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Use of contrast-enhanced ultrasonography with a perflubutane-based contrast agent performed one day after transarterial chemoembolization for the early assessment of residual viable hepatocellular carcinoma

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ABSTRACT

Objective: We evaluated the efficacy of contrast-enhanced ultrasonography (US), compared with contrast-enhanced computed tomography (CT), for early assessments after transarterial chemoembolization (TACE) for the treatment of hypervascular hepatocellular carcinoma (HCC) lesions.
Subjects and methods: Thirty-two patients with 59 HCC lesions who were scheduled to receive TACE were enrolled in this prospective study. TACE was performed by injecting a mixture of iodized oil and miriplatin hydrate, followed by a gelatin sponge. Digital subtraction angiography (DSA) and/or contrast-enhanced CT were performed 2–6 months after TACE and were used as the reference standard for residual HCC; the detection rates for residual viable HCC using contrast-enhanced US with a perflubutane-based contrast agent and a high mechanical index (MI) mode performed one day after TACE were also compared with those obtained using contrast-enhanced CT performed one month after TACE. The comparisons were made using the McNemar test.
Results: Forty-seven (79.7%) of the 59 HCC lesions were diagnosed as having residual viability based on DSA and contrast-enhanced CT findings obtained 2–6 months after TACE. Eight (17.0%) of the 47 HCC lesions that were diagnosed as having residual viability using one-day contrast-enhanced US were not detected using one-month contrast-enhanced CT because of artifacts produced by the high attenuation of the iodized oil. The detection rate for residual HCC lesions using one-day contrast-enhanced US (95.7%, 45/47) was significantly higher than that using one-month contrast-enhanced CT (78.7%, 37/47) ($P < 0.05$).
Conclusion: Contrast-enhanced US performed one day after TACE is more sensitive than contrast-enhanced CT performed one month after TACE for detecting residual viable HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is a malignant tumor responsible for approximately 600,000–700,000 deaths worldwide and is becoming more prevalent not only in South-East Asia and Africa, but also in Western countries [1]. Transarterial chemoembolization (TACE) with an emulsion of iodized oil has been widely performed for the treatment of unresectable HCC [2–6].

Contrast-enhanced computed tomography (CT) is commonly used to evaluate the efficacy of TACE. However, evaluations using this modality must be delayed by more than one month [7] because tumor regression is rarely observed immediately after TACE [8] and dense iodized oil accumulation is often observed in both HCCs and non-neoplastic liver parenchyma within 4 weeks after TACE [9]. Furthermore, contrast-enhanced CT cannot be used to evaluate tumor residue correctly because of artifacts from the accumulation of iodized oil in the tumor [10–12]. To obtain a better survival rate, the need for additional treatment must be

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determined early and correctly so that additional treatments, such as repeated TACE or the administration of sorafenib, can be planned [13,14].

Contrast-enhanced ultrasonography (US) using a perflubutane-based contrast agent (Sonazoid; Daiichi Sankyo, Tokyo, Japan) can be used to detect viable HCC lesions accurately [15–19]. Contrast-enhanced US with Sonazoid is commonly performed using a low mechanical index (MI) mode imaging software at a low MI (0.2–0.3); this mode allows the visualization of tumor vessels and tumor enhancement in real time [16,18,19]. To evaluate the efficacy of TACE, Xia et al. [20] reported that contrast-enhanced US using a low MI mode imaging software at a low MI at 1 week after TACE was significantly more sensitive than contrast-enhanced CT for depicting residual viable HCC lesions. However, contrast-enhanced US using a low MI mode imaging software at a low MI cannot remove the influence of hyper-echogenicity caused by the deposition of iodized oil within the tumor after TACE, and this hyper-echogenicity disturbs the accurate evaluation of the presence or absence of residual viable HCC lesions [21,22]. Contrast-enhanced US using a high MI mode imaging software, known as coded harmonic angio (CHA), at a high MI (0.7–1.0) can eliminate background B-mode features, such as the hyper-echogenicity caused by the deposition of iodized oil [10,22]. Therefore, contrast-enhanced US using a high MI mode imaging software at a high MI is more sensitive than contrast-enhanced US using a low MI mode imaging software at a low MI for diagnosing the presence or absence of residual viable HCC areas within hyper-echoic lesions [22].

The purpose of the present study was to investigate the potential benefit of contrast-enhanced US using a high MI mode imaging software at a high MI performed one day after TACE for the early assessment of the therapeutic effectiveness of TACE, compared with contrast-enhanced CT performed one month after TACE; dynamic contrast imaging, such as digital subtraction angiography (DSA) and/or contrast-enhanced CT, performed 2–6 months after TACE was used as the reference standard for determining the actual presence or absence of residual viable HCC.

