Imaging manifestation of conventional and contrast-enhanced ultrasonography in percutaneous microwave ablation for the treatment of uterine fibroids

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ABSTRACT

Objectives: To evaluate the image changes and the relationship between conventional ultrasonography and contrast-enhanced ultrasound (CEUS) in the perioperative period of microwave (MW) ablation for uterine fibroids; to guide clinical ablation therapy and evaluate the efficacy of MW.

Methods: Twenty-nine patients with 31 uterine fibroids were recruited in this study. All patients received conventional ultrasonography as well as CEUS examination before, immediately after and 12–24 h after MW, in order to detect variations of echo and characteristics of blood supply. T-Tests were used to compare the hyperecho area on gray-scale ultrasound to immediately after ablation non-enhanced CEUS measurements, as well as to compare the immediately after ablation non-enhanced CEUS measurements to the 12–24 h after ablation measurements.

Results: Immediately after ablation, the average hyperecho area in gray-scale was 82.20 ± 72.32 cm²; the average non-enhancement area was 76.34 ± 70.63 cm² by CEUS, showing a strong correlation (r = 0.997, P < 0.01) to the hyperecho area in gray-scale. The average non-enhancement area measured by CEUS immediately after ablation was 90.55 ± 74.41 cm² and average 12–24 h after ablation was 98.29 ± 78.25 cm²; no statistically significant difference was detected between the two time points (P > 0.05).

Conclusions: Measurements made by hyperechoic range on gray-scale ultrasonography is strongly correlated to the non-enhancement area by CEUS. The hyperechoic range on gray-scale image can represent the ablated area immediately after MW.

1. Introduction

As minimally invasive treatment technology in clinical practice is rapidly developing, ultrasound-guided thermal ablation technique has received increasing attention from medical professionals worldwide due to its safety, and minimally or even non-invasive features [1–3]. Ultrasound-guided (US) percutaneous microwave ablation (PMA), as a thermal ablation technique, is a non-surgical treatment of uterine fibroids universally applied in clinics [1]. The purpose of PMA of uterine fibroids is to alleviate or eliminate symptoms, and eventually improve patients’ quality of life. Critical issues during the ablation process include controlling the range of thermal field, preventing damages to normal uterus tissues, bladder, and intestinal tract, and reducing the risk of severe complications. The process of microwave (MW) ablation was performed under ultrasonography monitoring. Fibroids sonographic images reflect its response of the thermal field. The study was designed to compare the variation features and the relationship between perioperative conventional and contrast-enhanced ultrasonography (CEUS), to explore respective variation pattern and correlation between two images, so as to provide guidance to clinical ablation therapy and evaluate the efficacy of ablation treatment.

2. Materials and methods

2.1. Patients

Between August 2007 and May 2011, 60 patients with 61 uterine fibroids were referred to Chinese PLA General Hospital and First Affiliated Hospital of PLA General Hospital for US-guided percutaneous microwave ablation PMA therapy. The average age...
at study entry was 40 (SD: 5.25, range: 26–50) years. Of all 61 uterine fibroids, 34 intramural myomas, 8 submucosal myomas, and 19 subserosal myomas were identified. Patient eligibility criteria were as follows: patient had been diagnosed with uterine fibroids by ultrasonography and contrast-enhanced MRI (ceMRI) in our hospital; patient had at least one of the following symptoms of menorrhagia or metrorrhagia: pelvic pain, bulk pressure, or urinary frequency, with no history of rapid enlargement of fibroids within a short period of time (eliminating the possibility of carcinomatous change of fibroids); patient had either completed childbearing and/or no longer desired fertility; patient sought treatment and rejected hysterectomy, myomectomy, HIFU and UAE. The following exclusion criteria were applied: patient desiring future pregnancy; number of fibroids on the same patient >3; the largest fibroid’s diameter >10 cm; patient in perimenopausal period; inability to exclude the possibility of leiomyosarcoma; patient with pelvic infection; heart or brain disease or malignant tumors. The treatment procedures, the expected benefits and the potential complications as well as the potential hazardous effects on reproductive and adjacent organs were explained in detail to the patients. The applications for treatment and informed consent were signed by patients themselves [1]. This study was approved by our hospital’s ethics committee and had completed online registration. Ratification number is ChiCTR-TRC-10001119.

2.2. Equipments

2.2.1. Instruments

Microwave tumor treatment device is a type KV2000 (Nanjing Kangyou Microwave Energy Sources Institute) with a microwave transmission frequency of 2450 MHz with two operating modes: continuous wave and pulse wave. The microwave antenna is 15 G, needle type, internal water-cooling, embedded aperture microwave emission, anti-sticking, and 180 mm long. The microwave emission gap was 1 mm, and the distance between the emission gap and the needle tip was 11 mm (Fig. 1). The antenna can be clearly seen on ultrasound image (Fig. 2).

