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ORIGINAL ARTICLE

Volumetric MRI-guided, high-intensity focused ultrasound ablation of uterine leiomyomas: ASEAN preliminary experience

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PURPOSE
We sought to present our preliminary experience on the effectiveness and safety of magnetic resonance imaging (MRI)-guided, high-intensity focused ultrasound (HIFU) therapy using a volumetric ablation technique in the treatment of Association of Asian Nations (ASEAN) patients with symptomatic uterine leiomyomas.

METHODS
This study included 33 women who underwent HIFU treatment. Tissue characteristics of leiomyomas were assessed based on T2- and T1-weighted MRI. The immediate nonperfused volume (NPV) ratio and the treatment effectiveness of MRI-guided HIFU on the basis of the degrees of volume reduction and improvement in transformed symptom severity score (SSS) were assessed.

RESULTS
The median immediate NPV ratio was 89.8%. Additionally, the median acoustic sonication power and HIFU treatment durations were 150 W and 125 min, respectively. At six-month follow-up, the median leiomyoma volume had decreased from 139 mL at baseline to 84 mL and the median transformed SSS had decreased from 56.2 at baseline to 18.8. No major adverse events were observed.

CONCLUSION
The preliminary results demonstrated that volumetric MRI-guided HIFU therapy for the treatment of symptomatic leiomyomas in ASEAN patients appears to be clinically acceptable with regard to treatment effectiveness and safety.

Uterine leiomyomas are the most common benign tumor of the smooth muscle cells of the uterus in females, with nearly 20% to 30% of reproductive-aged women likely to experience symptoms of pain, menorrhagia, pelvic pressure, urinary disorders, and infertility (1, 2). Although conventional surgical treatment options for symptomatic uterine leiomyomas include myomectomy and hysterectomy, the treatment outlook of this common gynecological disease has shifted from the use of invasive surgical procedures to the application of minimally invasive, image-guided ablation techniques such as uterine arterial embolization and noninvasive ultrasound or magnetic resonance imaging (MRI)-guided, high-intensity focused ultrasound (HIFU).

Since the United States Food and Drug Administration first approved MRI-guided HIFU as a noninvasive approach in the treatment of uterine leiomyomas in 2004 (3), the use of HIFU has increased worldwide and a large number of clinical studies (4–16) to date have demonstrated not only the clinical effectiveness of MRI-guided HIFU for the treatment of uterine leiomyomas but also the ability of HIFU to decrease the volume of uterine leiomyomas and its correlation with the nonperfused volume (NPV) of the tumor immediately after treatment. However, there are still some complications and adverse events (AEs) that should be taken into consideration in considering HIFU for therapeutic use (17).

The aim of this study was to present our preliminary experience regarding the effectiveness and safety of MRI-guided HIFU therapy using a volumetric ablation technique in the treatment of symptomatic uterine leiomyomas in Association of Asian Nations (ASEAN) patients.

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Methods

Patient selection

The relevant institutional review boards approved this multicentric retrospective study on 27 February 2015 and written informed consent was obtained from each study participant prior to the initiation of any HIFU-related procedure.

The inclusion criteria for this study were as follows: 1) women aged older than 18 years who were either pre- or perimenopausal; 2) patients with symptomatic uterine leiomyomas with a tumor diameter of at least 3 cm; 3) having the ability to lie in a prone position during the treatment procedure; 4) able to communicate during the procedure; and 5) willing and able to participate in the post-treatment six-month follow-up. Exclusion criteria included the following: 1) Other pelvic disease (malignant leiomyoma diseases, endometriosis, ovarian tumor, acute pelvic disease, significant adenomyosis); 2) positive pregnancy test; 3) no evidence of degeneration in the uterine leiomyomas; 4) distance from the posterior surface of the fibroid to the skin exceeding 12 cm; 5) calcifications around or throughout leiomyoma tissues; and 6) MRI contrast agent contraindications.

Between May 2015 and June 2017, a total of 70 Vietnamese and Malaysian women were screened for inclusion in this study, with 33 women (23 Vietnamese and 10 Malaysian; median age 41 years (interquartile range [IQR], 9 years) with 104 leiomyomas (median, 1; IQR, 1.94) ultimately included. The main reasons for exclusion were MRI findings (75.7%), including leiomyomas being located too deep, a suspicion of malignancy, ovarian tumor, endometriosis, and a preference for alternative treatment options. In addition, 24.3% of the screened participants withdrew from the study prior to HIFU treatment due to financial difficulties or personal reasons. Fig. 1 presents the complete clinical workflow of this study from patient enrollment until the end of the six-month follow-up.

Main points

- In practice, there are two classifications of uterine leiomyomas based on T2-weighted imaging and T1-weighted perfusion imaging.
- Volumetric HIFU under the guidance of MRI is an innovative treatment alternative to conventional therapeutic options.
- The effectiveness and safety of volumetric HIFU under the guidance of MRI are acceptable.

Screening MRI: patient's suitability

MRI-guided HIFU ablation was performed using two clinical HIFU systems, Sonalleve-V1 and Sonalleve-V2 (Profound Medical), which were integrated into a 3 T MRI Achieva TX system or a 1.5 T MRI Ingenia system (Philips Healthcare), respectively.

