

Angio-Computed Tomograph-Guided Immediate Lipiodol Computed Tomograph for Diagnosis of Small Hepatocellular Carcinoma Lesions during Transarterial Chemoembolization

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Abstract

Background: The diagnosis and treatment of small hepatocellular carcinoma (HCC) play a vital role in the prognosis of patients with HCC. The purpose of our study was to evaluate angio-computed tomography (angio-CT)-guided immediate lipiodol CT (a CT scan performed immediately after transarterial chemoembolization [TACE]) in the diagnosis of potential HCCs ≤ 1 cm in diameter.

Methods: This study retrospectively analyzed 31 patients diagnosed with HCCs after routine imaging (contrast-enhanced CT or magnetic resonance imaging) or pathologic examinations with undefined or undetermined tumor lesions (diameter ≤ 1 cm) from February 2016 to September 2016. After TACE guided by digital subtraction angiography of the angio-CT system, potential HCC lesions with a diameter ≤ 1 cm were diagnosed by immediate lipiodol CT. The number of well-demarcated lesions was recorded to calculate the true positive rate. The correlation between the number of small HCCs detected by immediate lipiodol CT and the size of HCC lesions (diameter > 1 cm) diagnosed preoperatively was analyzed 1 month after TACE. A paired *t*-test was used to analyze differences in liver function. Pearson analysis was used to analyze correlation. Chi-square test was used to compare the rates.

Results: Fifty-eight lesions were detected on preoperative routine imaging examinations in 31 patients including 15 lesions with a diameter ≤ 1 cm. Ninety-one lesions were detected on immediate lipiodol CT, of which 48 had a diameter ≤ 1 cm. After 1 month, CT showed that 45 lesions had lipiodol deposition and three lesions had lipiodol clearance. Correlation analysis showed that the number of small HCCs detected by lipiodol CT was positively correlated with the size of HCC lesions diagnosed by conventional imaging examination ($R^2 = 0.54$, $P < 0.05$).

Conclusion: Immediate lipiodol CT may be a useful tool in the diagnosis of potential HCC lesions with a diameter of ≤ 1 cm.

Key words: Chemoembolization; Diagnostic Imaging; Hepatocellular Carcinoma; Lipiodol Computed Tomograph; Liver Neoplasms; Therapeutic

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for one-fifth of the most common cancers worldwide. The prognosis in patients with HCCs remains poor because most patients are not diagnosed until the disease is in an advanced stage.^[1] The exact number and distribution of tumor nodules are crucial for formulating appropriate treatment regimens for such patients.^[2,3] According to the European Association for the Study of the Liver Conference, hepatocellular lesions ≤ 1 cm in size do not have a significant clinical impact, so physicians should focus on lesions > 1 cm in size.^[4] For multifocal intrahepatic lesions, however, physicians are not likely to wait until the lesions meet noninvasive diagnostic criteria.

Without immediate curative or palliative therapy, such lesions would exhibit rather aggressive behavior, unlike single primary tumors of small size.^[5]

Transarterial chemoembolization (TACE) is one of the effective therapeutic options for inoperable HCC lesions;^[6-8] however, angiography often has difficulties in demonstrating

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HCC lesions ≤ 1 cm in size due to decreased hypervascularity, and TACE is often performed in a relatively large area because of difficulty in identifying the feeding vessel.^[9] The possibility of a diagnostic intervention (i.e., image-guided percutaneous biopsy) is limited for potential HCCs ≤ 1 cm, considering the false-negative results caused by sampling error and technical difficulties such as the target location, coagulation disorders, ascites, and the prevalence of needle tract seeding.^[10] Lipiodol computed tomograph (CT), which involves a CT scan after intrahepatic arterial injection of iodized oil, has been reported to be the most sensitive preoperative imaging modality for HCC.^[11,12]

Lipiodol CT has been widely used because of its high rate of detecting potential HCC lesions.^[13] Cone-beam computed tomography (CBCT) can also be used for lipiodol CT imaging after TACE, but CBCT images are reconstructed CT-like images. CBCT clarity and real resolution are not equivalent to CT. Moreover, for the diagnosis of small HCC lesions, a waiting time between 1 and 4 weeks is always required for lipiodol CT.^[13]

The current study was designed to investigate a new imaging modality (immediate lipiodol CT) in HCC patients after TACE.

