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ORIGINAL ARTICLE

Prospective Study

C-arm Lipiodol CT in transcatheter arterial chemoembolization for small hepatocellular carcinoma

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Abstract

AIM: To investigate the value of C-arm Lipiodol computed tomography (CT) for intra-procedural hepatocellular carcinoma (HCC) lesion detection during transcatheter arterial chemoembolization (TACE).

METHODS: Forty patients (37 male, 3 female; mean age, 52.6 ± 12.5 years, age range: 25-82 years) diagnosed with HCC were enrolled in this study. All patients underwent 64-slice CT 1-2 wk before TACE. During the procedure, hepatic angiography was performed first. Following diagnostic embolization with Lipiodol injected into the hepatic artery, a C-arm CT scan was immediately conducted (C-arm Lipiodol CT). If new HCC lesions were confirmed, gelfoam particles were super-selectively injected into the tumor-nourishing blood vessel. A Lipiodol CT scan was performed 7-14 d after TACE. All images acquired from 64-slice CT, digital subtraction angiography (DSA), C-arm Lipiodol CT and Lipiodol CT were retrospectively reviewed by four radiologists and the number of detected lesions in each examination was counted, respectively. The results of Lipiodol CT were taken as the diagnostic reference. Alpha-fetoprotein values were examined both before and after TACE. This study only takes into account the lesions that were not found or were considered suspicious on 64-slice CT before TACE.

RESULTS: Preprocedural 64-slice CT detected a total of 13 suspicious lesions in the 40 patients. DSA detected ten definite and four suspicious lesions. C-arm Lipiodol CT detected 71 lesions in total and Lipiodol CT confirmed 67 lesions with a diameter range of 3-12 mm. Four false-positive lesions, which were detected by C-arm Lipiodol CT, were considered to be hepatic artery-portal vein fistulas. The average alpha-fetoprotein values before and after TACE were significantly different (452.3 ± 192.6 ng/mL *vs* 223.8 ± 93.2 ng/mL; $P = 0.039$).

CONCLUSION: C-arm Lipiodol CT has a higher diagnostic sensitivity for small HCC lesions. This technique may help physicians make intraprocedural

decisions to provide patients with earlier treatment.

Key words: Hepatocellular Carcinoma; C-arm computed tomography; Chemoembolization; Angiography; Digital subtraction; Lipiodol; Therapeutic

Core tip: This article describes a new imaging modality for detecting small hepatocellular carcinoma (HCC) lesions during transcatheter arterial chemoembolization (TACE). C-arm Lipiodol computed tomography (CT) is defined as a plain C-arm CT scan performed immediately after Lipiodol embolization during TACE, which allows an early diagnosis and reduces the use of contrast medium. Use of the method can reduce the radiation dose to patients and provide a higher diagnostic sensitivity for small HCC lesions at an early stage during TACE. This technique may help physicians make intraprocedural decisions to provide earlier treatment and reduce the recurrence rate of HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third most common cause of cancer mortality[1]. Surgery is the main treatment for HCC. As the majority of patients have middle or late stage HCC at diagnosis, less than 30% of patients may undergo radical resection[2]. Transcatheter arterial chemoembolization (TACE) has been widely accepted as a standard palliative treatment for HCC[3]. However, the five-year survival rate after TACE is still low. The main factor affecting survival is tumor stage[4]. Many studies have reported significant benefit in patients if treatment is given at an early stage when HCC is small in size. Therefore, early diagnosis and treatment is of great importance as it affects the prognosis of HCC patients following TACE.

Hepatic angiography has high diagnostic sensitivity for HCC, especially for large and hypervascular HCC, but is not sensitive for small-sized HCC. C-arm computed tomography (CT) is a novel imaging modality that can be performed on the flat-detector angiography system inside a cath-lab. It can provide three-dimensional reconstructed VRT (volume rendering technique) images as well as thin-slice MPR (multi-planar reformation) images comparable to conventional CT. It was reported that iodinated-enhanced C-arm CT improved the detection rate of small HCC lesions during TACE[5].

