Radiofrequency Thermal Ablation of Hepatocellular Carcinoma: Using Contrast-Enhanced Harmonic Power Doppler Sonography to Assess Treatment Outcome

OBJECTIVE. We evaluated the accuracy of contrast-enhanced harmonic power Doppler sonography in assessing the outcome of radiofrequency thermal ablation of hepatocellular carcinoma.

SUBJECTS AND METHODS. Fifty patients with 65 hepatocellular carcinoma nodules (1–5 cm in diameter; mean diameter, 2.5 cm) were studied using unenhanced and contrast-enhanced harmonic power Doppler sonography before and after IV administration of a microbubble contrast agent. The examinations were repeated after treatment of the tumors with radiofrequency ablation. Findings of the Doppler studies were compared with those of dual-phase helical CT, which were used as points of reference for assessing treatment outcome.

RESULTS. Before radiofrequency treatment, intratumoral blood flow was revealed by unenhanced power Doppler sonography in 48 (74%) of 65 hepatocellular carcinoma nodules. After injection of the contrast agent, intratumoral enhancement was observed in 61 (94%) of 65 hepatocellular carcinomas (p < 0.01). After radiofrequency treatment, all 51 (84%) of the 61 hepatocellular carcinomas found to be necrotic on helical CT scans failed to show enhancement on power Doppler sonograms. In nine of the 10 lesions that showed a residual viable tumor on helical CT scans, persistent intratumoral enhancement—matching the enhancing areas on helical CT images—was revealed by power Doppler sonography. These nine hepatocellular carcinomas were subjected to repeated radiofrequency thermal ablation with the guidance of contrast-enhanced power Doppler sonography. Complete necrosis was seen after the second treatment session in six of the nine lesions.

CONCLUSION. Contrast-enhanced harmonic power Doppler sonography is an accurate technique for assessing the outcome of radiofrequency thermal ablation of hepatocellular carcinoma and may be useful in guiding additional treatment in patients with incomplete response to initial efforts.
of patients with hepatocellular carcinoma before and after radiofrequency ablation, and we compared the findings of the Doppler studies with those of dual-phase helical CT.

**Subjects and Methods**

**Patient Population**

We enrolled 50 consecutive patients (39 men and 11 women; 45–78 years old, mean age, 61.5 years) admitted to two different institutions in Pisa and Milan, Italy, for treatment of histologically proven hepatocellular carcinoma lesions with sonographically guided radiofrequency ablation. Requirements for entering the study were that the patient had either a single nodular (i.e., expanding) hepatocellular carcinoma smaller than or equal to 5 cm in diameter or multiple (up to three) nodular hepatocellular carcinoma lesions smaller than or equal to 3 cm each; no portal vein thrombosis or extrapancreatic metastases; an established liver cirrhosis classified as Child-Pugh class A or B; a prothrombin time ratio (i.e., standard time/patient's time) greater than 50%; and a platelet count greater than 50,000/μL.

The 50 patients who met these criteria and were enrolled in our study had coexisting cirrhosis induced by hepatitis B virus (n = 7), hepatitis C virus (n = 21), or combined hepatitis B and hepatitis C viruses (n = 22). Liver function was classified as grade A (n = 36) or grade B (n = 14) according to the Child-Pugh classification. The α-fetoprotein level was normal (<20 ng/mL) in 19 patients, slightly increased (20–200 ng/mL) in 27 patients, and markedly increased (>200 ng/mL) in four patients. All of the patients had been excluded as candidates for surgical resection because of liver dysfunction, the presence of lesions in locations that made hepatic resection inappropriate, advanced age, or a concomitant medical illness that increased the surgical risk.

Pretreatment gray-scale sonography identified 65 hepatocellular carcinoma lesions with a maximum diameter ranging from 1 to 5 cm (mean ± SD, 2.5 ± 0.8 cm). Four patients had three lesions, seven patients had two lesions, and 39 patients had one lesion. The maximum diameter in 46 of the lesions was 1–3 cm; the maximum diameter of the remaining 19 lesions was 3–5 cm. One lesion was located in hepatic segment I, seven lesions in segment II, five lesions in segment III, 13 in segment IV, 16 in segment V, five in segment VI, 10 in segment VII, and eight in segment VIII. Histologic confirmation of hepatocellular carcinoma was obtained by performing sonographically guided percutaneous tissue-core biopsy of the main lesion.

