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• LIVER CANCER •

Assessment of hepatocellular carcinoma vascularity before and after transcatheter arterial chemoembolization by using first pass perfusion weighted MR imaging

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Abstract

AIM: To assess the vascularity of hepatocellular carcinoma (HCC) before and after transcatheter arterial chemoembolization (TACE) with the quantitative parameters obtained by first pass perfusion weighted MR imaging (FP-MRI).

METHODS: Seventeen consecutive patients with one to three lesions in liver underwent FP-MRI before treatment. FP-MRI was also performed one, three, six, nine months, and one year after TACE. The baseline signal intensity (S0) of pre-TACE and one month after TACE was analyzed, the vascularity of HCC assessed by steepest slope of the signal intensity versus time curves (SS) was blindly correlated with their DSA feature and clinical outcome.

RESULT: No significant difference was found on baseline signal intensity (S0) between pre-TACE and one month after TACE (F=0.309, P=0.583), The SS (mean, 32% per second) of lesion one month after TACE was lower than that of pre-TACE (mean, 69% per second), but with no statistical significance (F=3.067, P=0.092). When local recurrence occurred, the time intensity curves became steeper. The vascularity of HCC before and after TACE graded by SS closely correlated with that by DSA (K=0.453, P<0.05).

CONCLUSION: FP-MRI is a useful criterion for selecting effective interventional treatment for patients with HCC in their initial treatment and during follow up.

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INTRODUCTION

Transcatheter arterial chemoembolization (TACE) has been applied as an effective therapy to improve the survival rate in unresectable hepatocellular carcinoma (HCC) and to decrease the recurrence of resected HCC[1,2]. The efficacy of TACE usually depends on the vascularity (arterial blood supply) of HCC, that is, when HCC with hypervascularity, TACE is effective, otherwise, the efficacy of TACE is poor[3,4], other ablation methods such as percutaneous radiofrequency and percutaneous ethanol injection are needed[5-8]. Furthermore, since TACE is difficult to kill the entire tumor cells at one time, and it is generally used repeatedly or in combination with other ablation modalities. So it is essential to evaluate the tumor vascularity and its distribution before TACE and during follow up. Angiography is the golden standard to evaluate the tumor vascularity, but it is an invasive technique and is therefore not suitable for routine follow up. Generally, computed tomographic (CT) images could be considered as a routine modality to judge the efficacy of TACE depending upon the homogeneous and completely deposition of lipiodol within the lesion, but previous results indicated that even in lipiodol retention area there were viable tumor cells[9]. So it is difficult to access the viability and necrosis of the tumor correctly depending upon the deposition of lipiodol. On the other hand, viable tumors could be enhanced on CT contrast scanning[10,11], but the enhancement area within the lesions could also be affected by artifacts of the high concentrations of lipiodol, which could somewhat disturb the evaluation of vascularity during follow up. Although power Doppler ultrasonography was used to assess tumor vascularity, the detected velocities in the tumor were too slow to be detected, there were too many blooming artifacts associated with micro-bubble injection as well as artifacts resulted from respiration, and the duration of enhancement was short. So vascularity of tumors can not be evaluated in detail by power Doppler US[12,13].

T1 weighted FP-MRI with excellent temporal resolution (more than one imaging per second) has been used to assess tumor angiogenesis of uterine cervical carcinoma, and has a good correlation with microvessel density (MVD)[14]. The purpose of this study was to monitor the angiogenesis of HCC before and after TACE by FP-MRI compared with angiography and patient outcome, and to find out its feasibility and value in assessing vascularity of HCC.

MATERIALS AND METHODS

Between December 2000 and March 2002, patients with HCC included in this study fulfilled the following criteria, namely three or less HCC nodules and no portal thrombosis or extrahepatic metastasis. Seventeen patients (15 males, 2 females) were enrolled in this study. The age was 31-69 years, mean 48.5 years. The diagnosis of HCC was confirmed by fine needle biopsy.

Digital subtraction angiography (DSA) was performed through the celiac or hepatic artery, HCC were classified into the following 3 groups on the basis of vascularity by two angiographers independently who had no information on the current study: Grade A, tumors with more vascularity than nontumorous hepatic parenchyma; Grade B, tumors with vascularity similar to that of nontumorous hepatic parenchyma; and Grade C, tumors with less vascularity than Grade B tumors.