METHODS

Ethical approval

This study was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital and informed consent was obtained from all of the patients before their enrollment in this study.

Patients

From February to September 2016, a total of 31 patients diagnosed with HCC were included in this study. All of the patients were diagnosed with HCC by at least two types of conventional imaging (contrast-enhanced CT or magnetic resonance imaging [MRI]) or pathologic examinations. All of the patients had a tumor focus which was not clear or not detected by routine imaging examinations.

The inclusion criteria included the following: (1) patients with unclear or undetected lesions under conventional imaging examinations; (2) Barcelona Clinic Liver Cancer stage B or C; and (3) Child-Pugh Class A or B. The exclusion criteria included the following: (1) severe coagulation disorders such as prothrombin activity < 40 or platelet count $< 30 \times 10^9/L$; (2) patients with an allergic reaction to iodine; and (3) patients who were expected to survive < 3 months.

Transarterial chemoembolization procedure

All interventional procedures were performed through digital subtraction angiography (DSA, MIYABI system) by an interventional radiologist who had > 5 years of experience in interventional radiology. After local anesthesia with 1% lidocaine (5–10 ml), the right femoral artery was accessed with a 4F or 5F arterial sheath (Terumo Co., Tokyo, Japan) using the modified Seldinger technique. Selective angiography of the

celiac-hepatic and superior mesenteric arteries was performed with a 4F or 5F hepatic artery catheter (Cordis, Miami, Florida, USA). Iodinated contrast medium (Iodixanol[®], 25–30 ml; Ge Pharmaceutical Co., Ltd., Shanghai, China) was injected at approximately 5 ml/s. According to the angiography, a 2.6F microcatheter (Terumo Co.) was super-selectively cannulated for chemoembolization. 30–50 mg doxorubicin hydrochloride powder (adriamycin; Pharmacia & Upjohn, Peapack, NJ, USA) was mixed with the iodized oil injection to form an iodized oil emulsion and was then used for infusion chemotherapy and embolization therapy. When the small portal vein branches were visualized or the blood flow was significantly static after embolization with iodized oil emulsion, gelatin sponge particles (350 μm ; Jinling Pharmaceutical Co., Ltd., Nanjing, China) were used for supplemental embolization. Finally, a 2.6F microcatheter was withdrawn back to the proper hepatic artery and 3–5 ml of super-liquid iodized oil was injected at a rate of 1 ml/s (Guerbet Inc., Paris, France) for diagnostic embolization.

Immediate lipiodol computed tomograph

A CT scan was performed immediately after TACE. The DSA machine was moved to the patient's foot, and the examination bed was moved to the designated coordinates after the TACE. The 16-slice spiral CT scanner was moved to the abdomen of the patient. The scanning parameters were as follows: 130 kV; 70 mA; slice thickness and interval, 3.0 mm; pitch, 0.75–0.95; and matrix, 512×512 . The curative effect of TACE and whether or not the sites of lipiodol deposition were consistent with the location and number of lesions detected by preoperative imaging examination were determined. For clear lesions in which lipiodol deposition was not ideal or new lesions under immediate CT, a second super-selective chemoembolization was performed for the blood vessels supplying the tumor. We performed a second super-selective TACE with or without granular embolic agents according to liver function to prevent additional liver function damage. Dense lesions with a clear boundary and homogeneously absorbed lipiodol were recorded as HCC lesions.^[14–16] The size of the target lesions was calculated as the maximum diameter for single lesions and the sum of the maximum diameter for multiple lesions. The number of target and nontarget lesions was recorded.