Lipiodol plays an important role in TACE as it selectively accumulates in liver tumors (mainly HCC). Lipiodol CT, which involves a CT scan performed 7-14 d after TACE, has a high detection rate for HCC lesions[6]. However, contrast medium in iodinated-enhanced C-arm CT is needed and involves a long waiting time of 7-14 d in Lipiodol CT for the diagnosis of small HCC lesions. The purpose of this study was to investigate a new imaging modality, C-arm Lipiodol CT (defined as a plain C-arm CT scan performed immediately after Lipiodol embolization) during TACE, which not only allows an early diagnosis, but can also reduce the use of contrast medium.

MATERIALS AND METHODS

Patients

Forty HCC patients (37 male, 3 female; mean age, 52.6 ± 12.5 years, age range: 25-82 years) were enrolled in this study from June 2011 to March 2013. All patients had hepatitis B and liver cirrhosis. Liver function, according to the Child-Pugh score, was grade A in 36 cases and grade B in 4 cases. The scores were 5.38 ± 0.87 and 5.35 ± 0.80 before and after TACE, respectively. Model for end-stage liver disease scores were 5.08 ± 3.14 and 4.97 ± 3.21 before and after TACE, respectively. In this study, 20 patients were new cases and the other 20 were reexamined patients. Sixteen cases (40%) had a normal alpha-fetoprotein (AFP) level < 7 ng/mL), 16 cases (40%) had an AFP level of 7-400 ng/mL, and 8 cases (20%) had an AFP level > 400 ng/mL. The 64-slice CT examination showed patients with no lesions, some with suspicious lesions, and some with definite lesions. The detailed patient characteristics are listed in Table 1.

Pre-procedure

All patients underwent 64-slice CT scan (Lightspeed 64 VCT; GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom) before TACE. First a plain scan, then a three-phase enhanced scan was performed. The scanning parameters were as follows: 120 kV; 250-300 mA; 0.5 s/rotation; thickness, 5.0 mm; intersection gap, 5.0 mm; helical pitch (beam pitch), 0.984; and matrix: 512 × 512. Ultravist (370 mg/mL, Bayer Schering Pharma AG, Germany) was administered with a unit dose of 1.5 mL/kg at an injection rate of 3 mL/s.

Intraprocedure

All TACE procedures were performed using an Axiom Artis dTA angiography system (Siemens AG, Forchheim, Germany). Digital subtraction angiography (DSA) was conducted first. Abdominal aortography was performed and the anatomic structure of the hepatic artery was obtained using a pigtail catheter. Selective celiac or

Table 1 Pre-transcatheter arterial chemoembolization results of the enrolled patients

AFP	Exam history	CT results	Case number
Normal	New patient	No lesion	0
Normal	New patient	Suspicious lesion	6
Normal	New patient	Definite lesion	1
Normal	New patient	Definite and suspicious lesion	1
Normal	Reexamined patient	No lesion	6
Normal	Reexamined patient	Suspicious lesion	1
Normal	Reexamined patient	Definite lesion	0
Normal	Reexamined patient	Definite and suspicious lesion	1
Abnormal	New patient	No lesion	6
Abnormal	New patient	Suspicious lesion	2
Abnormal	New patient	Definite lesion	5
Abnormal	New patient	Definite and suspicious lesion	0
Abnormal	Reexamined patient	No lesion	8
Abnormal	Reexamined patient	Suspicious lesion	1
Abnormal	Reexamined patient	Definite lesion	2
Abnormal	Reexamined patient	Definite and suspicious lesion	0

Normal AFP level is 0-7 ng/mL. AFP: Alpha-fetoprotein.

common hepatic angiography was then performed *via* a 5 F catheter (flow rate 5-6 mL/s, total volume 20-30 mL). If clear tumor staining was revealed by DSA, Lipiodol (Guerbet, France) and then a gelatin sponge (350 μm, ALICON Pharm Sci and TEC Co., Ltd, Hangzhou, China) was super-selectively injected into the tumor-nourishing blood vessel, after which another 2-3 mL Lipiodol was injected into the hepatic artery supplying the non-tumor-bearing liver for diagnostic embolization. If no lesions were identified, 2-5 mL Lipiodol was then injected into the proper hepatic artery.