TACE was performed by injection of 8-10 mg mitomycin C mixed 30-50 mg doxorubicin and 10 mL of lipiodol (Guerbet,

Roissy, France) in either the right or left segmental branch of hepatic artery. Embolization was subsequently completed with gelform powder and a small amount of contrast medium under fluoroscopic guidance.

Before TACE and one, three, six, nine months, and one year after first TACE, patients with HCC underwent MR imaging by using a 1.5 T system (Magnetom Vision, Siemens Medical Systems) with a phased array coil, including T1WI (TR=525 ms, TE= 14 ms), T2WI (TR= 4.4 ms, TE=90 ms) and FP-MRI scanning. T1WI and T2WI were used to identify the satisfactory plan and section for perfusion study. For the FP-MRI, a strong T1-weighted, turbo-FLASH sequence was used with a high temporal resolution of 1.196 s per section, two axial or coronal images (TR=3.3 ms, TE=1.4 ms, TI=300 ms) were acquired sequentially with 65 repetitions. At the end of the 4th acquisition, a total dose of 0.1 mmol/kg body mass of gadopentetate dimeglumine (Bellona, Beijing, China) was administered intravenously; 10 mL of saline was immediately flushed to ensure completely delivery of the entire dose of gadopentetate dimeglumine.

To quantitative analysis of FP-MRI, four circular region of interesting (ROI) were drawn, signal intensity time curve was obtained over ROI, the baseline signal intensity (S0) of pre-TACE and one month after TACE (that is, the signal on FP-MRI without gadopentetate dimeglumine) and the steepest slope of the curve (SS) were calculated according to previous method[14]. When the nodules were similar to that of nontumorous hepatic parenchyma, they were classified into group II, while the nodules had larger or smaller SS than those of nontumorous hepatic parenchyma, and they were classified into group I or group III respectively.

All data were expressed as mean±SD, comparison was made by ANOVA, and the correlation between SS and DSA was assessed by Kappa statistic analysis. Significance was accepted when $P<0.05$.

RESULTS

Lesion signal intensity characteristics before and after TACE

MR studies were performed 53 times in 17 patients, twenty-nine lesions were evaluated, the mean size of which was 6 cm (range, 2-16 cm). Almost all the lesions assessed before TACE were hypo- to isointense relative to the surrounding liver parenchyma on T1-weighted images, and the most portion of tumors was iso- to hyperintense relative to the surrounding liver parenchyma on T2-weighted images, and the heterogeneous signal intensity was observed when liquefied necrosis or fat degeneration occurred. All the lesions demonstrated inhomogeneous enhancement on the FP-MRI. One month after TACE, all the lesions also demonstrated hypo- to isointense relative to the surrounding liver parenchyma on T1-weighted images. The signal intensity became higher on T2-weighted images compared to that of pre-TACE. No significant difference was found on S0 between pre-TACE and one month after TACE (F=0.309, P=0.583) (Table 1), only rim enhancement was found on FP-MRI in all the patients.

Quantitative analysis of HCC angiogenesis before and after TACE

Time intensity curves derived from ROIs drawn in the most-enhancing portion of the tumor before TACE showed different enhancement patterns: Type A (10 cases, 59%) showed a rapid initial increase in signal intensity followed by a plateau, representing hypervascularity. Type B (7cases, 41%), however, showed a slow initial increase in signal intensity followed by a plateau, indicating mild hypervascularity or hypovascularity of the tumor (Figure 1). The SS (mean, 40%) in three patients with arterioportal shunting associated with HCC was lower than the mean value of total patients (mean, 69% per second).

After TACE, Time intensity curves drawn in the rim-enhancing portion of the tumor showed less steep (mean SS, 32% per second), and its central area demonstrated a horizontal line. No significant difference was found on SS obtained in rim-enhancing portion of the lesions between pre-TACE and post–TACE (F=3.067, P=0.092) (Table 1).When local recurrence occurred (2 cases), Time intensity curves became steeper than the previous ones (Figure 2). There was a good co1rrelation between SS and DSA in assessment of the vascularity of HCC (K=0.453, P<0.05) (Table 2).