Assessment of T2-weighted images and T2-based classification

The aim of acquiring T2-weighted, three-dimensional (3D) turbo-spin echo (TSE) data (Table 1), as a part of our routine clinical screening protocol, was two-fold, as follows:

1. To assess tissue characteristics of uterine leiomyomas including diameter; distance from the posterior surface of the leiomyoma to the skin; leiomyoma type (e.g., intramural, submucosal, or subserosal); signal intensity (SI) of uterine leiomyomas, SI ratio of the leiomyoma to muscle, and SI ratio of the leiomyoma to myometrium; lengths of transverse and longitudinal scar; thickness of the subcutaneous fat layer in the anterior abdominal wall; and uterus position (i.e., anteverted or retroverted).

2. To categorize leiomyomas into one of the following three types (4): dark leiomyomas as T2-type I, which have a very low SI value, similar to that of the skeletal muscle (n=8); iso leiomyomas as T2-type II, which have an SI value higher than that of skeletal muscle but lower than that of myometrium (n=15); or bright leiomyomas as T2-type III, which have an SI value higher than that of the myometrium (n=10).

Furthermore, in this study, 33 patients who underwent HIFU treatment were also divided into those with scar tissue (Group 1, n=7) and without scar tissue (Group 2, n=26).

Assessment of perfusion images and T1 perfusion-based classification

A dynamic contrast-enhanced (DCE) perfusion MRI (Table 1) was carried out during the screening examination as a part of our routine clinical screening protocol after initiating the intravenous administration of a gadolinium-based contrast agent (0.1 mmol/kg Gd-DO3A-butrol, Gado-

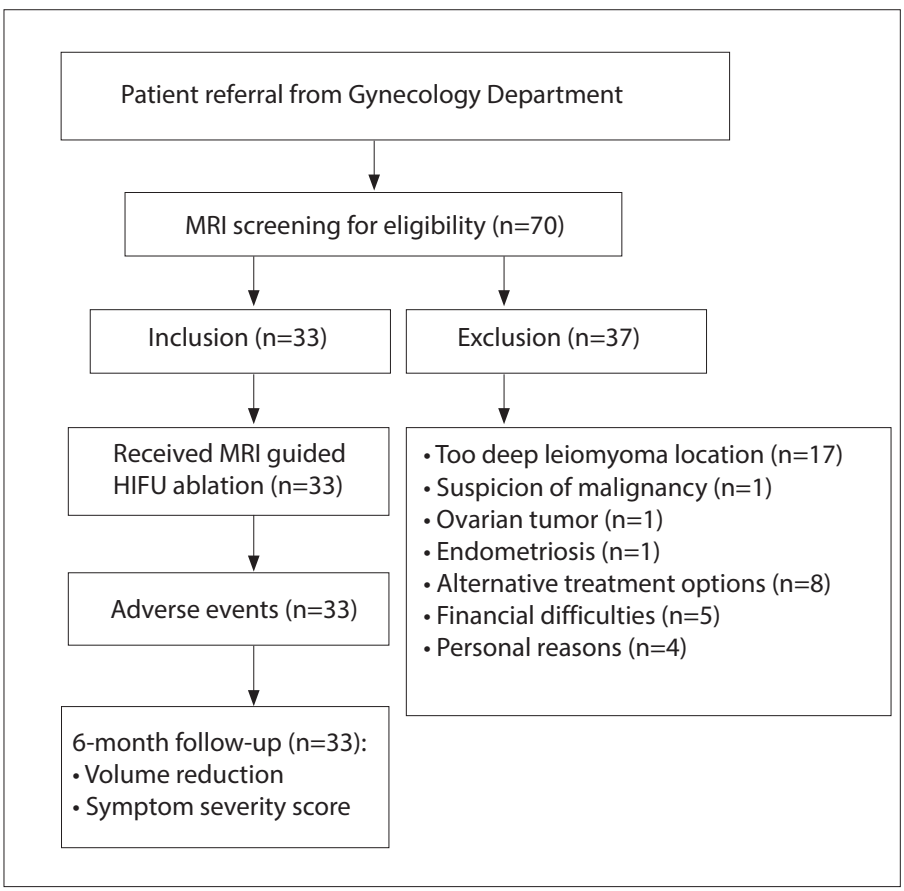

Figure 1. Diagram of the complete clinical workflow of this study from patient enrollment until the end of six months of follow-up.

vist; Bayer Schering Pharma). The time–SI curves of leiomyomas and the myometrium at selected regions of interest (ROIs) on perfusion axial magnetic resonance images, based on the slice in which the largest diameter of leiomyoma was present, were obtained using commercial software (IntelliSpace Portal, version 6.0; Philips Healthcare).

In this study, as an alternative MRI-based classification method (15), uterine leiomyomas were also categorized by the comparison of T1 perfusion-based time–SI curves of leiomyoma tissue and the myometrium on DCE-MRI images as follows: perfusion group A if the time–SI curve was lower than that of the myometrium (n=20) and perfusion group B if the time–SI curve was equal to or higher than that of the myometrium (n=13).