Postoperative management

Pressure bandaging puncture point and monitoring vital signs postoperatively, anti-infection, hydration, liver protection, and nutritional support were carried out. All of the patients were followed with a CT scan and liver function-related biochemical parameters: aspartate transaminase (AST), alanine transaminase (ALT), and total bilirubin (TBIL) 1 month after TACE. The number of lesions with lipiodol deposition and lipiodol clearance were recorded.

Image analysis

The CT, MRI, DSA, and immediate lipiodol CT images were scanned and interpreted independently by two interventional

radiologists who specialize in imaging diagnosis and had experience in interpreting liver images in their daily practice for at least 5 years. The examiners were unaware of the results of previously performed imaging studies, and the number of HCC lesions was counted independently.

Statistical analysis

Normally distributed continuous variables are expressed as the mean \pm standard deviation (SD). Statistical analysis was performed using SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA). A paired *t*-test was used to analyze differences in liver function. The relationship between the number of small HCC lesions (diameter ≤ 1 cm) and the diameter of the preoperatively diagnosed HCC lesions (diameter > 1 cm) was analyzed by Pearson's correlation analysis. A *P* < 0.05 was considered to be statistically significant.

RESULTS

Radiographic outcomes

The immediate CT scan revealed that lipiodol was concentrated in the tumor and the effect of TACE was significant. Representative images are shown in Figures 1 and 2.

Forty-eight tumor lesions were identified by routine preoperative imaging in 31 patients. Among the 58 lesions, 12 tumors were > 3 cm and ≤ 5 cm in diameter, 31 lesions were > 1 cm and ≤ 3 cm in diameter, and 15 lesions were ≤ 1 cm in diameter. Immediate lipiodol CT detected a total of 91 tumor lesions, of which 48 were ≤ 1 cm in diameter. After 1 month, among 48 lesions detected by immediate lipiodol CT,

45 lesions had persistent lipiodol deposition and 3 lesions had lipiodol clearance based on CT examination [representative images are shown in Figures 3 and 4]. Lipiodol CT yielded a higher detection rate of small HCCs compared with conventional imaging examinations (51.14% vs. 25.86%, $\chi^2 = 5.56$, *P* = 0.002) [Table 1].

Pearson's correlation analysis

Pearson's correlation analysis showed that the number of small HCCs detected by lipiodol CT was positively correlated with the size of HCCs diagnosed by conventional imaging examinations [*R*² = 0.54, *P* < 0.05 ; Figure 5].

Complications

The baseline characteristics of the 31 patients are summarized in Table 2. Common postoperative adverse events, such as fever, hypertension, abdominal pain, and hiccups, were improved by symptomatic treatment; no serious complications, such as upper gastrointestinal bleeding, liver and renal failure, and ectopic embolism, occurred. The preoperative ALT, AST, and TBIL levels were 34.81 ± 11.81 U/L, 40.12 ± 25.12 U/L, and 18.21 ± 10.94 $\mu\text{mol/L}$, respectively. Three days after immediate lipiodol CT (postoperatively), the liver function was as follows: ALT, 247.10 ± 181.74 U/L (*P* < 0.01); AST, 218.70 ± 138.30 U/L (*P* < 0.01); and TBIL, 33.78 ± 16.18 $\mu\text{mol/L}$ (*P* < 0.01). After 1 month, the liver function-related biochemical parameters were as follows: ALT, 43.55 ± 30.61 U/L (*P* = 0.33 > 0.05); AST, 48.94 ± 47.55 U/L (*P* = 0.54 > 0.05); and TBIL,