Table 1 SS (% per second) and S0 of HCC before and after TACE

	cases	mean	minimum	maximum	F	P
SS						
Pre-TACE	17	69	37	101	3.067	0.092
After-TACE	15	32	11	52		
S0						
Pre-TACE	17	14.04	6.76	21.32	0.309	0.583
After-TACE	15	16.94	9.72	24.12		

Table 2 Relationship of DSA and SS in assessment of vascularity

DSA[1]	SS		
	I	II	III
A	7	2	1
B	2	8	0
C	5	0	3

[1]K=0.453, P<0.05 *vs* SS.

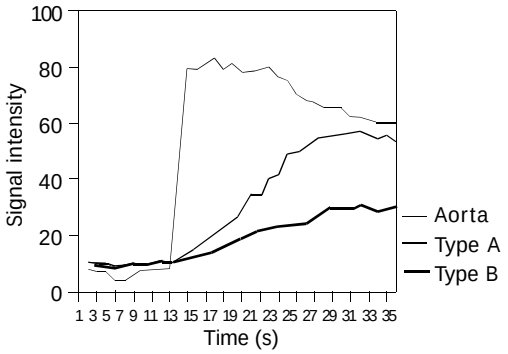
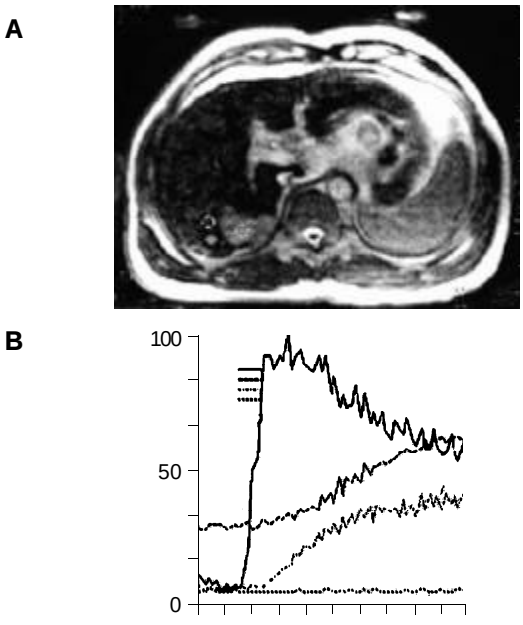


Figure 1 Signal intensity time curves of HCC in different groups before TACE. Type A represents hypervascularity, type B shows mild hypervascularity or hypovascularity of the tumor.