C-arm Lipiodol CT

A non-contrast C-arm CT (8 s rotational acquisition, 0.5°/f) was performed immediately after diagnostic embolization with Lipiodol while the agent was still diffusing in the liver. For patients with an extra large liver (n = 2), two C-arm CT scans of the left and the right liver lobe were acquired. Three-dimensional image reconstruction was conducted automatically on a dedicated workstation (Syngo X Workplace; Siemens AG). Multiplanar reconstruction images in the coronal, sagittal and transverse directions were generated. All images were evaluated by experienced interventionists. Dense lesions with homogenously absorbed Lipiodol that had a clear boundary were diagnosed as HCC lesions[7-9], which we embolized further with gelatin sponges.

Table 2 Diameter of 67 lesions according to Lipiodol computed tomography after transcatheter arterial chemoembolization

Diameter (mm)	Number of lesions
3	2
4	19
5	19
6	11
8	6
9	1
10	3
12	6

Post-procedure

All patients underwent 64-slice CT 7-14 d after TACE using the same protocol as described above for Lipiodol CT.

Image analysis

All images acquired from 64-slice CT, DSA, C-arm Lipiodol CT and Lipiodol CT were reviewed by four physicians and the number of lesions was noted. Results from Lipiodol CT were used as the diagnostic reference in this study to evaluate the findings of C-arm Lipiodol CT. Lesions that were detected by all four imaging modalities were not included in the statistical analysis.

AFP results

The AFP values 7 d before TACE and 7-14 d after TACE were recorded and analyzed with the paired t test (SPSS 19; IBM Corp., Armonk, NY, United States). A $P < 0.05$ was considered statistically significant.

RESULTS

Images

Thirteen suspicious lesions were found in 40 patients with 64-slice CT, of which two were verified by DSA, one remained suspicious, and ten were negative. In total, ten definite and four suspicious lesions were revealed by DSA. C-arm Lipiodol CT detected 71 lesions (Figure 1). Lipiodol CT identified 67 lesions in 40 patients. The diameter of the confirmed lesions ranged from 3 to 12 mm (Table 2). Four false-positive lesions, which were detected by C-arm Lipiodol CT, were considered to be hepatic artery-portal vein fistulas after carefully reviewing DSA and Lipiodol CT images.

AFP

The average AFP value in the 40 patients was 452.3 ± 192.6 ng/mL 7 d before TACE, and 223.8 ± 93.2 ng/mL 7-14 d after TACE (t = 2.131; P = 0.039). The difference was statistically significant.

DISCUSSION

Imaging plays a very important role in the diagnosis of HCC. Indeed, in high-risk patients, a noninvasive

