

Sonography-Guided Percutaneous Microwave Ablation of High-Grade Dysplastic Nodules in Cirrhotic Liver

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OBJECTIVE. Our objective was to evaluate the effect of sonography-guided percutaneous microwave ablation of high-grade dysplastic nodules in the cirrhotic liver.

MATERIALS AND METHODS. From July 1997 to May 2003, 49 histologically proven high-grade dysplastic nodules in 30 patients with liver cirrhosis were treated by microwave ablation. Three patients had concomitant small hepatocellular carcinomas ($D < 3.0$ cm), whereas another three had undergone liver segmentectomy for hepatocellular carcinoma 1 year earlier. The mean size of the nodules was 1.8 cm (range, 0.9–4.6 cm). Sixty-eight insertions with 78 applications were administered to the 49 nodules.

RESULTS. The follow-up period was 12–82 months (mean, 45.1 ± 19.0 months). Five patients died during this study: three from advanced hepatocellular carcinoma, one from bleeding in the upper gastrointestinal tract, and another from cerebral hemorrhage. All nodules showed decreased density on unenhanced CT and no enhancement on contrast-enhanced CT after microwave ablation. Posttreatment biopsy performed in 16 patients with 18 nodules 1–3 months after microwave ablation showed no evidence of viable tissue but replacement by fibrotic tissue in all nodules.

CONCLUSION. Percutaneous microwave ablation as a minimally invasive therapy is effective for ablating high-grade dysplastic nodules, thus preventing their potential malignant transformation, which may improve survival. The preliminary data warrant further prospective, randomized studies.

Small hepatic nodular lesions are detected more frequently owing to the extensive use of modern imaging techniques such as sonography, CT, and MRI in patients with liver cirrhosis [1–2]. Sonography-guided biopsy, which is widely performed in patients with hepatic occupying lesions clinically, has facilitated pathologic diagnosis in dysplastic nodules (DNs). Even though the premise that DNs should be viewed as pre-neoplastic lesions is still under debate, many studies have shown the potential for malignant transformation in DNs, especially in high-grade DNs [3–7], and therefore treatment of high-grade DNs has been seriously considered [1, 7–9]. We investigated the use of percutaneous microwave ablation for high-grade DNs in patients with liver cirrhosis; despite the lack of reports on percutaneous local thermal ablation of DNs, we sought to determine the therapeutic efficacy and safety of using microwave for ablating high-grade DNs.

Materials and Methods

Of 41 liver cirrhosis patients with histologically proven high-grade DNs evaluated between July 1997 and May 2003, 30 preferred to receive percutaneous microwave ablation. All 30 patients were treated in our department with institutional review board approval. Informed consent was obtained from each patient at enrollment.

Thirty patients (29 males and one female) with an average age of 55 years (range, 36–76 years) who had DNs were treated by percutaneous microwave ablation from July 1997 to May 2003 and followed up to May 2004. The distribution of DNs by size and the number of DNs per patient are shown in Table 1. The widest diameter of the nodules ranged from 0.9–4.6 cm (mean, 1.8 ± 0.4 cm). Twenty-eight patients had histologically proven liver cirrhosis from infection with hepatitis B, and two had infection with hepatitis C virus. Six patients were Child's class A, 23 were Child's class B, and 1 was Child's class C. Three patients were also found to have small hepatocellular carcinoma (HCC) ($D < 3.0$ cm in diameter), and three others had undergone liver segmentectomy for HCC 1–3 years earlier.

Received June 23, 2004; accepted after revision August 26, 2004.

Supported by grant 30271252 from the National Scientific Foundation Committee of China.

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AJR 2005;184:1657–1660

0361–803X/05/1845–1657

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Histologic diagnoses of the DN's were confirmed by sonography-guided biopsies with an 18-gauge cutting-edge needle through an automated gun device. Specimens were taken from different parts of the nodules (three to five pieces) and from the surrounding hepatic parenchyma (three pieces). The specimens were assessed blindly by two pathologists independently. In case of interobserver disagreement, the final decisions were reached with consensus. These 49 DN's were all determined to be high grade according to the standard of the International Working Party in 1995 [4].