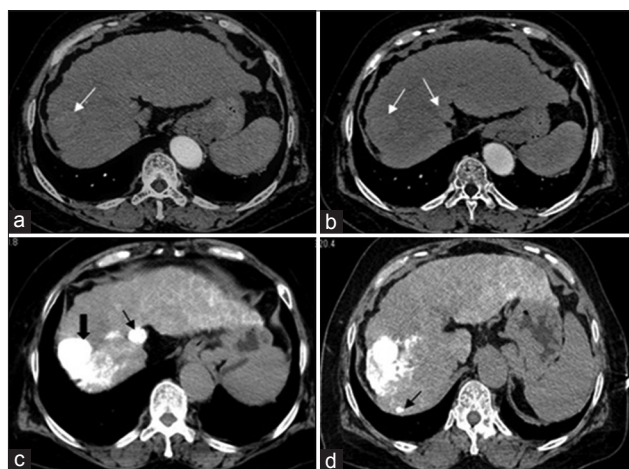


Figure 1: The small HCC lesion was detected by immediate lipiodol CT in a 72-year-old female patient with HCC who received TACE in angio-CT. (a and b) Preoperative enhanced CT showed a homogeneous enhancement in the right lobe of the liver and caudate lobe enlargement (white arrows); (c) immediate lipiodol CT showed lipiodol deposition in the right lobe of the liver, which was consistent with the results of preoperative enhanced CT (black thick arrow: TACE treatment area), and the caudate lobe of the liver had obvious lipiodol deposition (black thin arrow); (d) immediate lipiodol CT imaging identified another small HCC lesion in the right lobe of the liver (black arrow). HCC: Hepatocellular carcinoma; CT: Computed tomograph; TACE: Transarterial chemoembolization.

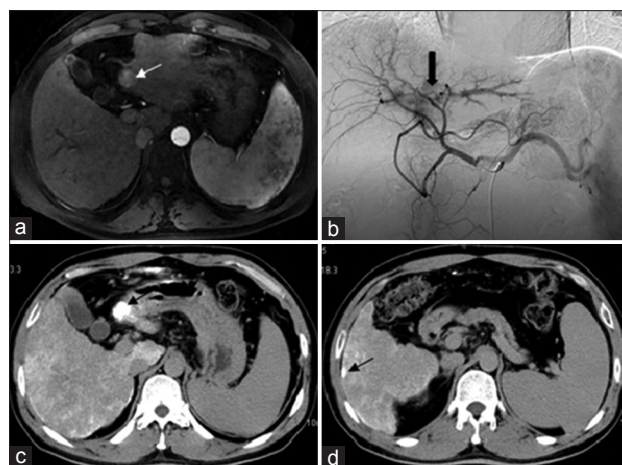


Figure 2: The small HCC lesion was detected by immediate lipiodol CT in a 42-year-old male patient with HCC who received TACE in angio-CT. (a) Preoperative MRI enhanced scan showed an obvious enhancement in the arterial phase of the left and right lobe of the liver (white arrow); (b) intraoperative DSA showed a mass shadow (black thick arrow) at the location consistent with the preoperative MRI examination; (c) immediate lipiodol CT showed an area of lipiodol deposition consistent with preoperative MRI examination (black thin arrow); (d) immediate lipiodol CT imaging identified another small HCC lesion (black thin arrow) but not by preoperative MRI and intraoperative DSA. HCC: Hepatocellular carcinoma; CT: Computed tomograph; TACE: Transarterial chemoembolization; MRI: Magnetic resonance imaging; DSA: Digital subtraction angiography.