2. Materials and methods

2.1. Subjects

This prospective study was approved by our institutional review board, and written informed consent was obtained from each patient. Between September 2011 and April 2012, a total of 46 consecutive patients who were suspected of having HCC lesions based on conventional US surveillance for HCC in patients with chronic liver disease and who were candidates for TACE were enrolled in this study. The inclusion criteria were as follows: (1) Child-Pugh grade A or B liver cirrhosis; (2) 2–3 lesions with a maximum diameter greater than 3 cm or multiple lesions equal to or greater than 4 in number and with a maximum diameter of more than 1 cm detected using both contrast-enhanced CT and contrast-enhanced US; (3) patients who were not candidates for surgical resection or percutaneous radiofrequency ablation even if they had less than or equal to 3 lesions and a maximum diameter less than 3 cm; and (4) a typical vascular pattern indicating hypervascular HCC (arterial hypervascularization and venous washout) on both contrast-enhanced CT and contrast-enhanced US. The exclusion criteria for this study were as follows: (1) patients who were unable to undergo contrast-enhanced CT because of a contraindication for the use of iodinated contrast agents (allergic reactions and impaired renal function); (2) lesions for which detailed evaluations using contrast-enhanced US were difficult because of non-visualization as a result of bowel gas or lesions located more than 12 cm from the skin surface; and (3) patients who exhibited macrovascular invasion or extrahepatic spread. Fourteen patients were excluded: 3 patients were allergic to iodinated contrast agents, 2 patients had HCC lesions that could not be visualized because of interference from bowel gas, 1 patient had an HCC lesion located more than 13 cm from the skin surface, 4 patients had invasions to the portal vein, and 4 patients had extrahepatic spread. In the 27 patients with multiple HCC lesions, the two largest lesions were selected for analysis in this study; the other 5 patients had solitary lesions. Finally, 32 patients with 59 HCC lesions were enrolled in this prospective study.

The patient population included 24 men and 8 women (mean age ± standard deviation [SD], 70 ± 7 years; age range, 51–83 years). The mean maximal diameter of the tumors was 29 ± 12 mm (range, 10–73 mm). Twenty-nine patients had Child-Pugh class A cirrhosis of the liver, and 3 patients had Child-Pugh class B cirrhosis. The cirrhotic background consisted of hepatitis B virus infection in 2 patients, hepatitis C virus infection in 24 patients, both hepatitis B and C virus infection in 4 patients, and alcohol abuse in 2 patients.

2.2. Imaging methods

2.2.1. Contrast-enhanced CT images

Contrast-enhanced CT imaging was performed using two devices: (1) a 16-channel multidetector scanner (Aquilion 16; Toshiba Medical, Tokyo, Japan) with a tube voltage of 120 kV, a tube current set at the automatic milliampere exposure setting, a reconstruction section and interval thickness of 5 mm, a pitch of 15, and a gantry speed of 0.5 s per rotation; and (2) an 80-channel multidetector scanner (Aquilion PRIME; Toshiba Medical, Tokyo, Japan) with a tube voltage of 120 kV, a reconstruction section and interval thickness of 5 mm, a pitch of 65, and a gantry speed of 0.5 s per rotation. A nonionic contrast agent (iopamidol [Iopamiron 300 or 370; Bayer HealthCare, Osaka, Japan]) was injected. Patients weighing less than 70 kg received 300 mg of iodine/mL, whereas those weighing 70 kg or more received 370 mg of iodine/mL. After a power injector (Dual Shot GX; Nemoto Kyorindo, Tokyo, Japan) was used to inject 100 mL of iopamidol at 3 mL/s through a catheter placed in the antecubital vein, the scanning time in the arterial phase was confirmed using an automatic bolus-tracking program (RealPrep; Toshiba Medical). The trigger point for starting arterial phase scanning was set at an attenuation of 230 HU from the baseline attenuation of the abdominal aorta at the celiac artery level and an additional start delay of several seconds (Aquilion 16, 10 s; Aquilion PRIME, 12 s). Hepatic venous phase scanning was performed 70 s after contrast injection, and equilibrium phase images were acquired 180 s after injection.

2.2.2. US imaging

2.2.2.1. Conventional US (B-mode) images. First, we assessed the detection of HCC lesions using the LOGIQ 7 ultrasound system (GE Healthcare, Milwaukee, WI, USA) with native tissue harmonic grayscale imaging using a convex probe with a frequency of 2–5 MHz and a micro-convex probe with a frequency of 2–5 MHz (hereafter referred to as conventional US).

2.2.2.2. Suitable contrast-enhanced imaging software for the detection of residual HCC lesions after TACE. After TACE, the tumor echogenicity changes to hyper-echogenicity (Figs. 1A,B and 2B,C) because of the deposition of iodized oil within the tumor and surrounding liver parenchyma. Contrast-enhanced US with a low MI mode imaging software at a low MI (0.2–0.3) cannot remove the influence of hyper-echogenicity after TACE, and this hyper-echogenicity disturbs the accurate evaluation of the absence or presence of residual viable HCC lesions (Fig. 1E). However, contrast-enhanced US with a high MI mode imaging software, known as CHA, at a high MI (0.7–1.0) can eliminate background B-mode features,