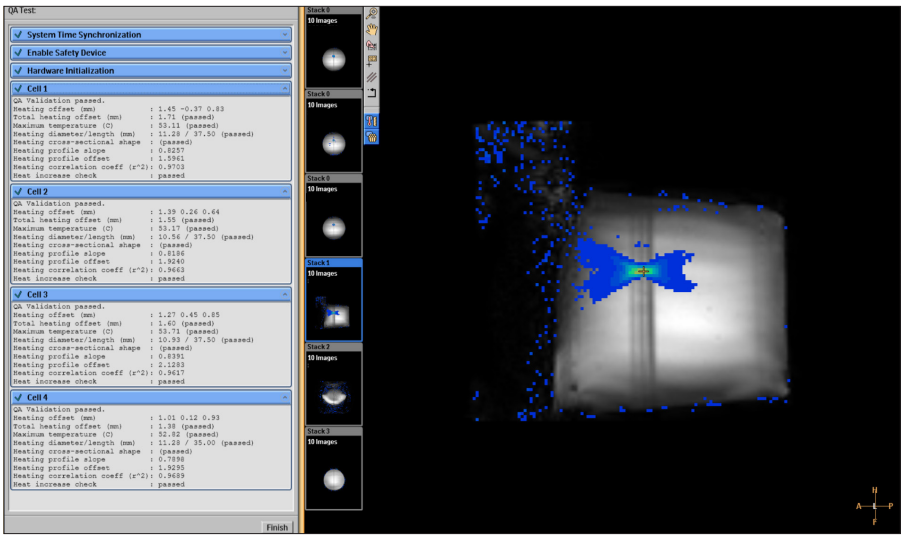

Figure 2. The results of a successful quality assurance (QA) test including correct positioning of the QA phantom, cross-sectional shape of the heating pattern, maximum temperature, heating dimensions (diameter and length), and location of the heating.

Patient preparation and pre-HIFU-treatment MRI protocols

All patients were required to depilate the lower abdomen and fast for at least 12 hours prior to HIFU treatment. On the treatment day, a double-lumen catheter with saline solution was inserted in order to prevent movement of the uterus due to filling of the bladder and an intravenous catheter was employed to allow administration of the contrast agent and intravenous sedation with fentanyl citrate (administered as 100 μg in 500 mL of normal saline when considered necessary per each patient) prior to HIFU treatment initiation. Patients were instructed to press the "patient emergency stop button" to abort sonication if they began to experience pain, numbness in the legs, nausea, an abnormal heating sensation, or other discomfort. The patient's rectal temperature was used as a baseline temperature reference during treatment. The patients were in direct visual and voice contact with the treating radiologist/gynecologist at all times.

Prior to initiating HIFU treatment, a quality assurance (QA) procedure using a manufacturer-provided QA phantom (Philips Healthcare), which contains residues of acrylamide in a hermetically sealed container, was performed to ensure that spatial targeting accuracy, thermal dose volume accuracy, and therapeutic power levels were within acceptable ranges according to the manufacturer's QA procedure guidelines. Following a successful QA procedure (Fig. 2), the patient was positioned in the prone position and pre-HIFU-treatment magnetic resonance images were obtained in the following order:

1. A "skin bubble sequence," consisting of a multislice, single-echo, 3D T1-weighted fast-field echo (FFE) was obtained to verify that the ultrasound beam would not be deflected into unwanted locations by air-containing structures such as air bubbles, skin folds, or the umbilicus.

2. A "scar and scar patch sequence" in the coronal-plane, single-echo 3D T2-weighted FFE was obtained for verifying the visibility and location of the scar and scar patch (but only if the patient had a scar near the beam path).

3. A "bowel sequence" (3D T1-weighted FFE), in which the contrast was optimized for showing the bowel was obtained to verify that the bowel is not in the ultrasound beam path. Bowel loops in the ultrasound beam path are generally considered to be a contraindication for HIFU treatment, as gas bubbles and hard particles contained in the bowels might reflect or absorb ultrasound energy in unpredictable ways, potentially leading to thermal damage.

4. A "3D T2-weighted TSE sequence" was obtained not only for treatment planning but also for distinguishing leiomyomas from healthy tissue and ensuring the safety of sensitive structures such as the skin or the subcutaneous fat layer in the near-field and the sacral nerves, the bowel, and the spine in the far-field.

Details of the pre-HIFU MRI protocols used in this study are presented in Table 1.

HIFU treatment via MRI guidance

After retrieving the 3D T2-weighted TSE planning dataset from the MRI console, the radiologist/gynecologist, aiming to ablate the uterine leiomyomas as close as possible to the point of full ablation without sacrificing patient safety, positioned the treatment cells on the treatment planning images on the HIFU therapy console. This was done using a dedicated software by carefully considering safety margins (in accordance with the manufacturer's safety guidelines) from the borders of the treatment cells to the capsule of the leiomyoma, and to critical organs such as the small bowel, or the bony structures such as the spine or the sacrum in the posterior part leiomyoma, and the pubic bone in the anterior part of leiomyoma depending on the treatment plane, treatment cell size, and therapy power defined for each sonication. In addition to its safety features, the software also allows the user not only to control the transducer and the power used in each sonication but also to monitor the heat and thermal dose accumulation on top of performing low-resolution anatomical monitoring scans during the sonication to safeguard adherence to the treatment plan.

Prior to the treatment, to ensure that there were no obstacles in the ultrasound beam path, the following precautions were taken: 1) scar tissues, horizontal or vertical, were covered with polyethylene foam scar patches (QuickCover US Protective Cover; Mectalent Oy) to prevent ultrasound energy from reaching the scar tissue immedi-

ately behind the patch; 2) when necessary, displacement of the small bowel loops was performed by a combination of urinary bladder-filling with normal saline solution and/or rectal-filling with ultrasound gel using a syringe; and 3) to detect any image distortion or patient movement that occurred after the planning stage during therapy, multiple fiducial markers were placed at the boundaries of the uterus and pelvic bones on the T2-weighted planning images.