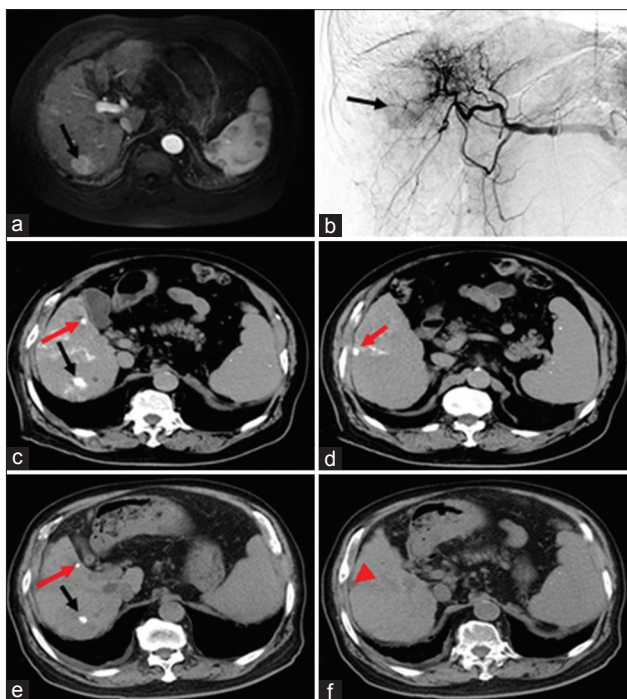


Figure 3: The false-positive lesions identified by immediate lipiodol CT after TACE in a 53-year-old male patient with HCC. (a and b) Preoperative MRI and intraoperative DSA revealed a tumor in the liver (black arrows); (c and d) immediate lipiodol CT showed an area of lipiodol deposition (black arrow) consistent with pre-operative MRI examination and intra-operative DSA. In addition, immediate lipiodol CT showed two small lesions (red arrows) which were not detected by pre-operative MRI examination and intraoperative DSA; (e) after 1 month, CT scan revealed that iodized oil was not cleared from one lesion (black arrow) diagnosed by pre-operative MRI and intra-operative DSA and another one lesion detected by immediate lipiodol CT (true positive, red arrow); (f) CT scan revealed that iodized oil was cleared in another one lesion detected by immediate lipiodol CT after 1 month (false positive, red triangle). CT: Computed tomograph; TACE: Transarterial chemoembolization; HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; DSA: Digital subtraction angiography.

16.12 ± 7.26 μmol/L ($P = 0.56 > 0.05$). The liver function indicators increased over a short period of time after immediate lipiodol CT and returned to normal 1 month later, which suggests that immediate lipiodol CT did not exacerbate liver damage.

DISCUSSION

The results of our study revealed that immediate lipiodol CT after TACE can detect small lesions which are not identified or diagnosed using conventional imaging techniques. Correlation analysis showed that the detection rate of small HCCs was higher in patients with larger diameter HCCs diagnosed by conventional imaging, which highlights the value of lipiodol diagnostic CT examinations after TACE in HCC patients.

The progress in various imaging modalities, including ultrasonography, CT, and MRI, has greatly promoted the diagnostic accuracy of HCC in recent years.^[17] As

Table 1: HCC lesions detected according to size by the conventional imaging and immediate noncontrast lipiodol CT, *n*

Tumor size	Conventional imaging	Immediate noncontrast lipiodol CT
≤10 mm	15	45
>10 mm	43	43
Total	58	88

Conventional imaging: Ultrasound, CT, and MRI. HCC: Hepatocellular carcinoma; CT: Computed tomograph; MRI: Magnetic resonance imaging.

Table 2: Baseline characteristics of the patients with hepatocellular carcinoma (*n* = 31)

Items	Value
Gender (male/female), <i>n</i>	27/4
Mean age (years), mean ± SD	55.13 ± 11.17
Child-Pugh class, <i>n</i> (%)	
A	25 (80.65)
B	6 (19.35)
PST score, <i>n</i> (%)	
0	31 (100)
AFP (ng/ml), <i>n</i> (%)	
<10	0 (0)
10–400	10 (32.26)
>400	21 (67.74)
Number of HCC lesions (diameter >1 cm) by conventional imaging, <i>n</i> (%)	
1	8 (25.81)
2	15 (48.39)
3	8 (25.81)
BCLC stage, <i>n</i> (%)	
B	24 (19.35)
C	7 (22.60)
History of prior treatment, <i>n</i> (%)	
Liver transplantation	0 (0)
Hepatectomy	14 (45.16)
Topical therapy	6 (19.35)
Medication	5 (16.13)
None	6 (19.35)

SD: Standard deviation; PST: Performance status; AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma; BCLC: Barcelona clinic liver cancer.

