Contrast-enhanced Doppler Ultrasound for Guiding Percutaneous Microwave Ablation of Hepatocellular Carcinoma: A Report of 32 Cases

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Objective: To evaluate the usefulness of contrast-enhanced Doppler ultrasound for percutaneous microwave ablation therapy (PMAT) of hepatocellular carcinoma (HCC).

Methods: A total of 51 hepatic tumors in 32 patients with HCC were treated using a microwave system with a frequency of 2,450 MHz. Before and after PMAT, color Doppler imaging with a bolus injection of Levovist® (Schering AG, Berlin, Germany), at a dose 5 mL at 400 mg/mL, was performed with an A 128 XP10/ART unit (Acuson, Mountain View, CA), with a probe frequency of 3.5 MHz.

Results: Immediately after PMAT, gray-scale ultrasound imaging of the treated tumor appeared as a hyperechoic area with an acoustic shadow around the electrode. Non-contrast-enhanced color flow signals were detected in all 51 nodules before treatment, while color flow signals disappeared in 49 (96.1%) nodules and were still present in two nodules after the treatment. Contrast-enhanced sonography with Levovist® demonstrated only 36 nodules without flow signals and 15 nodules still having flow signals, 30 days after PMAT. Based on contrast-enhanced ultrasound findings, the residual tumor regions with blood flow signals were treated again within 1 month. Twenty-one of 32 patients had follow-up within 18 months (65.6%).

Conclusion: Contrast-enhanced Doppler ultrasound is useful for evaluating ultrasound-guided PMAT for HCC.

(KEY WORDS: • liver neoplasm • microwave coagulation • interventional ultrasound • Levovist®)

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading killer from the class of malignant tumors in China [1]. Surgical resection is still the treatment method of choice, but only less than 20% of cases are eligible for resection, due to advanced tumor stage and underlying liver cirrhosis [2,3]. HCC also has a high tendency to recur, even after successful tumor removal, which typically requires repeated
treatment. This additional intervention may result in severely impaired liver function. To maximally preserve liver function for surgically non-resectable patients, effective treatment should be as minimally invasive as possible.

Ultrasound-guided percutaneous microwave ablation therapy (PMAT) is one of the relatively new thermal coagulation techniques for the treatment of HCC. In 1994, Seki et al first reported PMAT as an effective method for the treatment of small (< 2 cm) HCCs [4]. Since then, satisfactory therapeutic results from PMAT for the treatment of small HCCs have been reported by many investigators [5–11]. A potential benefit of this technique is that it offers treatment for patients who are not surgical candidates, and it may reduce morbidity associated with surgery. However, the efficacy of PMAT for hepatic tumors larger than 2 cm has not been well investigated. The purpose of this study was to use contrast-enhanced ultrasound imaging (CEUSI) to evaluate the usefulness of PMAT for hepatic tumors larger than 2 cm, commonly seen in a clinical setting.

PATIENTS AND METHODS

Thirty-two patients with pathologically confirmed HCC were treated with PMAT, from May 1999 to July 2001. There were 24 males and eight females with a mean age of 52.4 years (range, 32–70 years). All patients were clinically classified as non-surgical candidates for tumor removal, based on one or more of the following factors: poor liver function, elderly patients with chronic kidney or heart disease, multiple segmental lesions, and recurrent HCC. Of the 32 patients, 22 had one lesion, three had two lesions, five had three lesions, and two had more than three lesions. The maximum dimension of the lesions ranged from 3 to 15 cm (8.27 cm ± 1.6 cm). Histologic diagnosis was established by ultrasound-guided biopsies with an 18-gauge cutting biopsy needle (Type Quickcut–2, Hakko, Japan). All PMAT procedures were performed at an interventional ultrasound room. Written informed consent was obtained from each patient at enrollment, and ultrasound follow-up was carried out continuously until December 2002.

Patients who had uncontrollable ascites or coagulopathy (prothrombin activity < 40%, prothrombin time > 25 seconds, platelet count < 50 × 10^9/L) were excluded from this study.

Microwave ablation

An HSE–8M microwave coagulation system (Microtaze, AZWELL Inc, Osaka, Japan) with a microwave frequency of 2,450 MHz and a power output ranging from 10 to 80 W was used. The system was equipped with a 14G needle electrode (1.4 mm in diameter) with a 3-cm uninsulated tip. The surface of the electrode was coated with a Teflon coating, to prevent tissue charring. Based on previous experience and tumor size [5], the microwave power setting was 60 W and the duration of each ablation ranged from 60 to 300 seconds (tumors < 4 cm = 60 seconds; tumors 4–6 cm = 120 seconds; tumors 6–10 cm = 200 seconds; and tumors > 10 cm = 300 seconds).

Ultrasound

A 128 XP10/ART unit (Acuson, Mountain View, CA) with a 3.5 MHz phased array transducer was used in this study. A contrast agent, Levovist® (Schering AG, Berlin, Germany), was administered intravenously at a dose of 5 mL at 400 mg/mL before and after PMAT. Contrast-enhanced color Doppler imaging (CECDI) was used to evaluate tumor vascularity.