2.2.2. Ultrasound system

Siemens sequioa 512 ultrasound system. The probe frequency was 2.5–4.5 MHz, and the system had a puncture guiding frame and low mechanical index imaging features.

Fig. 1. The microwave antenna and microwave emission gap (red arrow).

Fig. 2. Two-dimensional ultrasound image during the MW ablation: shows the antennae and emission gap clearly (arrow).

2.3. Methods

2.3.1. Conventional ultrasound examination

Prior to MW ablation, gray-scale ultrasonography and color Doppler ultrasound were performed to identify locations of uterine fibroids, echo and blood supply, and measure length, height, and width of uterine fibroids. Gray-scale ultrasound revealed hyperecho with relatively distinct boundary in ablation area immediately after ablation. Meantime, the top–bottom and anterior–posterior diameters on the longitudinal section of uterine fibroids presented with the largest hyperecho range were measured. The left–right diameter on the largest transverse section of uterine fibroids was measured (Fig. 3). The mean value d1 of the three diameters was calculated. Then, the volume of uterine fibroids before ablation and hyperecho (V1) after ablation were calculated using the formula $V = \frac{4}{3}\pi (d_1/2)^3$.

2.3.2. Intravenous contrast-enhanced ultrasound

Contrast agent: SonoVue (manufactured by Bracco Company in Italy). Five milliliter of physiological saline was injected into a portion of 4.98 mg frozen dry powder, fully shaken and intermingled, forming milk white suspension containing sulfur hexafluoride capsule wrapped by phospholipid. 2.4 ml of contrast agent was injected via elbow vein quickly, followed by 5 ml of physiological saline for washing. Contrasting time points: before ablation,
immediately and in 12–24 h after ablation. Observed parameters: the enhancement condition of uterine fibroid tissues. The top-bottom and anterior-posterior diameters on the longitudinal section of uterine fibroids presenting the largest echo range were measured prior to treatment. The left-right diameter on the largest transverse section of uterine fibroids was measured. The non-enhanced region in contrast-enhanced sonography was measured following ablation. The mean value \( d_2 \) of the three diameters was calculated. The volume of non-enhanced area \( (v_2) \) was calculated according to \( 4/3\pi(d_2/2)^3 \). Informed consent was obtained from each individual participated in this study.

### 2.3.3. MW ablation therapy procedures

The ablation was performed under intravenous conscious sedation. The patients adopted a supine position. Under US guidance, a biopsy of the fibroid was performed via percutaneous puncture with an 18-gauge core needle for pathological diagnosis. Along the path of biopsy, the MW antenna was then inserted into the center of the fibroid with the tip of antenna located at 0.5 cm from the distal end of the tumor to avoid thermal damage to tissues outside the uterus. The output energy of the MW was set at 50W. During the ablation, variations in the echo from the fibroid were monitored by real-time ultrasonography. The MW therapy was stopped when the hyperecho covered the whole nodule [1].

### 2.4. Statistical analysis

Descriptive statistics, namely the means and standard deviations, were computed on all ultrasound measurements. Pearson’s correlation test was used to analyze the correlation between the volume of ablation region displayed by gray-scale ultrasound and the volume of ablation coagulated area presented by contrast-enhanced ultrasound; in addition, paired two-sample t-test was used to compare these two volumes. Paired two-sample t-test was used to test the association between the volume of non-enhancement area by CEUS measured immediately after ablation and the said volume measured one day after ablation. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL).

### 3. Results

A total of 31 pieces of uterine fibroids from 29 patients had complete data at all time points, and thus were included in statistical analyses.

#### 3.1. Variations in conventional sonography of uterine fibroids before and after ablation

Prior to ablation therapy, conventional sonography of uterine fibroids suggested sphere or round-alike, homogeneous or inhomogeneous low echoes with regular morphology and distinct boundary. Coloring Doppler ultrasound indicated ring-shaped blood signals of varying degree inside or around tissues (Fig. 4). MW electrode was implanted into lesions, and then gray-scale ultrasound could clearly display the locations of electrode and seam (Fig. 2). After MW began to emit, gray-scale ultrasound showed hyperecho starting from the seam of microwave electrode (microwave emission point), enhanced as the time of microwave emission prolonged, steadily increased to sphere shape, until fully covered the uterine fibroids (Fig. 5). During microwave emission process, coloring Doppler presented the five-color signals with sphere or round-alike shape in hyperecho region (Fig. 6). After microwave emission stopped, the hyperecho microbubbles in target sites gradually vanished. The echo in effective ablation area was still significantly higher than that in adjacent tissues. Above all, the needle passage displayed bar-type hyperecho, while low echo surrounding needle passage. The subserosal of uterine fibroids was presented with hyperecho, and the high echoes in ablation area and needle passage were able to last for a relatively long period (Fig. 7: ablation area and needle passage 24 months after ablation).