HCC lesions are often multifocal, intrahepatic metastatic HCC nodules are frequently observed.^[18-20] Improper surgical removal is often caused by an underestimation of HCC lesions. Thus, precise imaging assessment of HCC nodules before surgery is crucial for appropriate surgical treatment and for judging the scope of liver resection.^[21] Radiologic imaging plays a prominent part in the diagnosis of HCC.^[22] The hallmark diagnostic features of HCC are early enhancement and fast washout corresponding to tumor hypervascularity followed by progressive washout of the contrast agent.^[23-28] It has been shown that helical CT has a higher sensitivity for well-differentiated HCC when compared to lipiodol CT and DSA, especially during the diagnosis of small tumors; however, with respect to the

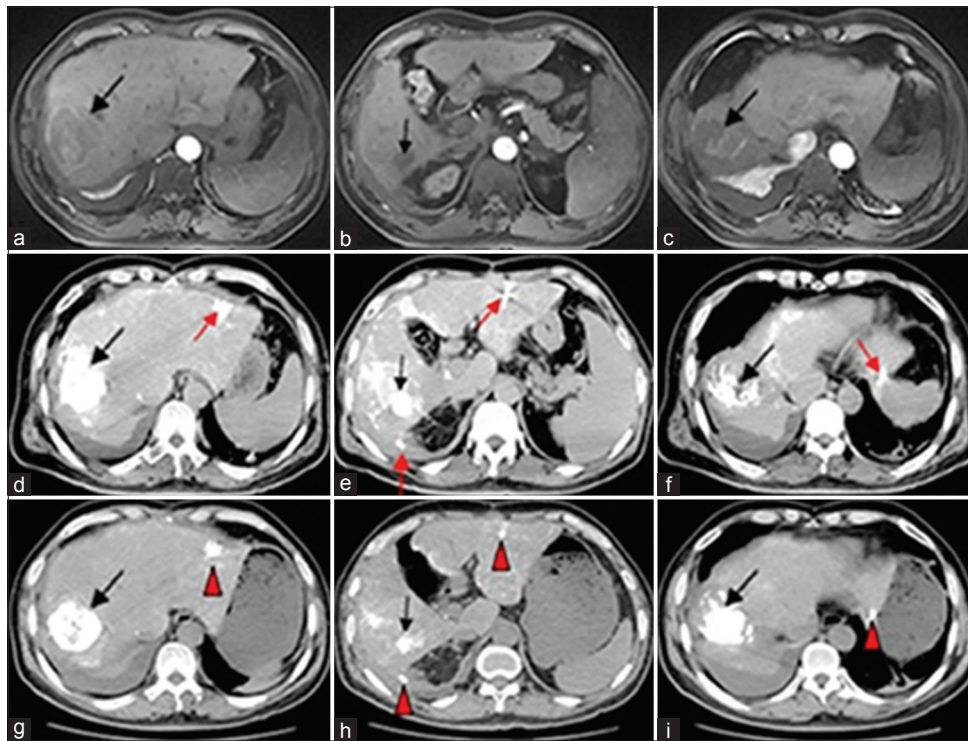


Figure 4: The true-positive lesions identified by immediate lipiodol CT after TACE in a 57-year-old male patient with HCC. (a-c) Preoperative MRI revealed two HCCs in the liver (black arrows); (d-f) Immediate lipiodol CT showed the two areas of lipiodol deposition (black arrows) consistent with the preoperative MRI. Immediate lipiodol CT identified four small lesions (red arrows) which were not detected by preoperative MRI; (g-i) after 1 month, CT scan revealed that diffuse lipiodol in the liver has cleared, and iodized oil was not cleared from the two lesions (black arrows) diagnosed by preoperative MRI and the four lesions detected by immediate lipiodol CT (true positive, red triangles). CT: Computed tomograph; TACE: Transarterial chemoembolization; HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging.

