Original Article

Clinical Efficacy of Ultrasound-guided High-intensity Focused Ultrasound Ablation for Treating Breast Fibroadenoma of Different Sizes: A Retrospective Study

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Abstract

Objectives: The aim of this study was to assess the clinical outcomes of ultrasound (US)-guided high-intensity focused ultrasound (HIFU) in patients with breast fibroadenoma (FA) of different sizes.

Materials and Methods: A total of 88 patients with 245 lesions diagnosed with FA by core needle biopsy from January 2021 to November 2023 were included in this study. US-guided HIFU was performed under local anesthesia. Baseline and treatment characteristics were recorded and analyzed. FAs were divided into three groups according to the longest diameter for further analysis. After the treatment, follow-up with volume evaluation and physical examination was performed at 3, 6, and 12 months.

Results: There were 56 FAs ≤10 mm (group 1), 144 FAs with a diameter of 10–20 mm (Group 2), and 45 FAs of 20–30 mm (Group 3). The sonication time of the three groups was 22.5 s, 45.0 s, and 83.0 s ($P < 0.05$). Based on contrast-enhanced ultrasound evaluation, the median nonperfused volume ratio of the three groups was 74.1%, 87.6%, and 79.2% ($P > 0.05$), respectively. The volume reduction rates (VRR) of the three groups were 47.3%, 77.0%, and 82.0% at 12 months after HIFU, showing statistical differences. All patients were tolerated well and there were no adverse events after HIFU.

Conclusion: The current evidence indicated HIFU was effective and safe in treating breast FA of different sizes, and the VRR of FA >1 cm at 12 months post-HIFU was greater than that of FA <1 cm.

Keywords: Breast fibroadenoma, clinical outcome, different sizes, high-intensity focused ultrasound

Introduction

Breast fibroadenoma (FA) is the most common breast benign tumor in women, discovered in 67%–94% of all biopsy masses in women under the age of 20 and diagnosed in 10% of all women in their lifetime.[1] The etiology of FA is unclear, but certain studies have revealed that it is mainly related to the abnormal response of the breast lobules to estrogen.[2] Although the malignant transformation rate of FA is as rare as 0.02%–0.13%,[3] only 25% of patients are asymptomatic and more than 50% can develop pain due to the superficial location

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of the lesion.[4,5] Thus, symptomatic FA may require active clinical intervention.

Recently, open surgery (OS), vacuum-assisted breast biopsy (VABB), and energy-based ablation are the most common treatment methods for FA. Although OS could remove the entire mass completely, the complications, such as scar keloids, loss of breast volume, and areola deformation and displacement, make it gradually become less preferred by young patients with breast cosmetic concerns.[6] VABB, with repeatedly cutting and vacuum suction of the lesion in strips using a biopsy system, has a small skin incision, but it is only applicable to lumps with a diameter of <3 cm.[7] The residual tumor and local hematoma have been reported by some studies in VABB for FA larger than 2 cm, and the risk of residue increases with the lesion size.[1,8] Energy-based ablation, including radiofrequency ablation (RFA), microwave ablation (MWA), laser ablation (LA), cryoablation, and high-intensity focused ultrasound (HIFU), could cause cellular destruction or coagulation necrosis of tissue *in situ* by delivery of energy into the lesion through antenna or extracorporeal transducer. The ablation techniques could offer several advantages, such as preserving breast cosmesis, low risk of complications, and a short hospital stay.[9] Compared with RFA, MWA, LA, and cryoablation, which require percutaneous antenna insertion, HIFU is the only noninvasive ablation method without skin scarring formation. After being approved by the FDA in 2004,[10] HIFU has been widely used for the treatment of a variety of benign and malignant diseases, such as breast cancer, uterine fibroids, and adenomyosis. Over the past two decades, a few studies reported that FA could be treated effectively and safely by ultrasound (US)-guided HIFU, resulting in significant volume reduction or even complete disappearance of the lesions.[11-19]

Despite the effective shrinkage of FA after HIFU, the volume reduction rate (VRR) reported by different studies has discrepancies, ranging from 62.0% to 84.8%.[20] It is unknown whether there are differences in the VRR of FA of different sizes. Therefore, this retrospective study tried to investigate the clinical outcomes, especially the volume change in follow-up, of breast FA of different sizes after US-guided HIFU treatment.

Materials and Methods

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Suining Central Hospital (LLSLH20210044). Written informed consent was received from all patients before treatment. The flow chart for the process of inclusion is shown in Supplementary Figure 1.