Ablation procedure

With intravenous anesthetics administered by an anesthesiologist, an electrode was inserted into the center of the tumor under ultrasound guidance. To achieve complete destruction of tumors larger than 4 cm, we first positioned the tip of the electrode in the distal margin of the tumor. Due to the fact that 60-W output and a 300-second duration can create a coagulation area of 4 × 2.7 × 2.6 cm, four or five insertions were used for the deep portion of the tumor. After the deep portion of the tumor was coagulated, the electrode was relocated to superficial areas for overlapping ablation, until the entire tumor was destroyed within four or five insertions. For the large tumor (> 4 cm), a complete treatment was performed over two sessions and within 1 week. When color Doppler imaging and CEUSI identified a feeding vessel within the tumor, the electrode was first placed within this vessel and destroyed it, before ablating the other areas.

ASSESSMENT OF EFFICACY

One month after PMAT, all patients were examined
via dynamic computed tomography imaging (CT). Two radiologists without knowledge of the treatment results reviewed the images separately. Tumor areas with uniformly low attenuation and no enhancement were considered to be necrotic tumor tissue.

CEUSI was performed for all patients at 15, 30 and 75 days after PMAT, by two independent radiologists who were unaware of the treatment sessions. Tumor size was measured in three dimensions before and after PMAT. The thermal lesions of a treated area appeared as hypoechoic areas. If blood vessels within the ablated area were detected by CECDI, local recurrence or incomplete necrosis of the tumor was considered present. Blood samples were tested to determine the serum \( \alpha \)-fetoprotein level and liver function before PMAT and 2–4 weeks after percutaneous microwave coagulation therapy.

**RESULTS**

Thirty-two patients had follow-up for 6–43 months after completion of PMAT. Of the 32 patients, 21 had follow-up within 18 months (65.6%) and were still alive. Twenty-seven patients survived past the end of 2002, and consulted periodically as outpatients. Five patients had died by the end of this study, where one fatality was from advanced HCC, three were from systemic metastasis, and one was from bleeding in the upper gastrointestinal tract.

Immediately after microwave ablation, gray-scale ultrasound imaging of the treated tumor appeared as a hyperechoic area, with an acoustic shadow around the electrode. This hyperechoic area diffused over time and completely disappeared within 6–8 hours. After PMAT, the changes of sonographic appearance depended on the initial echogenic pattern of the tumor. In most cases (48 of 51 nodules), the hypoechoic tumors increased echogenicity, and hyperechoic lesions showed heterogeneous hyper-echogenicity after therapy. Two weeks after treatment, all of the 51 nodules began to shrink to some degree (7.5–11.9% decrease in diameter).

Non-contrast-enhanced color flow signals were detected in all 51 nodules before the treatment. However, contrast-enhanced sonography with Levovist® demonstrated only 36 nodules without flow signals and 15 nodules still having flow signals 30 days after PMAT (Table and Figure 2). Based on the contrast-enhanced ultrasound findings, combined with contrast-enhanced CT, the residual tumor regions with blood flow signals received additional ablation within 1 month (residual tumors were confirmed pathologically by ultrasound-guided biopsy in 5 of 15 nodules).

CEUSI was performed 15 days after ablation revealed 31 nodules without flow signals, and 20 nodules still showed flow signals. At 75 days after ablation, CEUSI revealed 17 nodules with flow signals, and 34 nodules without flow signals.

Forty-two of 51 nodules (82.3%) showed enhancement on contrast-enhanced CT before treatment. The other nine nodules failed to show enhancement. Two possible reasons for this failure include tumors with portal vein supplying or tumors with sclerosis may not show enhancement. One month after the treatment, contrast-enhanced CT revealed that blood vessels (arteries) within the tumors were not evident in 38 of 51 lesions (74.5%).

Serum levels of \( \alpha \)-fetoprotein were tested in all 32 patients before treatment. Of these patients, 12 had normal serum \( \alpha \)-fetoprotein levels (< 20 mg/L), and 20 patients (59.40%) had elevated serum \( \alpha \)-fetoprotein levels. Within 2–4 weeks after treatment, the \( \alpha \)-fetoprotein levels had decreased in 16 of 20 patients who had elevated \( \alpha \)-fetoprotein values before ablation.

**DISCUSSION**

Percutaneous ethanol injection therapy is widely used for the treatment of small liver cancers. Because of the uneven distribution of ethanol in tumor tissue, tumor destruction can be incomplete, especially tumors larger than 2 cm in size [12,13]. Radio-frequency ablation and PMAT are two thermal ablation therapies developed in recent years [14,15]. Compared to percutaneous ethanol injection therapy, these two modalities have the advantage of creating a relatively even coagulation area, thereby providing more reliable ablation for HCC [10]. At present, PMAT is mainly used for tumors smaller than 4 cm. For larger tumors, the local effectiveness of this method is less promising.
Fig. 1. A 45-year-old man with liver metastasis. (A) Ultrasound showed a mass of 55 mm × 50 mm before percutaneous microwave ablation therapy (PMAT). (B) Metastasis was confirmed by pathology. (C) Specimen after PMAT. (D) After ablation, necrosis was confirmed by pathology.