#### 3.2. Imaging manifestations of vein CEUS of uterine fibroids before and after ablation

Prior to ablation, intramural uterine fibroids exhibited peripheral enhancement with branched vessels extending from exterior to interior in the early phase; then the entire masses were enhanced homogeneously or heterogeneously. During this period, some patients presented with dendritic nurturing vessels extending from periphery to central region, and the boundary of uterine fibroids was distinct (Fig. 8). The enhanced intensity occurring in uterine fibroids gradually approached to the level in myometrium. The uterine fibroids were enhanced earlier than myometrium. In the late phase, the uterine fibroids displayed faster washout than the myometrium, seen as hypo-enhancement (Fig. 9). As the disappearance of contrast agent, uterine fibroids displayed mixed echo nodule dominated by low echoes, with clear boundary [4]. Submucosal and subserosal uterine fibroids displayed enhanced from basal nurturing vessels at early stage, gradually enhanced surrounding uterine fibroids and then filled into central region. Contrast agent displayed faster washout than the myometrium, and low echo nodule was detected after recession. CEUS was performed immediately after microwave ablation. No contrast-agent microbubbles flew in effective ablation region, while line, lamellar hyperecho was observed to contain no flowing hyperecho bubbles inside, which was caused by remnant microbubbles in MW thermal field (Fig. 10). Twelve to twenty-four hours after ablation, the ablated area in CEUS displayed continuous non-enhancement. Ultrasound imagings indicated spherical curative area with distinct boundary containing no echo, which was in sharp contrast with surrounding enhanced non-ablated normal muscle tissues (Fig. 11).

#### 3.3. The relationship between hyperecho area detected by two-dimensional gray-scale and non-enhancement area displayed by CEUS following ablation therapy

Immediately after ablation treatment, the hyperecho area in two-dimensional gray-scale was slightly larger compared with that in non-enhancement area by CEUS presenting with a favorable correlation, as shown in Table 1. The non-enhancement area in lesions

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between uterus and surrounding organs were measured and evaluated by conventional ultrasound, which provided guidance to ablation plan design and selection of the optimal needle inserting approach. During ablation operation, conventional ultrasound was able to distinctively display the implantation of microwave electrode into lesions and the whole process of thermal field with hyperecho changing from none, small to large size. When the microwave began to emit, the echo in ablation area was instantly intensified because microwave apparatus converted electromagnetic wave energy possessed by high-frequency oscillation current at certain frequency into emission energy, intervened inside lesions via ablation needle. And the emission energy was absorbed by tissues and then converted into heat energy [5,6]. Local tissues produced microbubbles when the heating temperature reached boiling point, which was featured as hyperecho [7]. Surgeons could conduct real-time monitoring ablation area, control the ablation range regarding the edges of hyperecho imagings as thermal field limits, and eventually guarantee the safety of ablation surgery. Postoperatively, line hyperecho was observed near puncture needle passage in ablation area. The echo in remaining region gradually decreased as time proceeded. However, hyperecho was still noted near ablation needle passage 24 months after ablation [8]. After observing longitudinal section in ablation area samples, we found that the tissues near needle passage showed coagulated necrosis, carbonization, and hard texture, which possibly explained the formation of hyperecho and the long-duration of hyperecho [9].

Color Doppler ultrasound can clearly display the distribution of vessels interior and surrounding uterine fibroids, suggesting that surgeons can possibly increase the frequency or time of microwave ablation in those lesions with relatively abundant blood supply to achieve desirable ablation outcomes. During ablation surgery, ablation area displayed round, five-color signals induced by Doppler affected by flowing microbubbles when interior heating. The

### Table 2

The volume of non-enhancement area by CEUS: immediately after ablation was compared with 12–24 h after ablation (mean ± SD).

<table>
<thead>
<tr>
<th>Time</th>
<th>Uterine fibroids number</th>
<th>Non-enhancement area volume (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediately after ablation (t₁)</td>
<td>14</td>
<td>90.55 ± 74.41</td>
</tr>
<tr>
<td>12–24 h after ablation (t₄)</td>
<td>14</td>
<td>98.29 ± 78.25</td>
</tr>
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*P > 0.05.*

center of five-color signal was microwave emission seam, which could be used to locate the ablation needle microwave emission seam. Postoperative Doppler examination indicated whether blood flow signal can be noted with ablation area. Compared with preoperative condition, it could be applied to instantly evaluate the ablation outcome. However, the small vessels in lesions might experience spasm immediately after ablation, blocking the blood supply pathway to local sites and leading to fake appearance of local necrosis tissues. Thus, the ablation range was measured roughly rather than accurately.