Patient enrollment

Inclusion criteria were as follows: (1) patients ≥16 years old; (2) FA visible clearly on the US and with a safe acoustic pathway; (3) the longest diameter of FA ≤30 mm; (4) the breast imaging reporting and data system (BI-RADS) grading ≤3 by the US; and (5) pathological diagnosis of breast FA confirmed by core needle biopsy. Exclusion criteria were as follows: (1) pregnant or lactating women; (2) patients with malignant tumors; (3) the maximum diameter of breast lesion >30 mm; (4) patients with severe coagulopathy or cardiopulmonary diseases; and (5) patients with acute or active infection.

Pre-HIFU evaluation

All patients underwent pre-HIFU ultrasonography (DC-80S, Mindary Medical, Shenzhen, China) to assess the location, size, and number of lesions using a 7.5 MHz linear array probe. Adler blood flow classification was performed by color Doppler flow imaging (CDFI). Breast FA was measured in three dimensions: longitudinal (a), anteroposterior (b), and transverse (c), and the FA volume was calculated according to the following formula: $V = 0.5233 \times a \times b \times c$. Distance from the superficial margin of FA to the skin and distance from the deep margin of FA to the chest wall in the supine position were also recorded. To evaluate the near-field acoustic pathway, the tissue between the breast skin and the FA was divided into three types, including mainly mammary glandular type, mixed type, and mainly fat type, which had been described in detail in our previous study.[21]

HIFU procedure

High-intensity Focused US Tumor Therapeutic System for Breast (Model JCQ-B, Chongqing Haifu Medical Technology Co. Ltd., China) was used to carry out US-guided HIFU ablation. Detailed treatment procedures have been previously described.[21] Briefly, the patient was placed prone on the treatment bed with the breast immersed in a tank of cold-degassed water after local anesthesia with 2% lidocaine. In the pretreatment scanning, the treatment plan was made by dividing FA into slices of 2–3 mm in software. Under dynamic real-time US monitoring (L9-3E, Mindray Medical, Shenzhen, China), the focus was manually moved from the deep side to the shallow side of each slice with US energy delivered in low power and adjusted according to the patient's response. Once the hyperechoic-grayscale change emerged, it was guided to diffuse around the FA until covering the whole lesion [Figure 1]. After the procedure, an ice bag was placed on the treated area for 0.5–2 h.

During treatment, sonication time (s), treatment time (min), hyperechoic change emerging time (s), and sonication energy (KJ) were recorded. The energy efficiency factor (EEF), defined as the amount of acoustic energy required for ablating 1 mm^3 of the biological tissue and calculated as the sonication energy divided by the FA volume,[22] was also recorded. A visual analog scale (VAS) score was used to evaluate the