Volumetric ablation with binary feedback (18, 19) using a nominal frequency of 1.2 MHz was conducted by electronically steering a single focus on a predetermined trajectory, which consisted of one or more subtrajectories that all had a predefined number of heating points with a constant sonication interval. The trajectories were classified according to the diameters of the heating volumes, i.e., 4 mm, 8 mm, 12 mm, 14 mm, and 16 mm. For real-time volumetric magnetic resonance (MR) thermometry, based on proton resonance frequency shift (20), using a two-dimensional radiofrequency (RF)-spoiled, gradient-recalled, echo-planar imaging (EPI) sequence (Table 1), multiplane temperature images were acquired: three coronal slices perpendicular to the beam axis centered at the target location, one sagittal slice aligned along the beam propagation direction, and two additional slices positioned to monitor potential excessive near-field (e.g., over the skin or the inner margin of the subcutaneous fat layer) and far-field (e.g., in front of the sacral nerves, the bowel, and the spine) tissue heating.

The multiplane MR thermometry provides good visibility of temperature elevations not only at the target location but also in critical structures in order to reduce the risk of unintended lesions. To provide accurate real-time control of the temperature evolution and show the clinical endpoint of the treatment, thermal dose maps, which can be overlaid on top of an anatomical image showing the thermal dose of the leiomyoma tissue, deducted from multiplane MR thermometry were calculated in units of equivalent minutes at 43°C as the standard for the biological effect of heat (21). Fig. 3 illustrates the multiplane MR thermometry and cumulative dose contour of the ablated volume (the 240 EM dose contour is presented as a white line, which is recognized as the possibility of irreversible coagulative necrosis, and the 30 EM dose contour is presented as an orange line, which is recognized as no thermal damage).

When a target volume was sonicated, some heating occurred in all the tissue layers through which the ultrasound beam traveled, both in the near- and far-fields. Cumulative heating in the patient's skin and subcutaneous fat layer is of particular concern and may potentially lead to the onset of severe skin burns. To assist the operator in preventing such skin burns, a fat-saturated T2-weighted TSE sequence was performed during HIFU treatment for monitoring abnormally increased SI values in the subcutaneous fat layer (Table 1).

Immediate post-HIFU and six-month follow-up outcomes assessment

Immediately after the treatment, a contrast-enhanced, T1-weighted 3D turbo-field echo (TFE) sequence (Table 1) was performed to determine the nonperfused volume (NPV) ratio, which was defined as NPV measured in the perfusion MR images acquired immediately post-HIFU treatment, divided by the leiomyoma volume measured in T2-weighted images acquired pretreatment.

The treatment efficacy of MRI-guided HIFU was evaluated on the basis of the degree of leiomyoma volume reduction (7, 10, 12, 22), which was calculated as a proportion of the baseline leiomyoma target volume and improvement in transformed symptom severity score (SSS) using a questionnaire described by Spies et al. (23). Any AEs during HIFU treatment were recorded and graded according to the Society of Interventional Radiology (SIR) guidelines (24).

Statistical analysis

Values are expressed as median and IQR for continuous variables and as number and percentage for nominal variables. The difference of immediate NPV ratio, volume ratio reduction, and transformed SSS improvement between T2-based classifications was defined first as Kruskal-Wallis and then non-parametric Post-Hoc Dunnett's T3. The difference of immediate NPV ratio, volume ratio reduction, and transformed SSS improvement between T1 perfusion-based classifications or scar presence was determined by Mann-Whitney U test. Spearman's test was used to calculate the correlation between two continuous variables. A *P* value of less than 0.05 was consid-

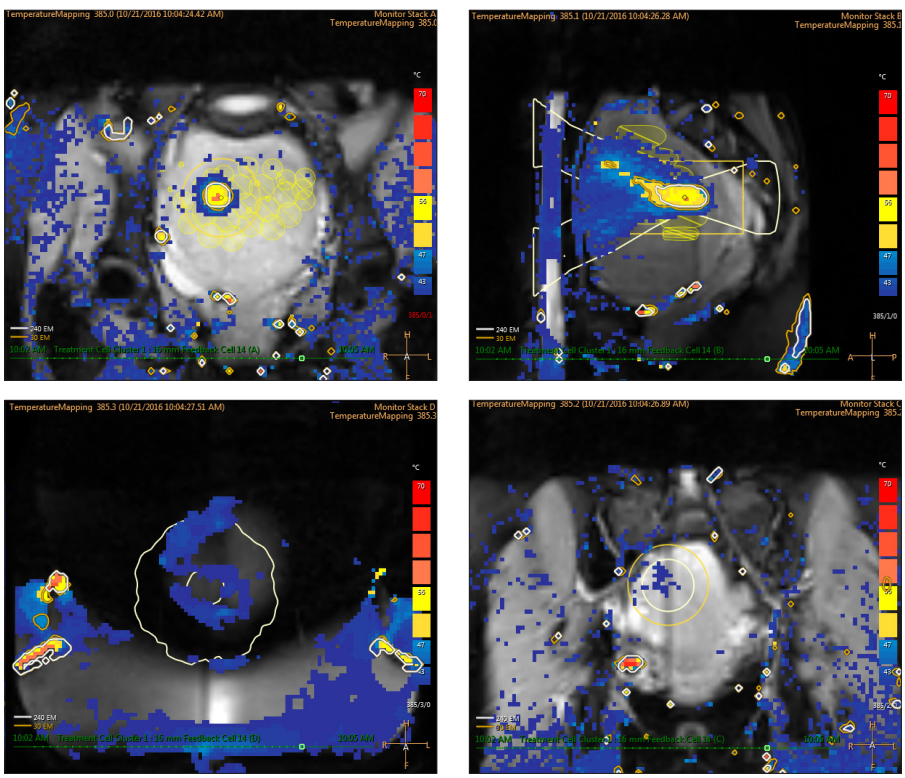

Figure 3. Coronal *(upper left)* and sagittal *(upper right)* multiplane magnetic resonance (MR) thermometry acquired during one of the sonications. The cumulative dose contour of the ablated volume (the 240 EM dose contour is shown as a white line, which is recognized as the possibility of irreversible coagulative necrosis, and the 30 EM dose contour is shown as an orange line, which is recognized as no thermal damage). MR thermometry also shows the temperature of abdominal skin in the near-field *(lower left)* and tissues adjacent to sacrum in the far-field *(lower right)*.

