Abstract

Purpose. The aim of this study was to assess and compare the sensitivity of power Doppler sonography, contrast-enhanced sonography, plain computed tomography (CT), and dynamic magnetic resonance imaging (MRI) for detecting hepatocellular carcinoma (HCC) nodules incompletely treated with transcatheter arterial embolization (TAE).

Methods. A total of 63 unresectable HCC nodules were examined in this study. The HCCs were treated with TAE. All patients underwent plain CT, power Doppler sonography, contrast-enhanced harmonic power Doppler sonography, and dynamic MRI 1 week after TAE. The sensitivity of each modality to incompletely treated HCC nodules was compared. Detection of the residual viable HCC on angiography or tumor biopsy was regarded as the gold standard for the diagnosis of incomplete treatment.

Results. Twenty-four nodules (38%) were diagnosed as incompletely treated. The sensitivities of plain CT, power Doppler sonography, contrast-enhanced harmonic power Doppler sonography, and dynamic MRI to these incompletely treated nodules were 42% (10/24), 46% (11/24), 88% (21/24), and 79% (19/24), respectively. Eighty percent (19 nodules) of the 24 incompletely treated nodules were located within a depth of less than 8 cm. The sensitivities of plain CT, power Doppler sonography, contrast-enhanced harmonic power Doppler sonography, and dynamic MRI to these superficial incompletely treated nodules were 37% (7/19), 53% (10/19), 100% (19/19), and 74% (14/19), respectively. In contrast, the sensitivities of each modality to deeply located nodules were 60% (3/5), 20% (1/5), 40% (2/5), and 100% (5/5), respectively.

Conclusion. Plain CT and power Doppler sonography had a low sensitivity to HCC nodules incompletely treated with TAE. Except for those that were deeply located, contrast-enhanced harmonic sonography showed the highest sensitivity in detecting incompletely treated HCC nodules.

Keywords therapeutic effect · transcatheter arterial embolization · hepatocellular carcinoma · contrast-enhanced harmonic power Doppler sonography · dynamic MRI

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in Japan, with the number of patients increasing annually. Because of advanced tumor stage or severe liver damage, operative indication is limited. Transcatheter arterial embolization (TAE) is one of the techniques used to treat unresectable HCCs.1-3 However, TAE does not guarantee complete necrosis of HCC nodules unless it is performed perfectly on all tumor vessels; HCCs have more than two supplying vessels. Early detection of incompletely treated HCC nodules enables additional treatments such as percutaneous ethanol injection (PEI) therapy, microwave coagulation therapy (PMCT), or radiofrequency (RF) ablation therapy before any obvious recurrence.

The blood supply to the nodule completely disappears in successfully treated HCCs. Color and power Doppler ultrasonography have been used to assess blood flow in HCCs after TAE treatment,4,6 and the superior sensitivity of contrast-enhanced sonography in detecting tumor flow has recently been reported.7-10 Furthermore, TAE evaluation using computed tomography (CT) or magnetic resonance imaging (MRI) has been conducted.11,12
It is unrealistic to perform all these examinations in every patient who undergoes TAE to assess its outcome because of both the cost and the time-consuming nature of the procedures. Knowledge about the sensitivity of each examination technique in detecting incompletely treated HCC nodules is, therefore, essential for avoiding unnecessary examinations. This study aimed to assess and compare the sensitivity of power Doppler sonography, contrast-enhanced sonography, CT, and MRI for detecting HCC nodules incompletely treated with TAE.

**Materials and methods**

**Subjects**

Between April 2001 and March 2004, 51 patients with HCCs were admitted to our hospital for TAE treatment. The subjects included 34 men and 17 women ranging in age from 32 to 87 years (mean age, 70 years). All patients had been excluded from surgical treatment because of liver dysfunction, advanced age, or refusal to undergo surgery. Although MRI and CT can evaluate multiple HCC nodules in a single scan, contrast-enhanced sonography has technical difficulties in scanning more than two nodules at the same time. Therefore, patients with solitary nodules were selected in this study. In 12 patients, solitary recurring nodules were enrolled in addition to the initial nodules. Thus, a total of 63 nodules were examined in this study. HCC size was assessed using fundamental sonography revealing a maximum diameter ranging from 1 to 9 cm (mean, 2.8 cm). All patients had cirrhosis caused by alcohol (2 patients), hepatitis B (5 patients), hepatitis C (39 patients), or non-B and non-C hepatitis (5 patients). HCC diagnosis was mainly made clinically. During CT examinations, all nodules showed HCC features such as the presence of both hyperattenuating areas in the arterial phase and hypoattenuating areas in the delayed phase. Informed consent was obtained from all patients.