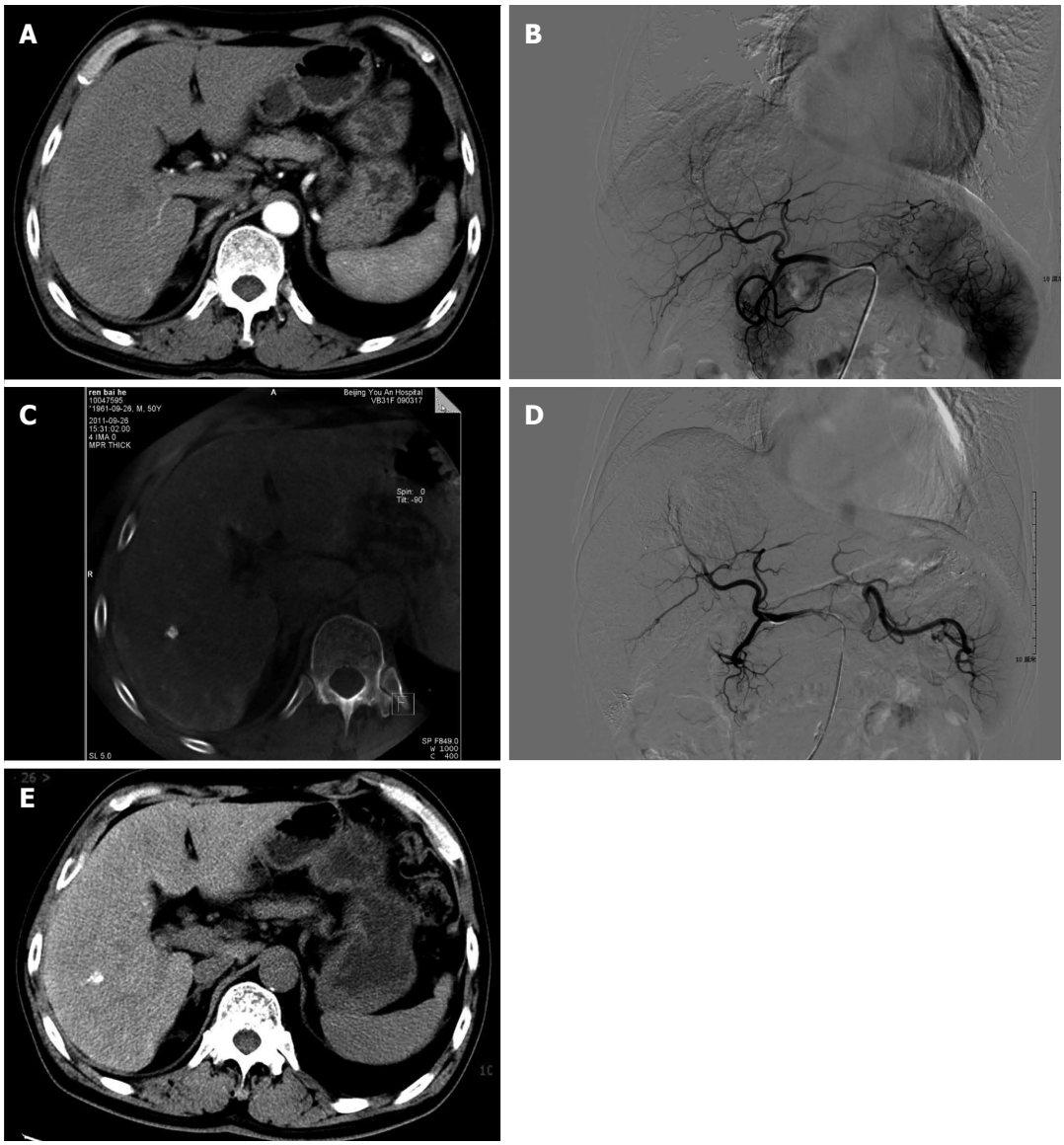

Figure 1 Imaging findings in a 50-year-old man diagnosed with hepatocellular carcinoma. Re-examination after transcatheter arterial chemoembolization (TACE). A: No clear lesion was found on pre-procedure 64-slice CT; B: No clear tumor staining was found following digital subtraction angiography examination; C: C-arm Lipiodol computed tomography (CT) scan after diagnostic embolization. A new Lipiodol lesion was found in the 6th liver segment; D: Gelfoam particles were injected into the tumor-nourishing blood vessel; E: New hepatocellular carcinoma lesion in the 6th segment was confirmed by CT examination performed 12 d after TACE.

diagnosis can only be obtained by imaging in the presence of typical features. These features include arterial enhancement followed by washout during the portal venous and/or delayed phases on CT scan or MRI. This pattern is quite specific and has been endorsed by both Western and Asian diagnostic guidelines. However, its sensitivity is not very high, especially for small lesions.

TACE is a means of diagnosis and treatment, and has become the most popular treatment method for non-surgical HCC patients. C-arm Lipiodol CT is a new imaging modality during the TACE procedure. This study only takes into account the lesions that were not found or were considered suspicious on 64-slice CT before TACE. The results confirmed that C-arm Lipiodol CT can diagnose HCC lesions without contrast medium compared with iodinated-enhanced C-arm CT, and identified more lesions than DSA or pre-TACE 64-slice CT, 94.4% (67/71) of which were confirmed by Lipiodol CT.