**Pretreatment Imaging**

All patients underwent unenhanced and contrast-enhanced dual-phase helical CT examinations and unenhanced and contrast-enhanced harmonic power Doppler sonography examinations within a week before they received radiofrequency ablation treatment.

Dual-phase helical CT studies were performed with either a HiSpeed Advantage scanner (General Electric Medical Systems, Milwaukee, WI) or a PQ 6000 scanner (Picker International, Highland Heights, OH), using 7-mm collimation and a 1:1 pitch in a craniocaudal direction with scanning beginning at the top of the liver. Unenhanced and contrast-enhanced images were obtained in all patients. For the contrast-enhanced study, patients received 130–150 mL of nonionic contrast material (Visipaque [iódixanol], Nycomed, Oslo, Norway; or Iopamiro [iopamidol], Bracco, Milan, Italy) at a rate of 4–5 mL/sec. CT scanning was initiated 25–30 sec after the start of contrast material injection to obtain arterial phase images. Portal venous phase images were then obtained beginning at 70–75 sec after the start of contrast material injection.

Gray-scale and Doppler sonographic studies were performed using AU 5 (Esato Biomedica, Genoa, Italy), EUB-8000 ASTRO S521 (Hitachi Medical, Tokyo, Japan), and HDI 5000 (ATL Ultrasound, Bothell, WA) equipment with 3.5–5.0 MHz curved array multipurpose transducers. Unenhanced and contrast-enhanced harmonic power Doppler sonographic studies were performed using a low pulse repetition frequency (750–1200 Hz) to optimize the detection of weak signals. The band-pass filter was set at 0–50 Hz. The power-encoded area was restricted as much as possible to maximize the power sensitivity and the frame rate. The power gain was adjusted at the beginning of each examination by selecting the highest value possible without causing the power image to be affected by artifacts and was then kept constant throughout the study. We searched carefully for intratumoral power signals and assessed the distribution of blood flow for each lesion. Through careful examination of lesions and surrounding vessels in different scan planes and evaluation of power signals with spectral analysis, we took care to differentiate liver vessels adjacent to tumors from intratumoral vessels.

The sonographic contrast agent used was a suspension of micrometer-sized microparticles of galactose and microscopic gaseous bubbles (Leovist; Schering, Berlin, Germany). A dose of 2.5 g was administered IV with a concentration of 300 mg/mL and an injection rate of 0.1 mL/sec. To perform the contrast-enhanced Doppler sonographic study, the harmonic mode was selected, and a mechanical index of 0.5–0.8 was used. All other Doppler parameters were left unchanged. A chor- nometer, displayed on screen, was started at the beginning of the infusion of the contrast agent to measure time delay between the injection and the enhancement of the power Doppler signals. Observation was maintained until the signal enhancement had completely diminished. In patients with multiple lesions, repeated injections were given after a minimum time of 15 min. The unenhanced and contrast-enhanced sonographic studies were recorded on videotape.

**Radiofrequency Technique**

Radiofrequency ablation was performed using a 450-kHz frequency, 50-W radiofrequency generator (Model 500 L; RITA Medical Systems, Mountain View, CA) in a monopolar mode coupled with an active 15-gauge expandable electrode needle with four retractable lateral exit jachkooks on the tip and a large dispersive electrode. The power output, hook temperatures, tissue impedance value, and procedure time were continuously displayed by the radiofrequency generator. The generator was connected to a computer that, through dedicated software, continuously recorded the temperature curves obtained during the radiofrequency ablation.