Before and after microwave ablation, all patients were carefully studied with sonography and contrast-enhanced CT, together with liver function tests. Sonography examinations were performed with state-of-the-art equipment (128XP/10 ART and Sequoia; Acuson) with a 3.5-MHz convex transducer and attachments for biopsy and antenna insertion. The patients were examined by either a helical CT or MDCT. Helical CT (Tomoscan SR 7000; Philips Medical Systems) was performed with a 5-mm section thickness and a 1:1 pitch (table speed, 5 msec) at 120 kV and 250 mA. MDCT (LightSpeed 16, GE Healthcare) was obtained with a 5-mm section thickness, a 1.35:1 pitch, and a detector row 16 at 120 kV and 250 mA. After unenhanced CT scans were obtained, biphasic CT scans began at 25–30 sec (arterial phase) and 50–60 sec (portal phase) after the start of contrast material injection. A power injector was used to administer 100 mL of a nonionic contrast agent (iopromide, Ultravist 300, Schering) at a rate of 3–4 mL/sec.

Microwave delivery system consists of a magnetron, a flexible coaxial cable, two microwave antennas (1.4 mm in diameter), and two thermal needles. The microwave applicator was designed by Chinese PLA General Hospital and Institute 207 of the Aerospace Industry Company, Beijing, China. A microwave frequency of 2,450 MHz and a power output range of 10–80 W are used by this applicator.

All patients were treated as inpatients only. Inclusion criteria were as follows: a definite histologic diagnosis of high-grade DN; a single nodule with a maximum diameter of < 5 cm; ≤ 4 multiple nodules with maximum diameters of ≤ 3 cm each; a prothrombin time of < 20 sec, a prothrombin activity of > 40%, and a platelet count of > 40 × 10⁹

cells/L; and an appropriate puncture sonographically guided route for microwave antenna insertion. IV anesthesia was given to all patients during the microwave applications. General anesthesia using a combination of two anesthetics—propofol (Diprivan, Zeneca Pharmaceuticals) and ketamine—were administered by two anesthetists in all patients via peripheral veins. Antennas were inserted, under sonographic guidance, into the nodules through a 14-gauge guiding needle. If the antennas were found in the proper position, one session with a single antenna application or two antennas activating simultaneously were used for nodules with a maximum diameter of ≤ 3.0 cm. For nodules larger than 3.0 cm, two sessions with an interval of 3–5 days were performed. An output setting of 60 W for 300 sec was used during ablations. Thirty nodules were completely covered by the microwave-induced ablation area in one session, and 19 nodules were enveloped in two sessions. Sixty-eight sessions with 78 applications were performed for the 49 nodules. The concomitant small HCCs in three patients were treated by percutaneous microwave ablation as well. All of these patients completed the treatment schedules as planned and entered into the follow-up study.

Follow-up studies consist of color-flow Doppler sonography at days 7 and 30 after microwave ablation and thereafter at 3-month intervals. Contrast-enhanced helical CT or MDCT was performed 1 and 3 months after ablation and thereafter at 6-month intervals. Sonographic examination and CT were used to evaluate the therapeutic results and to monitor the possible emergence of any new lesion. If a new nodule was found, a biopsy was performed.

Results

Thirty patients were monitored for at least 12 months (range, 12–82 months; mean, 45.1 ± 19.0 months). The observation period lasted 2 years or more in 26 patients, 3 years or more in 21 patients, and 4 years or more in 19 patients. Five patients were dead by the end of this study but did not die of DN's specifically. The three patients with concomitant small HCCs died of advanced HCC 2, 3, and 5 years after microwave ablation, respectively; one

patient died of bleeding in the upper gastrointestinal tract because of portal vein hypertension 2 years after treatment, while another died of cerebral hemorrhage 5 years after treatment.