Table. Evaluation of tumor arteries 30 days after percutaneous microwave ablation therapy, using Levovist® contrast ultrasound and color Doppler flow imaging (CDFI)

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<th>CDFI</th>
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For percutaneous thermal ablation, coagulation of the whole tumor and its margin is essential for achieving complete tumor necrosis. Therefore, finding methods of expanding the coagulated area is a key issue worth studying. A number of investigators have implemented novel methods of creating larger volumes of coagulated necrotic tissue. Goldberg et al showed that increased tissue destruction could be achieved using multiple electrodes [15]. McGahan et al, for their part, showed that bipolar radiofrequency can be effective in increasing the volume of tissue coagulation, compared with the monopolar techniques [16].

Seki et al reported long-term results of PMAT for solitary HCCs 2 cm or smaller in diameter; the 5-year survival rate was reported as more than 70% [10]. In their study, PMAT was performed in 50 patients with 107 nodules, which included 61 nodules larger than 2 cm in diameter. The 1, 2, and 3-year survival rates were 96%, 83%, and 73%, respectively. In contrast, the 3-year survival rate in untreated patients with HCCs smaller than 3–5 cm is only 12.8–21.0% [17,18]. These results suggest that PMAT can improve the survival rate in patients undergoing PMAT.
Another important factor affecting therapeutic efficacy is the management of tissue blood perfusion. In a study by Rossi et al, the volume of coagulated necrosis was limited because of the proximity of large vessels that acted as a heat sink during radiofrequency thermal therapy [17]. After occlusion of arterial blood flow to the tumor, the researchers found that the area of coagulated necrosis was significantly enlarged. From our study, we feel that ablation of the feeding vessels was a useful technique for coagulating the tumor. With the help of CEUSI, we could easily find the feeding vessels for the tumor.

Many modalities, such as CT, magnetic resonance imaging, ultrasound, and fine-needle aspiration biopsy, have been used to assess the efficacy of PMAT. Each has its advantages and disadvantages. CT is generally accepted as the standard and most reliable method of evaluating the extent of tumor necrosis induced by treatment, because, after the administration of a contrasting agent, the presence of vascular enhancement usually signifies the persistence of viable tumors. Furthermore, non-enhancement normally represents the absence of visible tumor tissue. However, hepatic artery-related enhancement can sometimes be observed in normal liver tissue adjacent to the necrotic region on follow-up CT, and such a reading may be misinterpreted as incomplete necrosis [20,21].

Characterization of liver cancer by ultrasound has traditionally been performed solely on the basis of gray-scale morphologic features. The addition of color, power, and spectral Doppler provides additional vascular information. Unfortunately, the use of conventional Doppler to provide this vascular information is often limited in the evaluation of liver

Fig. 2. (A) In a 42-year-old man with a solitary mass on the left lobe, contrast-enhanced ultrasound imaging shows multiple vessels within the tumor before microwave ablation. (B) Ultrasound-guided biopsy with pathology confirmed hepatocellular carcinoma. (C) 15 days after ablation, ultrasound contrast imaging shows residual viable tumor with multiple vessels. (D) After the second ablation, contrast-enhanced imaging shows no tumor vessels detected.
masses, which may be located deep in the abdomen, small in size, and prone to motion artifacts from either respiratory or cardiac movements. In order to overcome these limitations, Doppler signals with the use of ultrasound contrast agents have greatly improved. The contrast agent used in this study was useful for assessing the completeness of ablation, in which hypoechoic change without vessel enhancement represented necrotic tissue. Based on our experience, contrast-enhanced color Doppler flow imaging (CDFI) ultrasound is more sensitive than CDFI for evaluating PMAT treatment \((p < 0.01)\). Our present and previous studies suggest that ultrasound contrast should be performed 1 month after ablation, and considered as a gold standard for evaluating and monitoring microwave ablation \([6, 7]\). According to our study, around 15 days after ablation, a hyperemic response surrounding the ablation area may be confused with peripheral tumor re-growth at CEUSI. Also, we found that 75 days after ablation was too late to evaluate local recurrence, therefore missing the best opportunity for treatment. Thirty days after ablation was our time of choice for assessing the response to ablation.

In conclusion, the use of CEUSI has several advantages over CT and conventional color Doppler. First, there are none of the problems related to working with X-ray; secondly, CEUSI has capabilities for easily detecting feeding vessels within tumors, important for ablation; and thirdly, the contrast agent is useful for assessing completeness of ablation and evaluating prognosis. Finally, our results showed a significant difference between contrast-enhanced ultrasound and conventional color Doppler for evaluating the completeness of ablation.

**REFERENCES**