**TAE treatment**

Digital subtraction angiography showed tumor stains for all the HCC nodules. A microcatheter was introduced into a segmental or subsegmental branch supplying blood to the HCC nodule. In the past, TAE was performed with iodized oil (Lipiodol; Andre Guerbet, Aulnay-sous-Bois, France) and epirubicin hydrochloride (10–40 mg per patient) (Farmorubicin; Pharmacia & Upjohn, Tokyo, Japan) was used. A 1-mm² gelatin sponge (Spong; Yamanouchi Pharmaceutical, Tokyo, Japan) was then placed in each HCC nodule.

Power Doppler sonography and contrast-enhanced sonography

All patients underwent power Doppler sonography and contrast-enhanced harmonic power Doppler sonography 1 week after TAE treatment. Sonography was performed with Powervision 8000 (Toshiba Medical Systems, Tokyo, Japan) using a 3.75-MHz convex probe.

With power Doppler sonography, color gain was adjusted by increasing it to the point at which the noise began to exceed the lowest level of color. After a fundamental gray-scale scan and power Doppler sonography, a 7-ml dose of galactose-palmitic acid mixture contrast medium (Leovist; Schering AG, Berlin, Germany) with a concentration of 300 mg/ml was injected at 1 ml/s through a 20- to 22-gauge cannula placed in an antecubital vein. About 10s after the bolus injection, the liver was scanned using contrast-enhanced harmonic power Doppler sonography. The patients were asked to hold their breath to focus the target nodule for about 30s while tumor enhancement was observed (observation of the arterial phase). After observation of the arterial phase, the images were frozen and stored on magneto-optical disks. Then, tumor enhancement was observed 60–180s after injection of contrast agent while patients held their breath for 20s. The scanning plane was gradually changed during the observation period to scan the entire tumor. The images were stored on magneto-optical disks with short pauses. These scans were repeated two to three times (observation of the portal phase).

Harmonic power Doppler sonography was performed with the intermittent mode. One frame per 1s was used during the arterial phase and one frame per 2s during the portal phase. The maximum mechanical index was used, ranging from 1.0 to 1.8, and the focus position was just below the bottom of the tumor. Color filter and pulse repetition frequency were set at 1335 Hz and 4.5 kHz, respectively. The monitor mode with low acoustic power output (mechanical index, <0.1) allowed the real-time image to focus on the targeted nodule without destruction of the microbubbles. The late-phase scans (5 min after injection of contrast agent) were sometimes omitted in this study, because the arterial and portal phases were considered to give more sensitive information on the detection of viable HCCs than the late phase. After TAE, the absence of positive enhancement inside the tumor during all vascular phases was confirmed. A diagnosis of unsuccessful treatment was made only when the obvious positive enhancement inside the tumor was detected, to avoid influence of the color blooming artifact in harmonic power Doppler sonography.

**CT**

Plain CT was performed on all patients using a Somatom Plus4 (Siemens, Erlangen, Germany) 1 week after TAE. All images were obtained with a section thickness of 8 mm. An enhanced study was not conducted.
Dynamic MRI

MR examinations were performed using a 1.0-T superconducting magnet (Harmony; Siemens), and MR images were acquired along the axial plane. Gradient-echo pulse sequences were used with a repetition time of 190 ms and an echo time of 6.2 ms for T1-weighted images and 4000 ms/93 ms for T2-weighted images. Contrast-enhanced T1-weighted images were acquired in all cases after intravenous bolus administration of 0.1 ml/kg gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany).