Radiofrequency procedures were performed with the study participants as inpatients; the length of their hospital stay was 1 day. Patients were placed in either the supine or left lateral decubitus position, depending on lesion site and planned needle track. Patients were connected to the radiofrequency generator by the dispersive electrode placed on the leg, and then they were prepared and draped in the usual sterile fashion. Local anesthesia was achieved by injecting a 1% lidocaine solution (Lidian; Bieffe Medical, Modena, Italy) from the insertion point on the skin to the peritoneum along the planned puncture line. The skin was pricked with a small lancet, and the electrode needle was then advanced precisely to the chosen area of the lesion using sonographic guidance. After the hooks had been deployed inside the lesion, the radiofrequency generator was activated, and the power was set to reach a temperature of 90–115°C. The target temperature was usually reached within 2–3 min.

In hepatocellular carcinoma lesions with a maximum diameter of 3 cm or smaller, a single 8-min time-at-temperature radiofrequency ablation was performed. In tumors with a maximum diameter ranging from 3.1 to 4 cm, two 8-min time-at-temperature radiofrequency ablations were performed. In tumors with a maximum diameter ranging from 4.1 to 5 cm, three 8-min time-at-temperature radiofrequency ablations were performed. The multiple radiofrequency ablations were made by a single needle insertion using a “pull-back” technique, in which the tip of the electrode needle was initially placed in the deepest margin of the lesion, and the radiofrequency generator was activated. Then the hooks were retracted, the needle was withdrawn 1.5 cm, and the generator was reactivated.

**Imaging After Treatment**

Between 3 and 7 days after the radiofrequency ablation procedure, all patients again underwent examinations using unenhanced and contrast-enhanced harmonic power Doppler sonography as well as dual-phase helical CT. The posttreatment Doppler sonography was performed using the same examination protocol as the one used for the pretreatment studies. The videotapes of pretreatment and posttreatment contrast-enhanced harmonic power Doppler sonographic studies were then reviewed by two radiologists who were unaware of the results of the helical CT examinations; their assessments were made by consensus. A complete disappearance of intratumoral blood flow signals in posttreatment Doppler studies was considered to represent complete tumor response. In contrast, any portion of the treated lesion showing either persistent intratumoral blood flow signals on unenhanced power Doppler sonographic studies or persistent intratumoral enhancement on contrast-enhanced harmonic power Doppler sonographic studies was considered to represent residual viable tumor tissue.

The outcome of therapy was established by means of dual-phase helical CT. Findings of dual-phased helical CT studies were reviewed by two radiologists who were unaware of the results of the Doppler sonographic studies and whose assessments were made by...
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consensus. Complete tumor response was judged to have occurred if the lesion failed to enhance during both the arterial and the portal venous phases; partial tumor response was judged to have occurred if enhancing areas—suggestive of the presence of residual viable tumor tissue—were observed in the treated tumor.

All patients in whom complete tumor ablation had been diagnosed on the basis of the helical CT scans obtained after therapy underwent repeated helical CT studies at 3-month intervals during the follow-up period. The duration of the follow-up period ranged between 6 and 24 months (mean ± SD, 12.8 ± 4.6 months). To confirm the diagnosis of complete tumor necrosis, a minimum of two CT studies showing no recurrence of a successfully treated lesion were obtained in all patients.

For patients diagnosed with a partial response to treatment, additional radiofrequency treatment was scheduled. In these instances, contrast-enhanced harmonic power Doppler sonography was repeated immediately before the procedure, and intratumoral power signals were used to target the placement of the radiofrequency electrode needle into the enhancing portion of the tumor. After the repeated treatment, contrast-enhanced harmonic power Doppler sonography and dual-phase helical CT were repeated to establish the outcome of therapy.

Statistical Analysis
The statistical analysis of the results was performed by the chi-square test and the Student’s *t* test. Values of less than 0.05 were considered to be statistically significant.

Results
Pretreatment unenhanced power Doppler sonographic studies showed intratumoral power Doppler signals in 48 (74%) of 65 hepatocellular carcinoma lesions. Seventeen hepatocellular carcinoma lesions showed vessels running along the periphery of the lesion, with branches radiating toward the center; 12 hepatocellular carcinoma lesions showed vessels running and dividing within the tumor; and 19 hepatocellular carcinoma lesions showed vascular spots inside the lesion without any distinct vessels. Doppler spectral analysis revealed intratumoral pulsatile arterial flow in all 48 hepatocellular carcinoma lesions. In 10 of 48 lesions, intratumoral continuous venous flow was also visible.