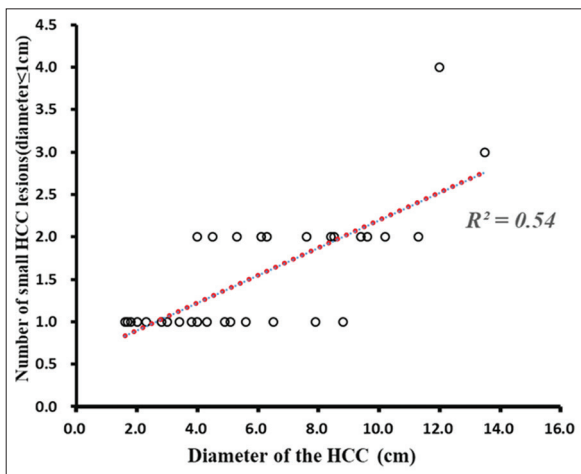


Figure 5: Pearson's correlation analysis for the relationship between the number of small HCC lesions (diameter ≤ 1 cm) detected by lipiodol CT and the size of HCCs diagnosed by conventional imaging examinations in 31 patients ($R^2 = 0.54$, $P < 0.05$). HCC: Hepatocellular carcinoma; CT: Computed tomograph.

detection of small but moderately to poorly differentiated HCC lesions, lipiodol CT reveals excellent sensitivity when compared to helical CT.^[21] TACE is the mainstay option for palliative treatment of unresectable HCC and has been proven to have survival benefits.^[2,3] Previous reports proposed that CT and DSA have low diagnostic sensitivity

in detection of HCC lesions < 10 mm in diameter.^[29,30] Rizvi *et al.*^[13] concluded that the diagnostic accuracy of lipiodol CT reached 91% within 1–2 weeks after TACE, and lipiodol CT had prominent sensitivity in early-stage HCC. A recent study by Choi *et al.*^[31] investigated the effectiveness of CBCT-guided chemoembolization for potential HCCs < 1 cm in diameter and reported that the 1-, 2-, and 3-year overall survival rates were 100%, 98.2%, and 88.5%, respectively; however, cone-beam CT has inherent shortcomings. Motion artifact, specifically from respiration, can degrade image quality. Unlike DSA, cone-beam CT has no recourse for motion correction. The smaller field of view of cone-beam CT limits coverage in large patients.^[32]

New lesions are revealed by lipiodol CT 1–2 weeks after TACE, unlike traditional methods.^[13] In the current study, lipiodol CT was performed immediately after TACE and a second TACE procedure was performed under the guidance of lipiodol CT. For those small lesions detected by lipiodol CT, we performed secondary super-selected TACE followed by gelatin sponge in patients with good liver function. In patients with poor liver function (Child-Pugh B), we only performed super-selected TACE without gelatin sponge particles to aid embolization, which is similar to TACE as a supplement therapy after surgical resection of HCC.^[33] Moreover, the blood examination indicators of patients with lipiodol injected into the proper hepatic artery had no significant changes in liver function after 1 month, which

demonstrates that it will not cause damage to the patients despite the diffuse distribution of iodized oil in the liver. This technique saves physician time, reduces the risk of delayed treatment, and greatly enhances the survival rate. This study only took into account the lesions that were not detected or were considered potential on routine imaging examinations (ultrasound, CT, and MRI) before TACE. The results confirmed that immediate lipiodol CT identified more lesions than routine preoperative imaging examinations or DSA (number of lesions, 91 vs. 58). It is not clear whether or not these small lesions detected by immediate lipiodol CT are early-stage HCC; however, lipiodol absorbed in benign lesions, such as dysplastic nodules and regenerative nodule, will wash out after 1 month, which will bring no threat to liver function and quality of life. Moreover, in our study, the sensitive diagnostic rate of immediate lipiodol CT for small lesions (≤ 1 cm) was 93.75% (45/48), which was similar to conventional lipiodol CT.^[34] Thus, there is a degree of certainty in the diagnosis of small HCCs by immediate lipiodol CT. If the dense lesions represent early-stage HCC, we could not only diagnose small HCC lesions but perform embolization through immediate lipiodol CT without liver damage, which is beneficial in improving the overall efficacy of TACE and reducing the recurrence rate of HCC. All in all, we suggest that immediate lipiodol CT should be used as a supplement to TACE, at the same time, lipiodol CT can help physicians make the tumor staging more accurate and enable patients to receive more appropriate treatment.