Image evaluation and definition of incompletely treated HCC nodules

To minimize procedural variations, power Doppler sonography and contrast-enhanced harmonic power Doppler sonography were performed by the same physicians (T.S. and M.M.), whereas CT and dynamic MRI were reviewed by T.S. and radiologists; any differences were resolved by consensus.

With power Doppler sonography, TAE treatment was considered successful if no signal was detected in the tumor. With contrast-enhanced harmonic power Doppler sonography, if the tumor was not enhanced in either the arterial or the portal phase and was also recognized as a perfusion defect with an oval or round shape in the portal phase, TAE treatment was considered successful. With CT examinations, the retention of iodized oil in the entire HCC lesion was diagnosed as successful treatment, whereas with dynamic MRI, the absence of contrast enhancement of the HCC was regarded as successful. The nodules diagnosed as successfully treated in all Doppler sonography, contrast-enhanced sonography, CT, and dynamic MRI examinations were defined as “completely treated nodules.” When diagnosis discrepancies arose in any of these examinations, angiography or percutaneous tumor biopsies were performed. Aspiration tumor biopsies were conducted using an 18-gauge needle (Sonopsy; Hakko, Tokyo, Japan) under conventional sonographic guidance. Nodules demonstrating persistent viable HCCs on angiography or biopsy were defined as “incompletely treated nodules.” Statistical analyses of the results were performed with both the chi-square test and the Fisher’s exact probability test. A P value of less than 0.05 with Fisher’s exact test was considered statistically significant.

Results

Sensitivity, specificity, and accuracy of each method

In total, 53, 52, 42, and 44 nodules were diagnosed as successfully treated HCCs using plain CT, power Doppler sonography, contrast-enhanced harmonic power Doppler sonography, and dynamic MRI, respectively. If discrepancies existed, the nodules were studied further based on the definition of incompletely treated HCC nodules. Overall, 39 (62%) of the 63 nodules were diagnosed as completely treated, whereas 24 (38%) were diagnosed as incompletely treated and treated with repeat TAE or PMCT. With plain CT, 10 nodules showed incomplete deposition of iodized oil and were diagnosed as incompletely treated tumors. The sensitivity of plain CT to incompletely treated nodules was calculated as 42% (10/24) (Fig. 1). Using power Doppler sonography, 11 nodules showed the Doppler signal and were diagnosed as incompletely treated tumors (Fig. 2c). The sensitivity of power Doppler sonography was calculated as 46% (11/24) (Fig. 1). The sensitivities of power Doppler sonography to incompletely treated nodules located in the left (seg. 2–4) and right (seg. 5–8) lobes were 22% (2/9) and 60% (9/15), respectively. The sensitivity of power Doppler sonography in the left lobe was lower than that of the right one. The difference was not statistically significant. Using contrast-enhanced sonography, positive enhancement was observed in 21 nodules diagnosed as incompletely treated (Figs. 2d, 3d, e). The sensitivity of contrast-enhanced sonography was calculated as 88% (21/24) (see Fig. 1). With dynamic MRI, 19 nodules demonstrated the tumor stain (Figs. 2b, 4b), and the sensitivity of dynamic MRI was calculated as 79% (19/24) (Fig. 1). Both contrast-enhanced sonography and dynamic MRI have significantly higher sensitivities to incompletely treated nodules than plain CT and power Doppler sonography (Fig. 1); their specificities were 100% on every test. The accuracies of plain CT, power Doppler sonography, contrast-enhanced harmonic power Doppler sonography, and dynamic MRI were 78 (49/63), 79 (50/63), 95 (60/63), and 92% (58/63), respectively.
Fig. 2. Images of an HCC diagnosed as an incompletely treated HCC with dynamic MRI, power Doppler sonography, and contrast-enhanced sonography. a Iodized oil (arrowhead) accumulated in the entire HCC lesion. CT diagnosis: successful treatment. b Enhancement (arrowhead) was observed in almost the entire HCC. MRI diagnosis: unsuccessful treatment. c A Doppler signal (arrow) was observed in the HCC. Power Doppler sonography diagnosis: unsuccessful treatment. d Portal phase of contrast-enhanced sonogram showing the positive enhancement area (arrows) of the tumor. The image on the right is the monitor image; arrowheads indicate the HCC. Contrast-enhanced harmonic power Doppler sonography diagnosis: unsuccessful treatment.