Table 1. MRI protocols for screening, pre-, peri- and immediately post-HIFU and at six months of follow-up

MRI parameter	DCE-MRI at screening and 6 m follow-up*	Scar & scar patch (pre-HIFU)	Bowel sequence (pre-HIFU)	Treatment planning and 6 m follow-up	MR thermometry during HIFU ablation	SI change in the subcutaneous fat (pre- & post-HIFU)	NPV ratio post-HIFU & 6 m follow-up*
Philips MR scanner	Achieva 3T / Ingenia 1.5T	Achieva 3T / Ingenia 1.5T	Achieva 3T / Ingenia 1.5T	Achieva 3T / Ingenia 1.5T	Achieva 3T / Ingenia 1.5T	Achieva 3T / Ingenia 1.5T	Achieva 3T / Ingenia 1.5T
Imaging sequence	Fat-saturated T1W FFE	T2W 3D FFE	T1W 3D FFE	T2W 3D TSE with DRIVE	RF-spoiled segmented EPI	Fat-saturated T2W TSE	Fat-saturated T1W TFE
Repetition time (ms)	4.0	10	2.7	130.0	37	11366	5
Echo time (ms)	2.0	6	1.5	1.3	19.5	70	3
Flip angle (degrees)	5, 10 (pre); 8 (post)	15	7	90	19	130	10
Slice thickness (mm)	5	1	3	1.25	7	4	1.5
Field of view (mm)	230×230	220×220	236×236	250×250	160×100	320×320	250×250
Matrix size	116×114	208×208	160×160	224×218	400×250	200×188	150×150
Imaging planes	axial	Coronal	Sagittal	Sagittal	Multiplane	Sagittal	Coronal
Other information	50 dynamics	N/A	N/A	N/A	121-binomial water-selective excitation	N/A	N/A

MRI, magnetic resonance imaging; DCE-MRI, dynamic contrast-enhanced MRI; HIFU, high-intensity focused ultrasound; NPV, nonperfused volume; T1W, T1-weighted; FFE, fast-field echo; T2W, T2-weighted; 3D, three-dimensional; TSE, turbo-spin echo; DRIVE, driven equilibrium; RF, radiofrequency; EPI, echoplanar imaging; TFE, turbo field-echo.
*Gd-DO3A-butrol (0.1 mmol/kg, Gadovist; Bayer Schering Pharma) was used for contrast enhancement.

ered to be statistically significant. Statistical analysis in this study was performed using the Statistical Package for the Social Sciences for Windows (version 24.0, 64-bit edition; IBM Corp.).

Results

Table 2 summarizes the baseline features and leiomyoma tissue characteristics of the 33 patients enrolled in this study. The median diameter of all leiomyomas was 5.9 cm (IQR, 3.25 cm). Of the 33 patients, eight patients (24.2%) had a single leiomyoma and 25 patients (75.8%) had multiple leiomyomas. Importantly, although all 104 leiomyomas were treated, only the largest leiomyoma (i.e., the most symptomatic one) per patient was considered for analysis in this study. On the basis of leiomyoma location in the uterus, intramural leiomyomas were the most common (n=15), followed by subserosal (n=9) and submucosal (n=9) ones. With regard to uterus position, there were 21 patients with an anteverted uterus and 12 patients with a retroverted uterus, respectively. Furthermore, five patients (15.1%) had a transverse scar and two patients (6.0%) had a longitudinal scar. The median transverse and longitudinal scar sizes in length were 120 mm (IQR, 135 mm) and 90 mm (IQR, 98 mm), respectively.

In order to push bowel loops away from in between the abdominal wall and the uterus, urinary bladder filling (200–500 mL of saline) and/or rectal filling (100–200 mL of ultrasound gel) were performed in 21 of 33 patients (63.6%). Twelve patients (36.4%) did not need bowel mitigation.

Among the baseline features of patients and leiomyoma tissue characteristics, we noted the following in particular:

1. On the basis of T2-based classification, there was no statistically significant difference among types I, II, and III for any variables. In addition, no significant difference was observed between patients with and without scars for any variables.

2. On the basis of T1 perfusion-based classification, the T2 SI ratio of leiomyoma to myometrium was larger in perfusion-group B ($P = 0.003$).

The median acoustic sonication power and HIFU treatment durations from the first sonication to the last one were 150 W (IQR, 40 W) and 125 min (IQR, 60 min), respectively. The median number of sonications used per treatment was 30 (IQR, 20). The median HIFU treatment speed was 0.89 mL/min (IQR, 0.89 mL/min).