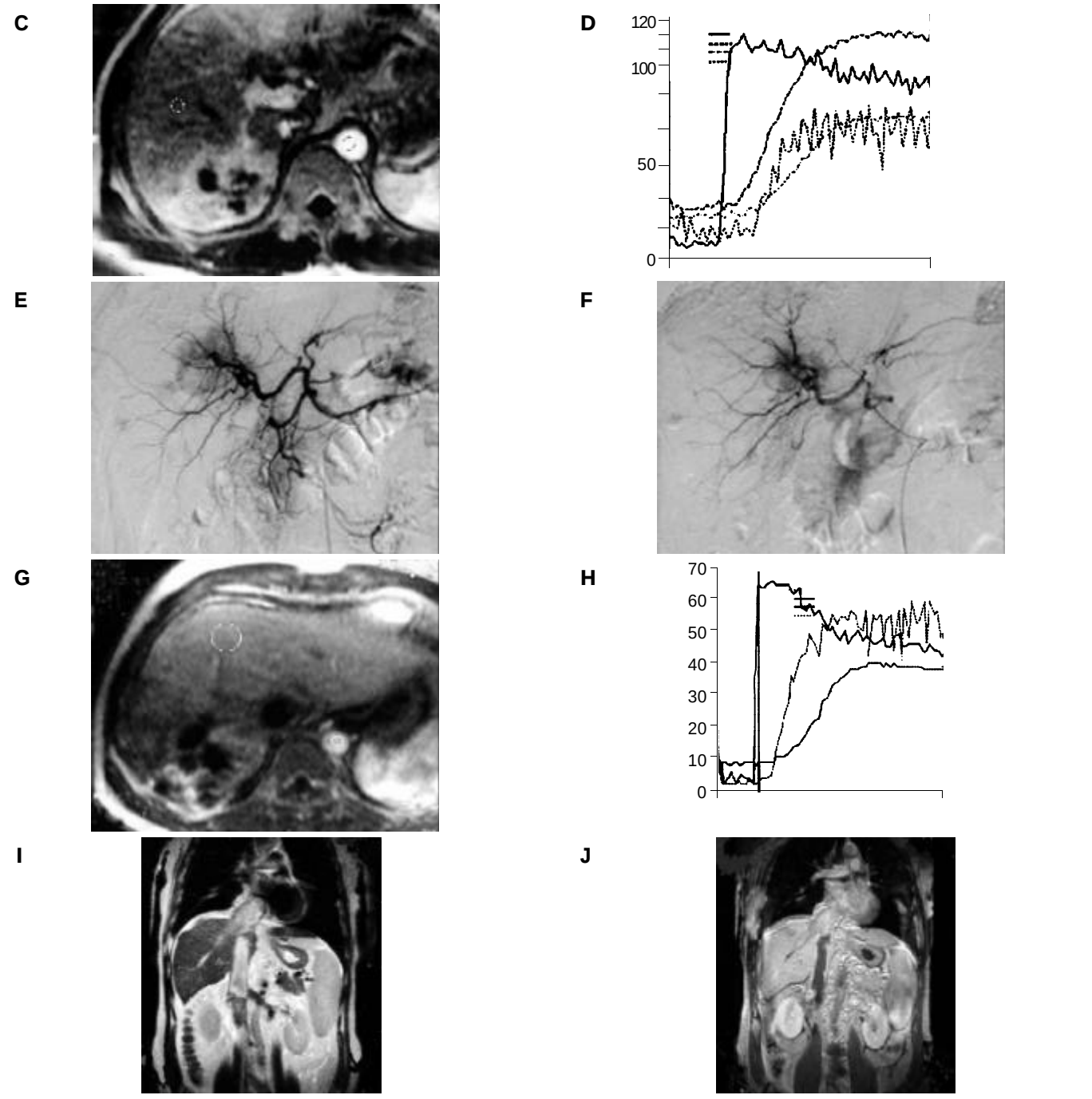


Figure 2 HCC before and after TACE. (A-B) FP-MRI and the signal intensity time curve derived from ROIs before TACE. (C-D) FP-MRI and the signal intensity time curve one month after TACE, the signal intensity time curve became steeper than that pre-TACE, indicating the remaining arterial blood supply of the lesion after TACE. (E) DSA before TACE and (F) DSA after TACE confirmed the FP-MRI finding. (G-H) one year after TACE, the lesion became larger and the signal intensity time curve became much steeper than that one month after TACE, suggesting the recurrence of the tumor. (I-J) T2 weighted image and enhanced T1 weighted image showing embolus in inferior vena cava and atrium dextrum.

DISCUSSION

Dynamic MR imaging with prior administration of gadopentetate dimeglumine has been used in a few studies to evaluate tumor angiogenesis[15-18]. Gadopentetate dimeglumine is rapidly distributed in the extra-vascular space during the signal acquisition, so the relative changes in signal intensity on dynamic MR imaging are not only correlated with MVD itself but also with perfusion rate, micro-vessel permeability, and the size of extra-cellular leakage space as well. Which of these pathophysiological mechanisms in HCC is the major contribution to the differences in the contrast media uptake is not clear. Because of high temporal resolution, FP-MRI can monitor the contrast medium first passing the microvessels, the relative changes of signal intensity is significantly associated with MVD, and has been used to access tumor angiogenesis[14]. T1 weighted FP-MRI or T2* weighted FP-MRI may be obtained depending upon the different sequences used[14,19,20].