Currently, the main methods used for evaluating the efficacy of tumor ablation treatment include enhanced-CT, enhanced-MRI and vein contrast-enhanced ultrasound. Venous ultrasound contrast agents are able to enter the microcirculation at blood capillary level, and show high sensitivity, specificity, and spatial resolution to the perfusion level in target organs, achieving the same effects as those by enhanced-CT and enhanced-MRI [10], which can be regarded as an index assessing remnant lesions [11]. All the patients in this study were subjected to ultrasound examination to locate the boundary of uterine fibroids and detect perfusion condition. Another contrast was performed immediately after ablation surgery, which could clearly display the boundary of ablation area. Therefore, it can be utilized to compare with the preoperative efficacy.

This study discovered that when venous CEUS was performed immediately after microwave ablation, partial enhanced line and lamellar area was found in the interior ablation region, which was likely to be disregarded as tumor remnant which could lead to another unnecessary ablation therapy. Actually, the region displayed hyperecho after a careful observation, unlike surrounding normal tissues having the process of perfusion and vanishing, but kept a static state at a certain intensity of hyperecho. Such CEUS imaging findings conform to the manifestation of microbubbles incomplete in ablation thermal field. In 12–24 h after therapy, another CEUS was performed and found that previously seen line and lamellar contrast area disappeared, and ablation area display uniform and continuous non-enhancement, indicating that the interior of uterine fibroids has been necrosis with no blood supply. The volume of non-perfusion area was presented by CEUS immediately and after ablation, respectively. The volume of non-enhancement area immediately after ablation was slightly smaller than that at 12–24 h after ablation, but the results showed no statistically significant difference between two measured data. Analysis of possible reasons: first, at immediately after ablation, CEUS noted ruffled boundary in certain cases, occasionally surrounded by thin line-shaped contrast agents. However, 12–24 h after the surgery, the boundary was sharp and distinct. It indicated that vascular spasm occurred to the edge of ablation area; second, immediately after ultrasound contrast, the thermal field bubble has not yet dissipated, there are artifacts around the ablation zone. The edge in the immediate postoperative angiography was still high echo, although it was necrosis. So the measured value was small; third, as the thermal field interference, the boundary of immediately after ablation zone by CEUS was attenuation apparently, and the diameter measurement error was increased.

In this study, we compared and analyzed gray-scale imaging and CEUS imaging, revealing that the volume of hyperecho displayed by gray-scale ultrasound was evidently larger compared with that of non-enhancement area detected by contrast-enhanced ultrasound following ablation therapy, with a significant correlation ($r = 0.997$, $P < 0.01$). The results indicate that there is activity tissue at the outer edge of the hyperecho. And it suggests that the application of gray-scale ultrasound into instant monitoring of the boundary of hyperecho can accurately estimate the range of ablation treatment. Microwave emission should be halted when the boundary of hyperecho reaches the assumed ablation limits. The actual ablation range will be smaller than hyperecho range. Activity tissue in the surrounding can form a natural “shell” to protect the ablation zone in a safe range, without harming the surrounding normal structures. So using hyperecho arrival site as ablation boundary can guarantee the safety of ablation therapy.

However, these two examinations have respective limits in practice. Gray-scale ultrasound displays the range of hyperecho, and some boundaries are not as clear as CEUS. In addition, how long the hyperecho endures in uterine fibroids and adenomyosis may cause coagulated necrosis remains to be elucidated. Venous CEUS serves as an invasion examination. Although the incidence of adverse events is significantly lower than that of contrast-enhanced agents, venous CEUS still has some allergic reactions [12]. Both the times of examinations and the amount of contrast agents accumulated in short time should be reduced. Besides, the findings displayed by CEUS may be influenced by the remnant microbubbles flowing in thermal field, which possibly interfere with the estimate and judgment on ablation range for inexperienced doctors.

In summary, the features in the manifestations of conventional and contrast-enhanced ultrasound during perioperative microwave ablation are significant and evident. The hyperechoic range of gray-scale ultrasound can basically represent the thermal field range immediately after microwave ablation. Both the gray-scale ultrasound and CEUS can evaluate ablation effects in different periods of microwave ablation.

Conflict of interest
We declare that the authors or authors’ institutions have no conflicts of interest. This includes financial or personal relationships that inappropriately influence his or her actions (such relationships are also known as dual commitments, competing interests, or competing loyalties) within 2 years of the work beginning submitted.

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