HC. Role of C-arm cone-beam CT in chemoembolization for hepatocellular carcinoma. *Korean J Radiol* 2015;16:114-124

11. Lee IJ, Chung JW, Yin YH, Kim HC, Kim YI, Jae HJ, et al. Cone-beam CT hepatic arteriography in chemoembolization for hepatocellular carcinoma: angiographic image quality and its determining factors. *J Vasc Interv Radiol* 2014;25:1369-1379; quiz 79-e1

12. Ahmed AS, Zellerhoff M, Strother CM, Pulfer KA, Redel T, Deuerling-Zheng Y, et al. C-arm CT measurement of cerebral blood volume: an experimental study in canines. *AJNR Am J Neuroradiol* 2009;30:917-922

13. Kaufmann S, Horger T, Oelker A, Kloth C, Nikolaou K, Schulze M, et al. Characterization of hepatocellular carcinoma (HCC) lesions using a novel CT-based volume perfusion (VPCT) technique. *Eur J Radiol* 2015;84:1029-1035

14. Bayraktutan Ü, Kantarci A, Oğul H, Kizrak Y, Özyiğit Ö, Yüceler Z, et al. Evaluation of hepatocellular carcinoma with computed tomography perfusion imaging. *Turk J Med Sci* 2014;44:193-196

15. Sahani DV, Holalkere NS, Mueller PR, Zhu AX. Advanced hepatocellular carcinoma: CT perfusion of liver and tumor tissue--initial experience. *Radiology* 2007;243:736-743

16. Petralia G, Fazio N, Bonello L, D'Andrea G, Radice D, Bellomi M. Perfusion computed tomography in patients with hepatocellular carcinoma treated with thalidomide: initial experience. *J Comput Assist Tomogr* 2011;35:195-201

17. Jiang T, Kambadakone A, Kulkarni NM, Zhu AX, Sahani DV. Monitoring response to antiangiogenic treatment and predicting outcomes in advanced hepatocellular carcinoma using image biomarkers, CT perfusion, tumor density, and tumor size (RECIST). *Invest Radiol* 2012;47:11-17

18. Zhuang ZG, Zhang XB, Han JF, Beilner J, Deuerling-Zheng Y, Chi JC, et al. Hepatic blood volume imaging with the use of flat-detector CT perfusion in the angiography suite: comparison with results of conventional multislice CT perfusion. *J Vasc Interv Radiol* 2014;25:739-746

19. Pung L, Ahmad M, Mueller K, Rosenberg J, Stave C, Hwang GL, et al. The role of cone-beam CT in transcatheter arterial chemoembolization for hepatocellular carcinoma: a systematic review and meta-analysis. *J Vasc Interv Radiol* 2017;28:334-341

20. Lucatelli P, Argirò R, Ginanni Corradini S, Saba L, Cirelli C, Fanelli F, et al. Comparison of image quality and diagnostic performance of cone-beam CT during drug-eluting embolic transarterial chemoembolization and multidetector CT in the detection of hepatocellular carcinoma. *J Vasc Interv Radiol* 2017;28:978-986

재발 또는 잔여 간세포암의 발견에서 콘빔 단층촬영을 이용한 실질혈류량 지도와 다중검출 전산화단층촬영의 비교 : 단일 기관 후향적 연구

김나래[1] · 김지대[2]* · 한현영[1] · 김희진[1]

목적: 경동맥화학색전술 후 재발 또는 잔여 간세포암 발견에 있어서, 콘빔 단층촬영을 이용한 실질혈류량 지도와 다중검출 전산화단층촬영을 비교하고 실질혈류량 지도의 유용성을 평가하고자 하였다.

대상과 방법: 2015년 5월부터 2016년 10월까지 이전에 경동맥화학색절술을 시행 받고 추적 다중검출 전산화단층촬영을 받은 26명의 환자의 총 49개의 색전된 결절을 대상으로 후향 연구를 시행하였다. 실질혈류량 지도와 다중검출 전산화단층촬영의 간세포암의 발견에 있어 진단적 정확도를 비교 분석하였다.

결과: 색전된 58개 결절에서 실질혈류량 지도의 간세포암 진단 민감도, 특이도, 양성 예측도, 음성 예측도는 각각 100%, 96.7%, 94.7%, 100%이었고 다중검출 전산화단층촬영의 민감도, 특이도, 양성 예측도, 음성 예측도는 77.9%, 93.5%, 87.5%, 87.8%였다. 콘빔 단층촬영을 이용한 실질혈류량 지도의 민감도가 의미 있게 높았으며($p < 0.005$) 간세포암 발견율에 두 검사 간 유의한 차이를 보였다($p = 0.037$, McNemar test).

결론: 실질혈류량 지도의 경우 선속 경화현상이 없기 때문에 이전에 경동맥화학색전술을 시행 받은 환자에서 재발 또는 잔여 간세포암 발견에 있어서 다중검출 전산화단층촬영보다 유용할 것으로 생각된다.

[1]을지대학교 의과대학 을지대학교병원 영상의학과, [2]안양샘병원 영상의학과