The therapeutic response was considered complete when posttreatment contrast-enhanced CT showed no areas of contrast material enhancement in the nodule (Fig. 1). Complete coagulation necrosis was shown on the images (sonography and contrast-enhanced CT) and rebiopsies. Posttreatment biopsy was performed in 16 patients with 18 nodules 1–3 months after microwave ablation. Three to five samples (mean, 3.3 specimens) taken from different parts of each nodule showed complete necrosis and no evidence of DN's. At 6 months after the microwave treatment, the treated nodules involuted gradually. Eight treated nodules were undetectable on imaging 18–36 months after microwave ablation. No local recurrence was observed in the follow-up period of 12–82 months.

No severe complications occurred. Twenty patients experienced mild pain after the microwave procedure. Mild pleural effusion was detected on sonography in two patients near the dome of the liver. Some developed a fever of 37.2–38.2°C for 1–3 days right after microwave ablation. Liver function tests showed a slight increase in transaminase levels in serum in 12 patients after ablation; this level gradually dropped to normal within 1 week.

Discussion

Many terms, such as adenomatous hyperplasia [10], macrogenenerative nodules [11], and adenomatoid hyperplasia [12], have been used to describe the presumed preneoplastic nodular lesions in the cirrhotic liver. In 1995, the International Working Party decided to use the term “dysplastic nodules” for premalignant nodular lesions of the liver [4]. The pathologic features of the DN's are as follows: the nodules are at least 1 mm in diameter, with hepatocytes containing dysplasia but no definite histologic criteria of malignancy [4]; histologically, DN's are subdivided into low-grade (dysplastic nodules with mild cytologic atypia compared to the surrounding hepatocytes) and high-grade (dysplastic nodules with a high nucleus-to-cytoplasm ratio); nuclear hyperchromatism is evident; pseudoglandular formation is evident; cell plates are more than two cells thick; and there is resistance to iron accumulation [5].

DN's in cirrhotic liver are commonly associated with HCC [6, 11–17]. DN's are found in

TABLE 1 Number and Size of Dysplastic Nodules (DN's) in 30 Patients

Diameter (D) of Largest DN's (cm)	No. of DN's in Patient				
	1	2	3	4	Total
D ≤ 2.0	3	4	0	0	7
2.0 ≤ D ≤ 3.0	9	3	2	1	15
D > 3.0	4	3	1	0	8
Total	16	10	3	1	30

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17–28% of autopsied livers in subjects with HCC [11, 13]. Foci of HCCs are sometimes found in DNs [14–16]. In the present study, DNs were in six (15%) of 41 patients with HCC. The association between DNs and HCC is highest for high-grade DNs, which were considered to be preneoplastic lesions with a high risk for developing HCC [6, 14–17]. The clonal origin showed that there is a similar integrated hepatitis B virus DNA pattern between high-grade DNs and associated HCCs that may be the genetic basis for hepatocarcinogenesis [17]. Some studies have shown a high chance of developing HCC in high-grade DNs. Takayama et al. [3] reported that 7 (35%) of 20 biopsy-proven high-grade DNs subsequently developed HCC by between 6 months and 4 years. In a series by Kaji et al. [6], HCC was noted during a follow-up period that ranged from 12–77 months in four (36%) of 11 high-grade DNs but in none of the 10 low-grade DNs.

Since high-grade DNs are at high risk of HCC in cirrhotic liver, they should be closely followed up once proven histologically. Moreover, treatment of high-grade DNs, such

as surgical resection or interventional therapy, should be considered.