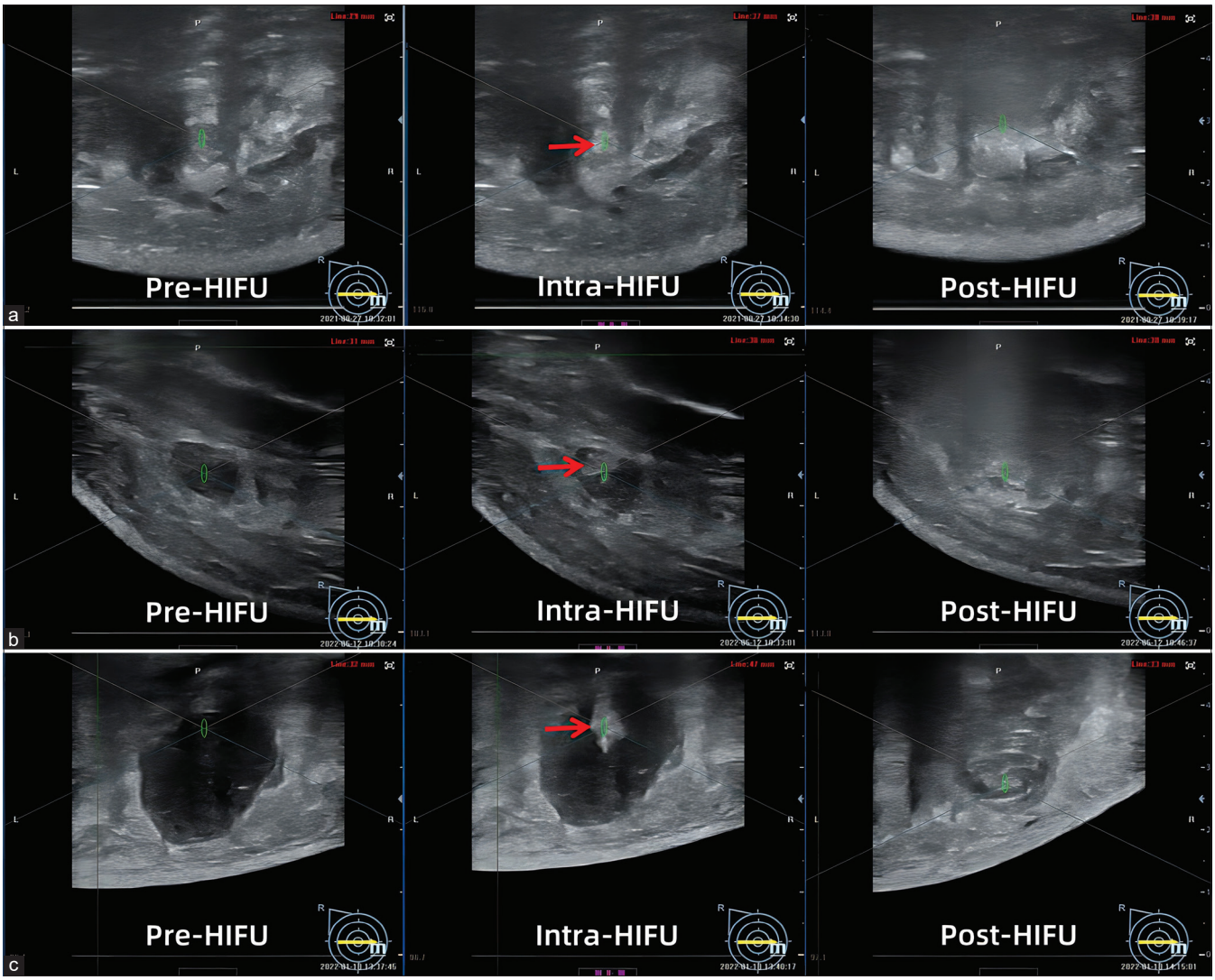

Figure 1: Typical gray-scale change of FA in different sizes under real-time US monitoring during HIFU treatment.(a-c) Typical change of FA with longest diameter of 9.7 mm, 17.9 mm 25.4 mm, respectively. Pre-HIFU: Before treatment, the ultrasound image showed a hypoechoic breast FA; Intra-HIFU: During treatment, a significant gray-scale change was observed (red arrow); Post-HIFU: After treatment, a significant gray-scale change covered the whole FA. FA: Fibroadenoma. US: Ultrasound. HIFU: High-intensity focused ultrasound

pain during HIFU ablation. Any adverse events during and after HIFU were recorded in detail.

Contrast-enhanced ultrasound

To evaluate the therapeutic results, contrast-enhanced US (CEUS) was performed on patients older than 18 years before and immediately after HIFU. SonoVue (Bracco, Milan, Italy), an intravenous microbubble agent for CEUS, was used through bolus administration of 5 ml, followed by a 5 ml saline flushing. Nonperfused volume (NPV) was measured in 3 dimensions and calculated according to the equation mentioned above. The NPV ratio was defined as NPV/FA volume × 100%.

Follow-up

Patients were followed up at 3, 6, and 12 months after HIFU. Each visit included a physical examination and US measurement of the ablated lesion. Any delayed adverse events were also recorded and followed until disappearance or the end of follow-up. The VRR was calculated as follows: VRR = (baseline volume − volume in follow-up)/baseline volume × 100%.

Statistical analysis

SPSS software (SPSS 27.0, IBM, USA) was used for statistical analysis. According to the normality result, categorical variables were described as numbers and percentages and compared using the Chi-squared test or Fisher's exact test. Continuous variables were described as medians and interquartile range (P25 and P75) and compared using the Kruskal–Wallis H test. P <0.05 was considered statistically significant.

Results

Baseline characteristics

From January 2021 to November 2023, a total of 170 patients with 512 FAs were screened, and finally, 88 patients with 245 FAs were included in this study [Supplementary Figure 1]. Of these, 31 patients had one single lesion, 18 patients had two lesions, and 39 patients had more than two lesions [Supplementary Table 1], among which one patient had up to 13 lesions. Fourteen patients had a history of breast OS and four had VABB due to previous FA [Supplementary Table 1]. The median age and body mass index (BMI) of the 88 patients were 26.5 (22.0, 34.0) years and 20.8 (19.0, 23.4) Kg/m^2 [Supplementary Table 1]. The median longest diameter of 245 lesions was 14.3 (10.4, 18.1) mm, and the median volume was 653.2 (280.4, 1389.1) mm^3 [Supplementary Table 1]. For the types of the near-field acoustic pathway, 13 lesions were mainly mammary glandular type, 99 lesions were mainly fat type, and 133 lesions were mixed type [Supplementary Table 1]. For the Adler blood flow classification, the number of FA with grades 0, I, II, and III was 98, 95, 19, and 5, respectively [Supplementary Table 1].