After the administration of the sonographic contrast agent, strong, rapid intratumoral enhancement was seen in 61 (94%) of 65 hepatocellular carcinoma lesions. The enhancement began 21–33 sec (mean, 25 ± 3 sec) after the start of the injection and persisted for 244–385 sec (mean, 310 ± 39 sec). These 61 hepatocellular carcinoma lesions showing clear-cut intratumoral enhancement were considered to be hypervascular lesions on harmonic power Doppler sonography studies. This group included all the 48 hepatocellular carcinoma lesions with intratumoral blood flow already shown by unenhanced power Doppler sonography as well as 13 additional lesions with no blood flow signals revealed by unenhanced power Doppler sonography (Fig. 1). The results of contrast-enhanced harmonic power Doppler sonography in showing tumor vascularity, therefore, were signifi-

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Fig. 1.—Complete response of hepatocellular carcinoma after radiofrequency thermal ablation in 67-year-old woman. 
A, Unenhanced oblique subcostal power Doppler sonogram obtained before radiofrequency thermal ablation shows no intratumoral blood flow within lesion (arrows).
B, Harmonic oblique subcostal power Doppler sonogram obtained 30 sec after contrast agent injection (but before radiofrequency ablation) shows rich vascularity of lesion.
C, Contrast-enhanced helical CT scan obtained in arterial phase before radiofrequency ablation shows clear-cut intratumoral enhancement of lesion (arrow).
D, Contrast-enhanced oblique subcostal power Doppler sonogram obtained after radiofrequency thermal ablation shows that intratumoral power signals have disappeared.
E, Contrast-enhanced helical CT scan obtained in arterial phase after radiofrequency thermal ablation shows lesion to have homogeneous hypoattenuation, suggesting complete response.
Doppler sonography (p < 0.01).

In the remaining four (6%) of 65 hepatocellular carcinoma lesions, no intratumoral enhancement was detectable on harmonic power Doppler sonographic studies, although the observation of enhanced power Doppler signal in liver vessels confirmed that the contrast agent had reached liver circulation. Two of these four lesions showed clear-cut arterial phase enhancement at helical CT, whereas the other two appeared as hypoattenuating compared with liver parenchyma. These four lesions were excluded from our study because the absence of intratumoral blood flow signals impeded the evaluation of the changes in tumor vascularity induced by radiofrequency treatment. Thus, the subject group for evaluation was formed by the 61 hepatocellular carcinoma lesions with hypervascular features on contrast-enhanced harmonic power Doppler sonographic studies.

Posttreatment dual-phase helical CT studies revealed complete tumor response in 51 (84%) of these 61 lesions and partial tumor response in the remaining 10 (16%) of the lesions. Intratumoral power Doppler sonographic signals were no longer detectable on either unenhanced or contrast-enhanced harmonic power Doppler sonographic studies in any of the 51 hepatocellular carcinoma lesions found to be necrotic on dual-phase helical CT scans (Fig. 1). Persistent intratumoral power Doppler signals were detectable in two of the 10 lesions with partial response by unenhanced power Doppler sonography and in nine of these 10 lesions by contrast-enhanced harmonic power Doppler sonography (p < 0.05) (Fig. 2). Doppler spectral analysis showed intratumoral pulsatile arterial flow in all nine lesions (Fig. 2). Contrast-enhanced harmonic power Doppler sonography failed to reveal residual viable tumor in a 3.2-cm lesion located in segment VIII of the liver that was visible on helical CT scans as a crescent-shaped peripheral area of residual enhancing tumor. Contrast-enhanced harmonic power Doppler sonography had a sensitivity of 90%, a specificity of 100%, and an accuracy of 98% in revealing residual viable tumor tissue in hepatocellular carcinoma lesions treated with radiofrequency ablation.