The time intensity curves derived from T1 weighted FP-MRI of HCC before TACE showed a rapid initial increase in signal intensity followed by a plateau corresponding to hypervascularity, while the time intensity curves showed a slow initial increase in signal intensity followed by a plateau representing mild hypervascularity or hypovascularity. Our study showed that there was a good correlation between SS derived from T1 weighted FP-MRI and DSA in assessment of

the vascularity of HCC. The different vascularity of HCC was due to its differentiation and size[4,21,22], which resulted in different uptake and deposition of lipiodol. HCC with hypervascularity often has homogeneous deposition of lipiodol, and leads to complete necrosis of tumor and a better prognosis. When HCC with hypovascularity it shows incomplete necrosis because of poor deposition of lipiodol and only other ablation techniques are effective. Otherwise, unnecessary repeated TACE may be offset by worsening liver function in patients with cirrhosis, so it is important to identify the angiogenesis of HCC before TACE.

After TACE, the center of the lesion demonstrated no vascularity. Although the time intensity curves drawn in the rim-enhancing portion of the tumor was less steep than before, no significant difference was found on SS of the lesions pre-TACE and post–TACE. This result indicated that vascularity existed even after TACE. The vascularity after TACE was mainly due to collateral blood supply after TACE[24,25]. Meanwhile, the expression of vascular endothelial growth factor (VEGF) of cancerous cells could be enhanced by TACE which might play an important role in reestablishing of blood supply to tumor after TACE[23]. In this study, the incomplete embolization (because of larger lesions, mean size, 6 cm. complete embolization is at the expense of liver function) might contribute to the remains of arterial blood supply. The arterial blood supply after TACE could offer nutrition and oxygen to the remaining viable tumor cells, resulting in partial or incomplete necrosis of the tumor, recurrence would occur sooner or later. When HCC recurred, the time intensity curves became steep again, and the SS increased (Figure 2). The angiogenesis after TACE is a challenge to TACE. Up to now, TNP-470, cyanoacrylate, Plcg-mitomycin-microsphere and bletilla have been shown to improve the therapeutic results[26-30]. On the other hand, how to correctly access the angiogenesis after TACE during follow up remains to be studied. The study presented here offers a noninvasive modality to evaluate the angiogenesis after TACE without artifact.

Our result also showed that there was no significant difference in the baseline signal intensity on FP-MRI pre-TACE and one month after TACE, indicating that the retention of lipiodol within the lesion did not influence the assessment of tumor vascularity after TACE. We encountered two patients with HCC who were treated with TACE in combination with percutaneous ethanol injection. Six months after the therapy, the patients were suspected of recurrence because of their increase of alpha-fetoprotein, although the lesion had high signal intensity on FP-MRI before administration of gadopentetate dimeglumine, the time intensity curves demonstrated the vascularity of the original lesion and intrahepatic metastatic lesions, which were confirmed by DSA.

The potential pitfall of the evaluation of HCC vascularity by using FP-MRI is that the arterioportal shunting (APS) coexists with HCC. APS breaks the equilibrium of normal dual blood supply to the liver tissue and affects the blood flow in tumors, the enhancement of tumors might be changed depending on the degree and location of the shunting[31-33]. Large HCC might be enhanced poorly, and the vascularity might be underestimated because of the limited amount of contrast material passed through the tumor bed. The SS in three patients with APS associated with HCC (mean, 40% per second) was lower than the mean value of the patients (mean, 69% per second). Nevertheless, when the APS coexisted with HCC, the vascularity of HCC evaluated by using FP-MRI should be with caution, only when the shunting disappeared after embolization, was the vascularity of HCC assessed correctly.

The discrepancy between SS and DSA in assessment of the HCC vascularity derived from T1 weighted FP-MRI was within group III and group I. When SS showed hypervascularity in five lesions, DSA demonstrated hypovascularity. SS showed hypovascularity in two lesions, DSA, however, demonstrated hypervascularity. The differences between these two techniques were due to the pattern of contrast media administrated. The contrast media were administered through I.V. before MRI performance and through hepatic artery during DSA. As a result, the extrahepatic blood supply could not be revealed by DSA during arterial phase. This is the limitation of DSA in evaluation of HCC vascularity. On the other hand, the two sections of axial or coronal MR imaging not correlating with DSA point by point might contribute to their difference.

In summery, T1 weighted FP-MRI has been proved to be practical and noninvasive in assessment of the vascularity, and provides semi-quantitative criteria for the selection of patients to be treated with TACE or other ablation in their initial therapy and during follow up.

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