To estimate the clinical efficacy of HIFU in FA of different sizes, lesions were categorized into 3 groups based on the longest diameter. Group 1 was defined as the maximum diameter of FA ≤10 mm, group 2 as 10 mm < maximum diameter ≤20 mm, and group 3 as 20 mm < maximum diameter ≤30 mm. There were 56 (22.9%), 144 (58.8%), and 45 (18.4%) lesions in group 1, group 2, and group 3, respectively. The baseline characteristics of the three groups are summarized in Table 1. In group 1, group 2, and group 3, the median distance from the superficial margin of FA to the skin was 7.1, 5.8, and 4.5 mm, and the median distance from the deep margin of FA to chest wall was 3.8, 2.6, and 1.4 mm, respectively ($P < 0.05$) [Table 1]. There was no difference in quadrant location in the three groups ($P > 0.05$) [Table 1]. For the types of the near-field acoustic pathway, the number of lesions with mainly fat type, mixed type, and mainly mammary glandular type was 16, 36, and 4 in group 1, 55, 83, and 6 in group 2, and 28, 14, and 3 in group 3 ($P < 0.05$) [Table 1]. For the Adler blood flow classification, there were 26, 20, 0, and 0 FA with grade 0, I, II, and III in group 1, 63, 51, 13, and 1 FA in group 2, and 9, 24, 6, and 4 FA in group 3 ($P < 0.05$) [Table 1].

HIFU treatment results

For lesions in different groups, the treatment results are shown in Table 2. The sonication time of group 1, group 2, and group 3 was 22.5 s, 45.0 s, and 83.0 s, and the treatment time was 4.0, 8.0, and 15.0 min, respectively ($P < 0.05$) [Table 2]. There was no difference in the hyperechoic change emerging time, which was 6.0 s, 7.0 s, and 4.0 s, respectively, and neither was the hyperechoic change emerging rate ($P > 0.05$) [Table 2]. There was a significant difference in the sonication energy in three groups ($P < 0.05$), which was 3.2 KJ in group 1, 7.1 KJ in group 2, and 15.7 KJ in group 3, and the EEF was 22.5, 10.4, and 5.8 J/mm^3 [Table 2]. Based on CEUS evaluation, the median NPV ratio of the 3 groups was 74.1%, 87.6%, and 79.2%, showing no statistical difference [Table 2].

Overall, the safety profile appeared good. Under local anesthesia, all the patients tolerated the treatment well. There was no difference in VAS score in the three groups ($P > 0.05$), which were 2.0 (0.0, 3.0), 2.0 (1.0, 4.0), and 2.0 (1.0, 4.0) in group 1, group 2, and group 3, respectively [Table 2]. No skin burn, pectoralis injury, or fever was found during the HIFU procedure.

Follow-up results

The follow-up time was 3 months for 173 lesions, 6 months for 218 lesions, and 12 months for 213 lesions. The median VRR of all lesions was 43.8% (17.5%, 58.4%), 61.2% (34.7%, 78.1%), and 75.9% (48.4%, 94.7%) at 3, 6, and 12 months after HIFU, respectively. Moreover, as shown in Table 3, the median VRR was 25.9%, 46.2%, and 46.8% in group 1, group 2, and group 3 at 3 months post-HIFU ($P < 0.01$). At 6 months after HIFU, the VRR of 3 groups was statistically different, which was 37.4%, 63.1%, and 65.7% [Table 3]. FA volume decreased by 47.3%, 77.0%, and 82.0% at 12 months after HIFU, respectively ($P < 0.05$) [Table 3]. The changes in volume and VRR at 3, 6, and 12 months after ablation between different groups are shown in Figure 2. The typical US images of follow-up in 3 groups are shown in Figure 3. After treatment, no adverse events were reported till the end of follow-up.