Fig. 3. Images of an HCC diagnosed as an incompletely treated HCC with contrast-enhanced harmonic sonography only. a Iodized oil (arrowhead) accumulated in the entire HCC lesion. CT diagnosis: successful treatment. b No enhancement was observed in the HCC (arrowhead). MRI diagnosis: successful treatment. c Subcostal scan of a conventional sonogram of the HCC in the right liver lobe showing heterogeneous hyperechoic SOL (arrowheads). d Arterial phase of a contrasted sonogram showing the hypervascular area (arrows) in part of the tumor. Arrowheads show the outline of the HCC. e The portal phase of the contrasted sonogram did not show enhanced defects in the entire tumor. Positive enhancement (arrows) remained in the left side of the tumor. Contrast-enhanced harmonic power Doppler sonography diagnosis: unsuccessful treatment. Arrowheads show the outline of the HCC.
Sensitivity of contrast-enhanced sonography and dynamic MRI to incompletely treated HCC nodules misdiagnosed on CT

Of the 24 incompletely treated nodules, 14 were judged as successfully treated on plain CT (Figs. 2a, 3a). Of these 14 misdiagnosed nodules, 13 (93%) and 9 (64%) were correctly diagnosed as unsuccessfully treated with contrast-enhanced sonography and dynamic MRI, respectively.

Dependence of diagnosis sensitivity on HCC nodule depth

Of the 24 incompletely treated nodules, 19 were superficial lesions with a depth of less than 8 cm from the sonographic transducer. The sensitivities of plain CT, power Doppler sonography, contrast-enhanced harmonic power Doppler sonography, and dynamic MRI to these superficial incompletely treated nodules were 37 (7/19), 53 (10/19), 100 (19/19), and 74% (14/19), respectively (Fig. 5a). Contrast-enhanced harmonic sonography showed a significantly higher sensitivity than the other modalities ($P < 0.05$; Fisher’s exact probability test). The mean diameter of the 5 nodules judged as unsuccessfully treated with contrast sonography and successfully treated with MRI was 2.0 cm (range, 1.2–3.0). On the other hand, 5 of the nodules were deeply located lesions with a depth of more than 8.1 cm from the transducer. The sensitivities of plain CT, power Doppler sonography, contrast-enhanced harmonic power Doppler sonography, and dynamic MRI to deeply located incompletely treated nodules were 60% (3/5), 20% (1/5), 40% (2/5), and 100% (5/5), respectively (Fig. 5b). Power Doppler sonography showed significantly lower sensitivity than dynamic MRI ($P < 0.05$; Fisher’s exact probability test).

Discussion

Since Yamada et al. reported the use of TAE therapy on patients with unresectable HCCs in 1983, it has become a widely performed HCC treatment in Japan. Randomized controlled studies in non-Asian areas during the 1990s failed to show any significant benefit to the survival of patients treated with TAE compared to untreated controls. However, a recent randomized controlled study clearly showed that TAE improved the survival rate of unresectable HCC patients in China. Other reports have shown excellent TAE outcomes in Japan. Therefore, TAE is considered an effective conservative treatment for unresectable HCCs in Japan.

Because iodized oil retention is easily detected on CT scans, CT evaluations of the therapeutic effects of TAE have been widely used. However, with CT examinations, it is difficult to assess residual blood flow in the tumors after
TAE treatment because the CT characteristic of iodized oil displayed as high density masks the tumor enhancement shown by the injection of contrast media. Therefore, enhanced studies of CT examinations were not carried out in this study. Our results showed that 14 (58%) of 24 incompletely treated HCC nodules were judged as successfully treated on plain CT. The blood flow of these 14 tumors was confirmed on contrast-enhanced sonography or dynamic MRI. This result shows that a sufficient accumulation of iodized oil does not guarantee the complete disappearance of tumor blood flow after TAE treatment. Taking CT characteristics of iodized oil into account, the low sensitivity (42%) of CT to incompletely treated nodules seems to be reasonable.