Of the 33 patients, the median immediate NPV ratio was 89.8% (IQR, 29.9%). When comparing the T2 and T1 perfusion-based classifications to the immediate NPV ratio, the following was observed: for types I, II, and III leiomyomas classified by the T2-based method, the median NPV ratios were 93.2% (IQR, 42.6%, n=8); 90.0% (IQR, 15.6%, n=15); and 71.8% (IQR, 50.0%, n=10; $P = 0.35$), respectively. For perfusion-groups A and B as classified by the T1 perfusion-based method, the median NPV ratios were 95.5% (IQR, 19.9%, n=20) and 64.3% (IQR, 13.8%, n=13; $P < 0.001$), respectively. The median NPV ratios were 86.4% (IQR, 31%) in patients without scars (n=26) and 91.7% (IQR, 29.4%) in patients with scars (n=7) ($P = 0.71$).

Fig. 4 shows sagittal T2-weighted images of uterine leiomyoma taken prior to HIFU treatment (Fig. 4a–4d) and corresponding contrast-enhanced T1-weighted images in the coronal plane obtained immediately after HIFU treatment (Fig. 4e–4h), respectively.

Six-month follow-up MRI data were obtained for all 33 patients. The present study demonstrated that the immediate NPV ratio showed a very strong correlation with leiomyoma volume reduction (r=0.822, $P < 0.001$; Spearman's correlation test) and transformed SSS improvement (r=0.784, $P < 0.001$; Spearman's correlation test).

The median leiomyoma volume decreased from 139 mL (IQR, 139.5 mL, n=33) at baseline to 84 mL (IQR, 112.5 mL, n=33) at six months, corresponding to a median percent reduction ratio of 0.32 (IQR, 0.56, n=33; Table 3). As shown in Table 4, based

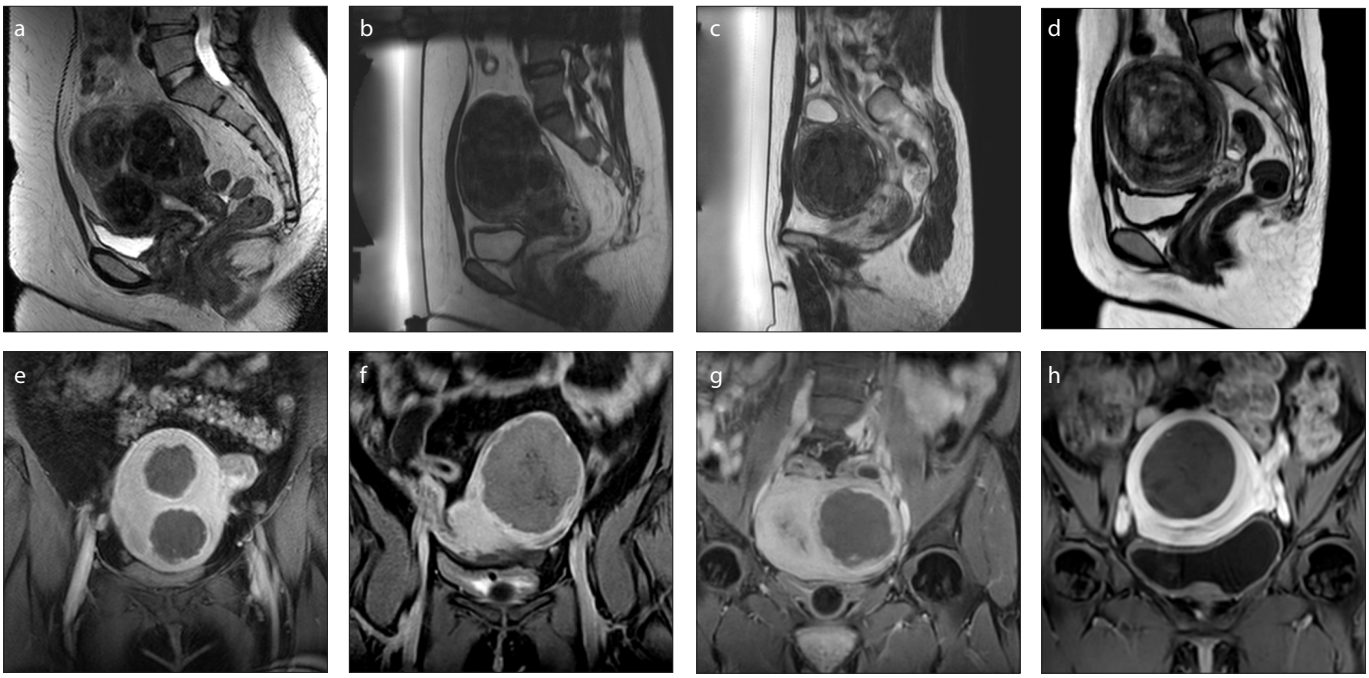

Figure 4. a–h. Sagittal T2-weighted planning MR images of four uterine leiomyomas prior to HIFU treatment: **(a)**, T2-type I, perfusion-group A; **(b)**, T2-type II, perfusion-group A; **(c)** T2-type II, perfusion-group A; **(d)**, T2-type III, perfusion-group A. Corresponding contrast-enhanced T1-weighted MR images **(e–h)** in the coronal plane obtained immediately after HIFU treatment.

on T2 and T1 perfusion-based classifications, the median percent reduction ratio was 0.57 (IQR, 0.57, n=8) in T2-type I, 0.36 (IQR, 0.24, n=15) in T2-type II, and 0.13 (IQR, 0.66, n=10; $P = 0.38$) in T2-type III. Additionally, values of 0.55 (IQR, 0.29, n=20) in perfusion-group A and 0.51 (IQR, 0.16, n=15; $P < 0.001$) in perfusion-group B were obtained. Also, the median percent reduction ratio was 0.31 (IQR, 0.54, n=26) in patients without scars (Group 2) and 0.52 (IQR, 0.50, n=7; $P = 0.31$) in patients with scars (Group 1).