Some authors have raised the possibility of resecting all nodular lesions in patients with cirrhosis even without evidence of malignancy [7, 15]. However, the high risk and high cost of surgical resection and the possible multifocal nodules occurring in cirrhotic patients limit such an aggressive surgical approach, which is not indicated in general [1]. Transarterial catheter embolization is effective for the treatment of HCC because most HCCs are hypervascular. However, several studies have revealed the difficulty in detecting and characterizing the DNs on images due to the hypovascularity in most DNs [18–21]. Thus, transarterial catheter embolization may be less effective than with HCCs. Sonography-guided percutaneous ethanol injection therapy (PEIT) has been used to treat HCCs and DNs because of its simplicity and low cost [1, 22–27]. PEIT can induce complete necrosis for DNs [1, 23], but since DNs are usually inhomogeneous, the injected ethanol is often blocked by fibrous capsules and fails to reach the nodule or even diffuses into the

surrounding hepatic parenchyma and vessels, damaging the liver tissue instead of causing nodular necrosis. Moreover, PEIT requires numerous treatment sessions and does not always lead to complete necrosis [24–27].

Percutaneous thermal ablation using different energy sources, such as radiofrequency, microwave, or laser, has received increasing attention as a promising technique for treating focal liver malignancy [28–34]. The potential benefits of these techniques include minimal invasiveness, a high percentage of complete tumor necrosis, easy treatment for multiple lesions, and improved quality of life. Thus, percutaneous microwave ablation, with its proven efficacy in the treatment of hepatic malignancy [28, 34], may be preferable for managing DNs.

Results revealed that percutaneous microwave ablation can induce complete necrosis for all treated DNs without any local recurrence after a mean follow-up period of 45 months. There were also no severe complications. Compared to PEIT for DNs, we have found that percutaneous microwave ablation requires fewer treatment sessions and causes less damage to the liver.