In the nine hepatocellular carcinoma lesions with persistent power Doppler signals on contrast-enhanced harmonic power Doppler sonographic studies obtained after radiofrequency ablation, the areas of intratumoral enhancement closely matched the enhancing portions of the tumor as depicted on dual-phase helical CT studies. In these hepatocellular carcinoma lesions, the distribution of intratumoral power Doppler sonographic signals was used as a guide to target locations for additional radiofrequency treatment (Fig. 3). After the second treatment session, intratumoral power Doppler sonographic signals completely disappeared from contrast-enhanced harmonic power Doppler sonographic studies in six of the nine hepatocellular carcinoma lesions, which also had been found to be necrotic on repeated dual-phase helical CT studies. In three of nine hepatocellular carcinoma lesions, intratumoral enhancing areas were still seen on contrast-enhanced harmonic power Doppler sonographic studies as well on dual-phase helical CT scans. These lesions were considered to be incompletely responsive to radiofrequency treatment, and patients were scheduled for completion of therapy with transcatheter arterial chemoembolization.

**Discussion**

Radiofrequency thermal ablation is now attracting attention because of the impressive technical evolution that has taken place over the past few years. Until recently, conventional radiofrequency treatment performed with a single monopolar electrode was capable of producing thermal necrotic lesions no larger than 1.6 cm in diameter [21–23]. Substantial improvements in the radiofrequency technique include the development of high-power generators coupled with dual-lumen, cooled-tip electrode needles or expandable electrode needles with multiple retractable lateral-exit jacks on the tip [5, 6]. Currently, thermal necrotic volumes of 5 cm in
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Fig. 3.—Complete response of hepatocellular carcinoma after repeated radiofrequency thermal ablation performed with contrast-enhanced power Doppler sonographic guidance in 65-year-old man.

A, Unenhanced oblique subcostal power Doppler sonogram obtained after first radiofrequency ablation shows small circumscribed area of residual blood flow in postero-medi al aspect of tumor (arrow).

B, Harmonic oblique subcostal power Doppler sonogram obtained 30 sec after contrast agent injection reveals larger area of enhancement in medial aspect of tumor (arrows).

C, Contrast-enhanced helical CT scan obtained in arterial phase after first radiofrequency ablation shows large enhancing area of residual viable tumor in medial aspect of lesion (arrow), corresponding to enhancing portion on contrast-enhanced power Doppler sonogram (B).

D, Contrast-enhanced helical CT scan obtained in arterial phase after repeated radiofrequency ablation performed under contrast-enhanced power Doppler sonographic guidance shows lesion to have homogeneous hypointensity, suggesting complete response.

diameter can be obtained with a single insertion of the probe [8, 9]. Nevertheless, viable tumor tissue can remain after radiofrequency ablation, especially if the tumor is located near large vessels, which act as heat sinks, or if tumor portions are isolated by septa that limit heat diffusion, such as in confluent multinodular hepatocellular carcinoma [3, 10–13].

Dual-phase helical CT is considered the standard imaging technique to determine whether the treated hepatocellular carcinoma tumor is completely necrotic or needs additional radiofrequency treatment [1–9, 14–16]. With dual-phase helical CT, hepatocellular carcinoma tumors successfully treated with radiofrequency ablation appear as hypointensities on unenhanced examination that are obliterated both in the arterial and the portal venous phases. On the other hand, in cases of incomplete response, the areas of residual viable tumor tissue can be easily recognized because in the arterial phase they stand out against the faintly enhanced normal liver parenchyma and the unenhanced areas of coagulation necrosis [1–9, 14–16].

Color Doppler sonography has long been used in attempts to assess hepatocellular carcinoma tumor vascularity in both native and treated lesions [24–26]. However, despite the improved results obtained with the use of newer Doppler sonographic technologies, such as power Doppler imaging, a reliable assessment of intratumoral blood flow was not possible in some instances, particularly in small lesions or in lesions located deep within the liver parenchyma [27–29].