Separately, the median transformed SSS decreased from 56.2 (IQR, 21.9, n=33) at baseline to 18.8 (IQR, 43.8) at six months, corresponding to a median transformed SSS improvement of 0.57 (IQR, 0.78; Table 3). As shown in Table 4, based on T2 and T1 perfusion-based classifications, the median transformed SSS values were 0.90 (IQR, 0.87, n=8) in type I, 0.60 (IQR, 0.30, n=15) in type II, 0.26 (IQR, 0.76, n=10; $P = 0.29$) in type III, 0.80 (IQR, 0.34, n=20) in perfusion group A and 0.11 (IQR, 0.10, n=15; $P < 0.001$) in perfusion group B,, respectively. Furthermore, the median transformed SSS values were 0.56 (IQR, 0.73, n=26) in patients without scars (Group 2) and 0.75 (IQR, 0.80, n=7; $P = 0.73$) in patients with scars (Group 1).

The following AEs were recorded during and immediately after HIFU treatment: first-degree skin burn (n=1), which resolved without intervention within 24 hours; pain that manifested as mild pain in the pelvic area (n=3), back (n=3), and buttock (n=3) during and after HIFU treatment, which was treated by an oral analgesic agent and resolved within one week in all cases; the appearance of abnormal vaginal discharge (n=1) that disappeared after two weeks; Foley catheterization-related cystitis symptoms (n=1) that subsided with help from antibiotics; self-limiting nausea (n=3); and a heating sensation on the skin along with discomfort (n=8).

A total of 22 AEs (95.6%) were classified as SIR class A (no medical intervention required) and 1 (4.3%) event was classified as SIR class B (nominal therapy or no consequence). Table 5 presents further on the incidence of AEs. One patient reported a natural pregnancy after six months of follow-up that led to a live birth by vaginal delivery (3200 g, Apgar score: 9).

Discussion

In general practice, the aim of HIFU treatment via MRI guidance is to reduce or eliminate leiomyoma-related symptoms in affected women. The merits of HIFU in the treatment of uterine leiomyomas include the capability to deliver acoustic energy into the target tissue precisely to generate cell death via local coagulative necrosis and the ability to preserve the uterus with a high level of safety. The capability of MRI, with its high-resolution 3D and multiplanar anatomic imaging, superior soft tissue contrast, and ability of real-time multiplanar temperature monitoring, enables real-time identification and localization of uterine leiomyomas, treatment planning, precise monitoring of the temperature evolution during the treatment, and immediate post-procedural evaluation of the treatment outcome. HIFU via MRI guidance can hence be used for selective tissue destruction by producing well-defined volumes of thermal coagulation and necrosis deep within the body while sparing the surrounding tissues. To the best of our knowledge, this is the first multicenter study of MRI-guided HIFU therapy using a volumetric ablation technique in the treatment of symptomatic uterine leiomyomas performed in ASEAN patients.

Our preliminary results revealed that there was no significant difference between the T2-based classification and immediate NPV ratio ($P = 0.35$), and between patients with and without abdominal scars and immediate NPV ratio ($P = 0.71$), whereas a statistically significant difference was observed between T1 perfusion-based classification and immediate NPV ratio ($P < 0.001$). This leads to the preliminary conclusion that only T1 perfusion-based classification

Table 2. Comparison of baseline parameters and tissue characteristics of uterine leiomyomas

Characteristics	All patients n=33
Age (years)	41 (9)
Body mass index (kg/m^2)	19.8 (2.9)
Subcutaneous fat thickness (mm)	13 (6)
Presence of abdominal scars	
Yes	7
No	26
Main symptoms	
Bulk effect	27
AUB	18
Uterus position	
Anteverted	21
Retroverted	12
Number of leiomyomas treated (total)	1 (1.94)
Single fibroid	8
Multiple fibroids (2–15)	25
Diameter (cm)[a]	5.9 (3.25)
Distance (mm)[b]	89 (17)
Bowel displacement technique[c]	
Yes	21
No	12
Location	
Intramural	15
Subserosal	9
Submucosal	9
T2-based classification	
T2-type I	n=8
T2-type II	n=15
T2-type III	n=10
T1 perfusion-based classification	
Perfusion-group A	n=20
Perfusion-group B	n=13

Continuous variables in the table are presented as median (IQR).
T2-type I, very low SI similar to that of the skeletal muscle; T2-type II, SI higher than that of skeletal muscle but lower than that of the myometrium; T2-type III, SI higher than that of the myometrium, based on selected region of interests on leiomyoma, myometrium, and skeletal muscle (4). Perfusion-group A, time–SI curve lower than that of the myometrium; perfusion-group B, time–SI curve equal to or higher than that of the myometrium based on selected region of interests on leiomyoma and myometrium (14).
[a]Largest treated fibroids only; [b]From skin to the most posterior part of the largest fibroid; [c]Bowel displacement technique: sequential application of urinary bladder and rectal filling and urinary bladder emptying.