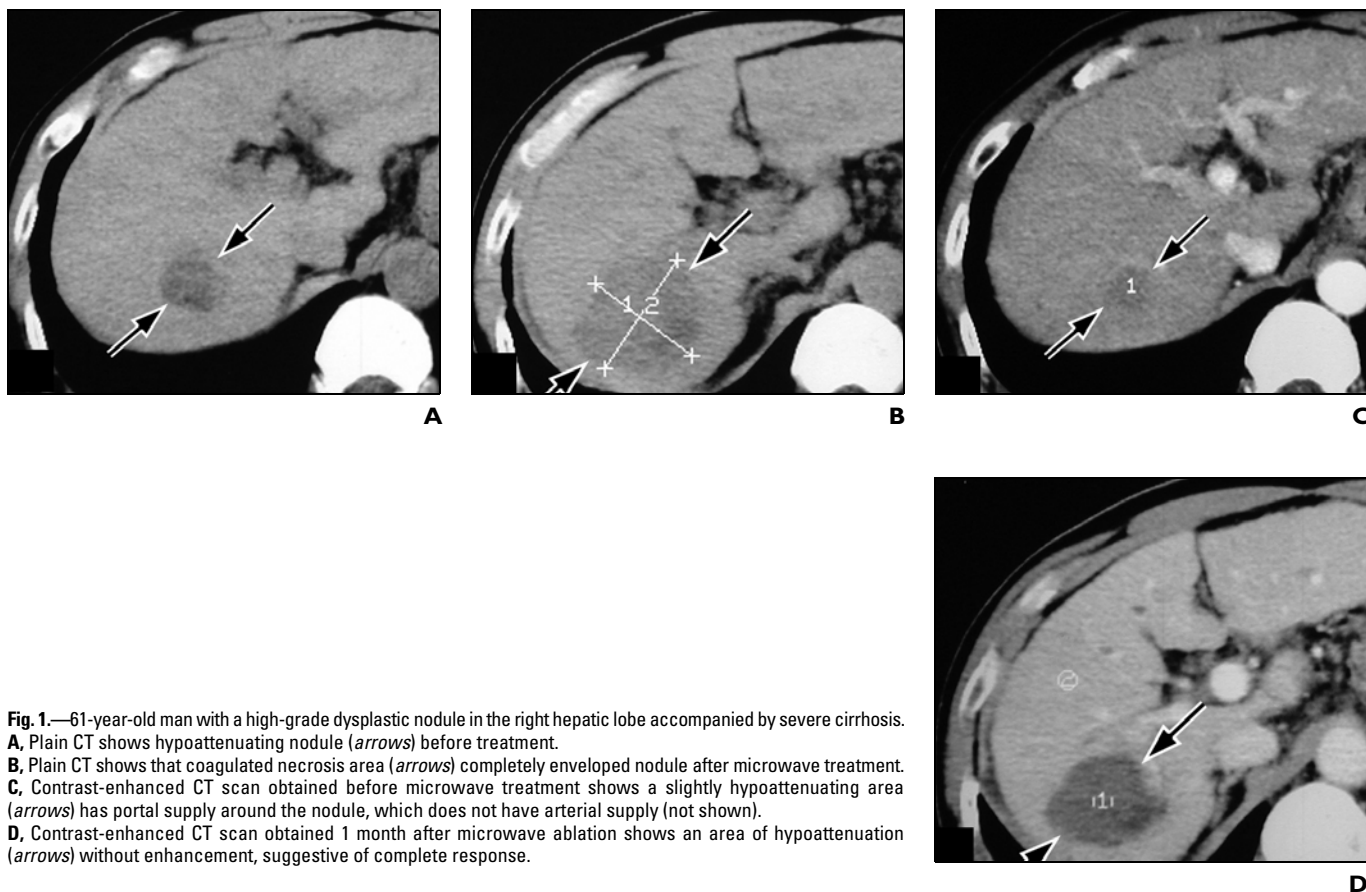


Fig. 1.—61-year-old man with a high-grade dysplastic nodule in the right hepatic lobe accompanied by severe cirrhosis. **A**, Plain CT shows hypoattenuating nodule (arrows) before treatment. **B**, Plain CT shows that coagulated necrosis area (arrows) completely enveloped nodule after microwave treatment. **C**, Contrast-enhanced CT scan obtained before microwave treatment shows a slightly hypoattenuating area (arrows) has portal supply around the nodule, which does not have arterial supply (not shown). **D**, Contrast-enhanced CT scan obtained 1 month after microwave ablation shows an area of hypoattenuation (arrows) without enhancement, suggestive of complete response.

DNs, especially high-grade ones, are likely to become HCCs and likely to coexist with HCCs. In the group of patients described here, three with DNAs had concomitant small HCCs. Three other patients had undergone liver segmentectomy for HCC 1–3 years earlier. Despite complete necrosis in the treated DNAs, HCC and new DNAs may appear in other hepatic segments. Hence, close follow-up for early detection of new hepatic lesions is warranted. HCC is the main threat to the survival of patients with DNAs. During the follow-up period, five patients died; three of these patients died from advanced HCC.

This study had some limitations. First, this was not a randomized controlled study; the malignant transformation rate of high-grade DNAs observed here may be different from that noted in previous reports [3, 6]. Additional randomized controlled studies are needed to ascertain whether percutaneous microwave ablation is a necessary and effective therapy for preventing malignant transformation. Second, the number of subjects described here is relatively small, and the follow-up period may not be long enough; further studies should include more patients and prolong the follow-up period. Third, the samples obtained by needle biopsy may not be adequate for correct histologic diagnosis. DNAs may contain foci of HCC [14–16], and they may be missed at biopsy, leading to false-negative results. However, DNAs with HCC foci could be ablated completely by microwave treatment as well.

In conclusion, sonography-guided percutaneous microwave ablation provides a safe, nonsurgical, and effective technique for the treatment of high-grade DNAs. It can yield complete necrosis in high-grade DNAs and prevent any malignant transformation in them. Microwave ablation is thus considered a favorable alternative in the treatment of high-grade DNAs.

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