Usually, if new lesions are revealed by Lipiodol CT performed 7-14 d after TACE, a second TACE procedure will be needed. This is not only time-consuming for the physician, but also adds the risk of delaying treatment. Some patients may even suffer from a missed diagnosis due to negative findings on DSA and thus no follow-up will be performed. As some researchers have stated, Lipiodol cannot be used as an embolization agent on its own as it does not result in complete arterial occlusion[10]. In this study, we immediately injected gelatin sponge super-selectively into the lesions found by C-arm Lipiodol CT for further embolization. Moreover, the average AFP value decreased significantly after TACE, which

indicated that C-arm Lipiodol CT may be beneficial in the early detection of HCC lesions and early treatment with TACE. In addition, the diameter of the lesions found in this study ranged from 3 to 12 mm, 91% (61/67) of which were smaller than 10 mm. Reports in the literature suggest that the diagnostic sensitivity of CT and DSA is low for HCC lesions smaller than 10 mm[11,12]. One of the most likely reasons for HCC recurrence after TACE is that micro-metastatic lesions fail to be detected by any imaging modalities before TACE[13].

It is hypothesized that if C-arm Lipiodol CT can replace Lipiodol CT, the radiation dose to patients could be reduced. The present study indicates that C-arm CT results in a significantly reduced radiation dose to the patient and achieves similar spatial resolution and low contrast detectability to standard diagnostic multi-slice CT[14].

Despite all the advantages of performing C-arm Lipiodol CT during the TACE procedure, there are some inevitable limitations of this study: small HCC lesions cannot be diagnosed by liver biopsy. Although the diagnostic sensitivity of Lipiodol CT was high, it may still have false-positive results. In this study, C-arm Lipiodol CT detected four more lesions than Lipiodol CT, which were later considered to be false-positive results. DSA images must be taken into account when reviewing the C-arm Lipiodol CT images to comprehensively evaluate the characteristics of lesions.

In conclusion, C-arm Lipiodol CT has high diagnostic sensitivity for small HCC lesions at an early stage during TACE. This new imaging modality may help physicians make intraprocedural decisions in order that patients may receive early treatment and reduce the recurrence rate of HCC. A multicenter study with a large sample size is needed to further confirm the application value of C-arm Lipiodol CT in TACE.

COMMENTS

Background

Imaging plays a very important role in the diagnosis of hepatocellular carcinoma (HCC). Indeed, in high-risk patients, a noninvasive diagnosis can only be obtained by imaging in the presence of typical features. These features include arterial enhancement followed by washout during the portal venous and/or delayed phases on computed tomography (CT) scan or magnetic resonance imaging (MRI). However, its sensitivity is not very high, especially for small lesions. The main factor affecting survival of HCC patients is tumor stage. Many studies have reported significant benefit in patients when treatment was given at an early stage and HCC was small in size. Therefore, early diagnosis and treatment is of great importance and affects the prognosis of HCC patients.

Research frontiers

The sensitivity of noninvasive diagnosis methods such as CT or MRI for small HCC lesions is not very high. C-arm Lipiodol CT was used to diagnose small HCC lesions during transcatheter arterial chemoembolization (TACE). This method has not yet been reported.

Innovations and breakthroughs

In the present study, the authors verified the usefulness of a plain C-arm CT scan performed immediately after Lipiodol embolization during TACE. By comparing C-arm Lipiodol CT with 64-slice CT and digital subtraction angiography to identify the number of small HCC lesions, where the results of Lipiodol CT were taken as the diagnostic reference, the role of C-arm Lipiodol CT in the early diagnosis of HCC during TACE was confirmed. Compared with iodinated-enhanced C-arm CT, C-arm Lipiodol CT can be used without contrast agent.

Applications

This study provides a new imaging modality that has high diagnostic sensitivity for small HCC lesions at an early stage during TACE. This technique is a new method for the early diagnosis and treatment of HCC in clinical practice.

Terminology

C-arm Lipiodol CT is defined as a plain C-arm CT scan performed immediately after Lipiodol embolization.

Peer-review

This is a well-written paper, with clear goals and a very nice design. The early diagnosis of HCC and the role of C-arm Lipiodol CT are very interesting. It provides a new imaging modality that has a higher diagnostic sensitivity for small HCC lesions in an early stage during TACE procedure.

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