During TACE, Miyabi angio-CT or CBCT systems can provide real-time information to adjust the treatment plan, discover small lesions which were not found by routine imaging, and immediately evaluate the efficacy to determine whether or not additional treatment is available. CBCT can also be used for lipiodol CT imaging during TACE, but CBCT images are reconstructed CT-like images. The clarity and real resolution of CBCT do not have the quality of CT. In addition, CBCT examinations require more time than CT. In our study, DSA-guided TACE and immediate lipiodol CT were both performed on an angio-CT system (Miyabi system; SIEMENS, Atris Zee, Germany). The angio-CT system, in which the angiography and CT systems are located in the same room and share an examination/treatment bed, was an epoch-making technological advance in abdominal intervention because the need to move the patient to another CT room was eliminated.^[35]

Despite all the advantages of performing immediate lipiodol CT during the TACE procedure, there were some inevitable limitations to this study. First, the retrospective design has inherent limitations. Second, small HCC lesions are difficult to diagnose by liver biopsy, so there may be false-positive results. Finally, our study lacked long-term follow-up, so the late curative effect of small lesions treated by TACE is unknown. Therefore, a large-scale study with long-term follow-up is warranted in the future.

In conclusion, immediate lipiodol CT can be a useful tool in the diagnosis of potential HCCs ≤ 1 cm in diameter. The main

clinical significance of lipiodol CT is to identify accurately small lesions that cannot be found by conventional imaging and guide a second embolization to newly discovered small lesions, which has great benefit to the reduction of the recurrence rate of HCCs and survival.

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Conflicts of interest

There are no conflicts of interest.

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Angio-CT引导经动脉化疗栓塞术后行即刻碘油CT成像 诊断微小肝癌的临床研究

摘要

背景: 微小肝癌的诊断和治疗对于肝癌(HCC)患者的预后有至关重要的作用。该研究的目的是探讨angio-CT引导的即刻碘油CT即angio-CT引导下经动脉化疗栓塞(TACE)后即刻行CT扫描在诊断微小肝癌($\leq 1\text{cm}$)中的应用价值。

方法: 回顾性分析2016年2月至2016年9月在常规影像学检查(增强CT或增强MRI)或病理学检查中未确诊或未发现的31例伴有微小肝癌(直径 $\leq 1\text{cm}$)的HCC患者。于angio-CT系统的数字减影血管造影(digital subtraction angiograph, DSA)引导下TACE治疗,术后即刻行CT扫描。记录边界清楚,碘油沉积良好的病灶数量。TACE后1个月行CT检查,分别记录碘油沉积和碘油廓清的病灶数量。两组间比较采用配对t检验,相关性分析采用Pearson correlation分析,率的比较采用卡方检验。

结果: 31例患者术前常规影像学检查共发现58个病灶,其中15个病灶直径 $\leq 1\text{cm}$ 。即刻碘油CT发现91个病灶,其中48个病灶直径 $\leq 1\text{cm}$ 。1个月后,CT检查提示即刻碘油CT发现的48个病灶中,45个病灶有碘油沉积,3个病灶出现碘油廓清。Pearson相关分析显示即刻碘油CT检测到的微小肝癌数量与已经确诊的HCC病灶大小呈正相关($R^2=0.54, P < 0.05$)。

结论: 即刻碘油CT可能是诊断直径 $\leq 1\text{cm}$ HCC的一种灵敏性较高的影像检查方法。