Doppler sonography has some benefits over other modalities, such as its less time-consuming technique and low cost, and it can provide clinically useful information relating to tumor blood flow. Therefore, Doppler sonography has been used in the past to assess the response of HCCs treated with TAE. However, Doppler sonography has some limitations such as angle dependency and a lack of sensitivity to slow flow. Power Doppler sonography has an increased sensitivity to tissue motion. The motion artifact accompanied by the sensitive detection of slow blood flow is inevitable in the left hepatic lobe because heartbeats result in periodic liver movements. In this study, the sensitivity in the left lobe was extremely low (22%). The low sensitivity (46%) to incompletely treated nodules seems to be attributable to the technical difficulty in distinguishing Doppler signals of blood flow from artifact signals.

In this study, the sensitivity (79%) of dynamic MRI to incompletely treated nodules was significantly higher than that of CT and power Doppler sonography. Dynamic MRI has a high sensitivity in enhancing viable HCCs, and, furthermore, the signal intensity of MRI is not affected by the retention of iodized oil in the tumors. The high sensitivity of dynamic MRI seems to be attributed to these MRI features. Recently, microbubble contrast agents for sonography became commercially available in Japan, and newly developed harmonic imaging techniques using these microbubbles enable sonographic observations of slow blood flow and tumor perfusion. In the past, contrast-enhanced sonography has shown excellent sensitivity to tumor blood flow. The accumulation of iodized oil has no obvious influence on contrast-enhanced sonography, and the high sensitivity (88%) of contrast-enhanced harmonic power

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**Fig. 5. Sensitivities of plain CT, power Doppler sonography, contrast-enhanced sonography, and dynamic MRI to superficial and deep incompletely treated HCCs.**

a Sensitivity to the 19 nodules with a depth of less than 8 cm from the sonographic transducer. Contrast-enhanced sonography showed a significantly higher sensitivity than the other modalities. b Sensitivity to the 5 nodules with a depth of more than 8.1 cm from the transducer. The highest sensitivity was observed in the dynamic MRI. Sonographic examinations showed low performance.
Doppler sonography to incompletely treated nodules shows that contrast-enhanced sonography is one of the best methods for assessing the efficacy of TAE treatments.

To our knowledge, there are few reports in English documenting comparisons of contrast-enhanced sonography and dynamic MRI in the assessment of TAE treatment of HCCs. With superficial nodules, the sensitivity of contrast-enhanced sonography to incompletely treated nodules was superior to that of dynamic MRI in this study. Most nodules can be observed as superficial nodules if the position of the sonographic transducer is carefully selected. In this study, 80% of the HCCs were observed as superficial nodules. Furthermore, HCCs judged as unsuccessfully treated on contrast-enhanced sonography and as successfully treated on MRI were those that were less than 3.0cm in diameter. The higher sensitivity of contrast-enhanced sonography compared to dynamic MRI seems attributable to the high spatial resolution of sonography. On the other hand, the sensitivity of dynamic MRI was superior to that of contrast-enhanced sonography with deeply located nodules. The low sensitivity of contrast-enhanced sonography to HCC nodules in the deep part of the liver has been reported. Sensitivities of both power Doppler sonography and contrast-enhanced harmonic sonography to incompletely treated nodules were less than 50% with deeply located nodules in our study. A serious decrease in the power of the ultrasound beam seems the major cause of the sensitivity problems in the deep part. The sensitivity of contrast-enhanced sonography has a strong dependency on machine performance, the kind of contrast agent, and the harmonic technique. The sensitivity decline of contrast-enhanced sonography to deeply located nodules might be improved in the near future with technical developments of ultrasonography.

Conclusions

Contrast-enhanced harmonic power Doppler sonography showed the best performance in detecting superficial incompletely treated HCCs at a depth of less than 8cm from the sonographic transducer. In our study, most (79%) of the HCCs were observed as superficial nodules. Furthermore, contrast-enhanced harmonic sonography is less expensive than enhanced MRI or enhanced CT. Therefore, in the case of superficial solitary HCCs, contrast-enhanced harmonic sonography would be the best modality for detecting incompletely treated HCCs 1 week after TAE treatment.

References