Table 3. Treatment outcomes at six months after MRI-guided HIFU ablation

Treatment outcome	All patients (n=33)
Leiomyoma volume	
Baseline volume, mL	139 (139.5)
Six months volume, mL	84 (112.5)
Reduction ratio (six months)	0.32 (0.56)
Symptom severity score[a]	
Baseline	56.2 (21.9)
Six months	18.8 (43.8)
Improvement ratio (six months)	0.57 (0.78)

Continuous variables in the table are presentedas median (IQR).
MRI-guided HIFU, magnetic resonance imaging-guided high-intensity focused ultrasound.
[a]Transformed symptom severity score (tSSS) can range from 0 to 100.

may play an important role for predicting an immediate NPV ratio in HIFU treatment. This is consistent with the findings of another recent study (15) and Pennes' bioheat transfer equation (25–29).

The effectiveness of MRI-guided HIFU ablation using a volumetric ablation technique in the treatment of symptomatic uterine leiomyomas was measured by assessing leiomyoma volume reduction and improvement in transformed SSS at the six-month follow-up point. The leiomyoma volume reduction was not statistically significant among the three groups according to T2-based classification ($P = 0.38$) and between the two groups according to patients with and without scar ($P = 0.31$), whereas it was significantly greater in perfusion-group A versus in perfusion-group B ($P < 0.001$). These findings are in agreement with those of earlier studies (15, 16, 22, 25–32).

The transformed SSS improvement was not statistically significant among the three groups according to T2-based classification ($P = 0.29$) and between the two groups according to patients with and without scar ($P = 0.73$), whereas patients in perfusion-group A exhibited a significantly greater improvement in symptoms than those in perfusion-group B did ($P < 0.001$). This is in line with the findings of a previous clinical study evaluating HIFU treatment of uterine leiomyomas (15).

There were no significant AEs reported in this study, while short-term AEs related to HIFU included first-degree skin burn due to location of the treatment plane, which was very close to the skin (lack of operator experience); back pain due to long procedure duration in the prone position; buttock pain due to stimulation of the sciatic nerve by ultrasound sonication energy; pelvic pain and vaginal discharge due to local edema of the treated region; cystitis due to Foley catheterization; nausea possibly due to the side effects of a gadolinium-based contrast agent or fentanyl citrate; and heating sensation due to repetitive sonication of adjacent treatment cells, which caused thermal build-up in the near-field area. These findings, which are known common AEs, are in line with the results of previous clinical studies on MRI-guided HIFU treatment of leiomyomas (3, 6, 13, 15, 17, 22, 30–32). Despite the effectiveness of HIFU ablation in the treatment of symptomatic uterine leiomyomas, all AEs that occurred in this study should be considered cautiously by clini-

Table 4. The difference of NPV ratios, leiomyoma volume reduction and transformed SSS improvement based on T2-based classification, perfusion-based classification, and scar appearance

	T2-classification			Perfusion-classification		Scar presence	
	T2-I	T2-II	T2-III	Perfusion-A	Perfusion-B	Group 1 (Yes)	Group 2 (No)
NPV ratio, (%)	93.2 (42.6)	90.0 (15.6)	71.8 (50.0)	95.5 (19.9)	64.3 (13.8)	91.7 (29.4)	86.4 (31.0)
Volume reduction ratio	0.57 (0.57)	0.36 (0.24)	0.13 (0.66)	0.55 (0.29)	0.51 (0.16)	0.52 (0.50)	0.31 (0.54)
Transformed SSS improvement	0.90 (0.87)	0.60 (0.30)	0.26 (0.76)	0.80 (0.34)	0.11 (0.10)	0.75 (0.80)	0.56 (0.73)
P	$P^{1} = 0.35$; $P^{2} = 0.38$; $P^{3} = 0.29$			$P^{1,2,3} < 0.001$		$P^{1} = 0.71$; $P^{2} = 0.31$; $P^{3} = 0.73$	

Continuous variables in the table are presented as median (IQR).
NPV, nonperfused volume; SSS, symptom severity score.
[1]*P* value for NPV ratio; [2]*P* value for volume reduction ratio; [3]*P* value for transformed SSS improvement.

Table 5. Adverse events during and after MRI-guided HIFU ablation

AEs	All patients (n=33)
Minor	
First-degree skin burn	1 (3)
Back pain	3 (9.1)
Buttock pain	3 (9.1)
Cystitis	1 (3)
Nausea	3 (9.1)
Vaginal discharge	1 (3)
Pelvic pain	3 (9.1)
Heating sensation	8 (24.2)
Major	N/A

Values in parentheses represent percentages.
MRI-guided HIFU, magnetic resonance imaging-guided high-intensity focused ultrasound; AE, adverse events; N/A, not available.

cians so as to maintain a good HIFU safety profile and promote effective outcomes for patients with leiomyomas.

This study has some limitations which have to be pointed out. Because of the retrospective nature of the study, HIFU treatment was not directly compared with other options for uterine leiomyomas therapy. Therefore, a randomized clinical trial might be required for large-scale evaluation of safety and treatment effectiveness. However, it is worth to note that randomization can be prohibitive for enrollment when one arm is invasive and the other noninvasive. Furthermore, further prospective studies with large sample size are required for validation of the findings in this study.

In conclusion, the preliminary results in the present study suggest that MRI-guided-HIFU therapy using a volumetric ablation technique in the treatment of symptomatic uterine leiomyomas in ASEAN patients appears to be clinically acceptable with respect to treatment effectiveness, volume reduction, and transformed SSS improvement as well as safety (i.e., AEs were manageable with acceptable therapeutic outcomes). Furthermore, the preliminary experience we gained in this study greatly improved our understanding of the basic concept of HIFU treatment and the confidence in its use among multidisciplinary clinical teams of the departments of radiology and gynecology.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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