The introduction of sonographic contrast agents has opened new prospects for Doppler sonography of focal liver lesions owing to the increased sensitivity in detecting small, low-velocity vessels in tumors [17, 19, 30, 31]. The combination of echo-enhancers with the harmonic mode was shown to be particularly helpful in the assessment of tumor vascularity because harmonic imaging has a higher signal-to-noise ratio and a higher lateral resolution than the fundamental mode. These attributes are especially useful in reducing models that are a well-known limitation of power Doppler imaging, particularly in examining lesions located in the left lobe of the liver near the heart [18, 20].

In our series, contrast-enhanced harmonic imaging considerably outperformed unenhanced power Doppler sonography in revealing tumor vascularity in both native and treated hepatocellular carcinoma tumors. The sensitivity of the contrast-enhanced harmonic power Doppler sonographic study in the detection of intratumoral flow in native hepatocellular carcinoma lesions reached 94% as opposed to 74% of the unenhanced examination. After treatment with radiofrequency thermal ablation, nine of 10 cases of treatment failure were correctly identified using contrast-enhanced harmonic imaging, whereas only two of the 10 cases were detectable using unenhanced power Doppler sonography.

We found a close correlation between findings of contrast-enhanced harmonic power Doppler sonography and those of dual-phase helical CT in revealing the outcome of radiofrequency thermal ablation of hepatocellular carcinoma lesions. In all patients with a complete tumor response that was visible on helical CT images, intratumoral blood flow signals were no longer detectable on contrast-enhanced harmonic power Doppler sonographic studies. In nine of the 10 instances of treatment failure, areas with residual blood flow signals—which clearly matched portions of tumor showing persistent enhancement on helical CT scans—were revealed by contrast-enhanced harmonic power Doppler sonography.

Precise delineation of the areas of residual viable tumor tissue after radiofrequency treatment is crucial in planning additional treatment. In fact, we found contrast-enhanced harmonic power Doppler sonography extremely useful in guiding subsequent radiofrequency ablation because it allowed precise targeting of the electrode needle in the viable portion of the tumor. After the second radiofrequency treatment, complete response was seen in six of nine tumors treated under contrast-enhanced harmonic power Doppler sonographic guidance.

This study has limitations. First, we did not perform any histopathologic correlation of hepatocellular carcinoma tumors after radiofrequency treatment. Therefore, small portions of viable tumor tissue might have gone undetected on contrast-enhanced helical CT scans, and the number of false-negative diagnoses made on contrast-enhanced harmonic power Doppler sonographic studies might have been greater than the number reported. To minimize the risk of overestimation of radiofrequency ablation results, we required a minimum follow-up period of 6 months—showing no sign of recurrence on helical CT...
studies repeated at 3-month intervals—to confirm the diagnosis of complete tumor response. Another limitation of contrast-enhanced power Doppler sonography is that we were forced to exclude from the series all patients whose studies showed no intratumoral enhancement before treatment. In these patients, the absence of intratumoral blood flow signals in native lesions would have impeded the evaluation of the changes in vascularity induced by radiofrequency ablation and, therefore, the evaluation of the therapeutic effect. However, because of the high sensitivity of the technique, this limitation occurred in only four (6%) of the 65 hepatocellular carcinoma tumors. Two of these four lesions (located deep within liver parenchyma) showed clear-cut arterial phase enhancement at helical CT. Hence, the lack of enhancement on harmonic power Doppler sonograms could be attributed to insufficient sensitivity of the technique. Finally, the direct use of the harmonic mode for contrast-enhanced power Doppler sonographic studies prevented comparison between harmonic imaging and conventional contrast-enhanced power Doppler sonography in the fundamental mode. Harmonic imaging has been shown to be superior to conventional contrast-enhanced power Doppler sonography as a tool for assessing vascularity of liver tumors. Harmonic power Doppler sonography, in fact, has the advantage of fewer Doppler artifacts, which are a crucial limitation of conventional contrast-enhanced power Doppler sonography [20].

In conclusion, we found that contrast-enhanced harmonic power Doppler sonography enables radiologists to assess confidently the therapeutic effect of radiofrequency treatment on hepatocellular carcinoma. Moreover, information provided by this technique may be used to successfully target additional radiofrequency treatment in patients with lesions that show only partial response after the first treatment.

References