Discussion

With the improvement of health awareness and the wide use of US screening, more and more FA has been screened in the early stage, making patients anxious and ask for clinical intervention. Nowadays, VABB is increasingly applied to patients with FA for its feature of minimally-invasiveness, but our previous study found that the cosmetic score and the patient satisfaction in breast cosmesis after HIFU were higher compared with those after OS and VABB.[23] What's more, different from VABB, which may cause lactation duct injury, HIFU does not damage normal breast tissue through focusing low-intensity US on the target tissue to cause coagulative necrosis and cavitation by an extracorporeal transducer under the guidance of imaging.[24,25] Therefore, HIFU might be a promising alternative for women with breastfeeding needs. Postoperative pressure bandaging is necessary for VABB, leading to limited mobility and even difficult breathing,[18] while HIFU is an outpatient procedure during which patients

Table 1: Baseline characteristics of fibroadenoma in different groups

	Group 1 (*n*=56), *n* (%)	Group 2 (*n*=144), *n* (%)	Group 3 (*n*=45), *n* (%)	*P*
Distance between the superficial margin of FA and skin (mm)	7.1 (4.1, 9.0)	3.8 (1.5, 5.7)	4.5 (2.8, 7.0)*	<0.01
Distance between the deep margin of FA and chest wall (mm)	3.8 (1.5, 5.7)	2.6 (0, 4.8)	1.4 (0, 3.5)*	<0.01
Lesion location				
Outer upper quadrant	30 (54.5)	50 (34.7)	18 (40.0)	>0.05
Outer lower quadrant	13 (23.6)	39 (27.1)	11 (24.4)	
Inner upper quadrant	4 (7.3)	31 (21.5)	11 (24.4)	
Inner lower quadrant	8 (14.5)	24 (16.7)	5 (11.1)	
Type of near-field acoustic pathway				
Mainly fat type	16 (28.6)	55 (38.2)	28 (62.2)*,†	<0.01
Mixed type	36 (64.3)	83 (57.6)	14 (31.1)*,†	
Mainly mammary glandular type	4 (7.1)	6 (4.2)	3 (6.7)*,†	
CDFI pattern				
Grade 0	26 (56.5)	63 (49.2)	9 (20.9)*,†	<0.01
Grade I	20 (43.5)	51 (39.8)	24 (55.8)*,†	
Grade II	0	13 (10.2)	6 (14.0)*,†	
Grade III	0	1 (0.8)	4 (9.3)*,†	

*Statistical difference between Group 3 and Group 1, †Statistical difference between Group 3 and Group 2. FA: Fibroadenoma, CDFI: Color Doppler flow imaging

Table 2: High-intensity focused ultrasound treatment results for fibroadenoma in different groups

	Group 1 (*n*=56)	Group 2 (*n*=144)	Group 3 (*n*=45)	*P*
Sonication time (s)	22.5 (14.3, 37.3)	45.0 (27.0, 70.0)	83.0 (63.0, 123.0)	<0.01
Treatment time (min)	4.0 (3.0, 6.8)	8.0 (5.0, 14.0)	15.0 (12.0, 28.0)	<0.01
Hyperechoic change emerging time (s)	6.0 (2.0, 18.3)	7.0 (2.0, 13.0)	4.0 (1.5, 13.3)	>0.05
Hyperechoic change emerging rate (%)	85.7	93.1	88.9	>0.05
Sonication energy (KJ)	3.2 (1.9, 4.9)	7.1 (4.0, 11.5)	15.7 (10.1, 19.9)	<0.01
EEF (J/mm^3)	22.5 (15.5, 31.7)	10.4 (5.7, 15.8)	5.8 (3.5, 8.9)	<0.01
VAS score	2.0 (0, 3.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	>0.05
NPV ratio (%)	74.1 (62.3, 135.0)	87.6 (53.8, 109.6)	79.2 (44.6, 96.3)	>0.05

EEF: Energy efficiency factor, VAS: Visual Analog Scale, NPV: Nonperfused volume

Table 3: Volume reduction rate after high-intensity focused ultrasound ablation

Follow-up	VRR (%)			*P*
	Group 1	Group 2	Group 3	
3 months	25.9 (-4.6, 45.5)	46.2 (18.6, 59.9)‡	46.8 (36.0, 58.7)*	<0.01
6 months	37.4 (-8.0, 66.9)	63.1 (40.4, 78.1)‡	65.7 (43.4, 79.1)*	<0.01
12 months	47.3 (21.1, 100.0)	77.0 (53.2, 94.9)‡	82.0 (65.0, 91.1)	<0.05
P	<0.01	<0.01	<0.01	-

*Statistical difference between Group 3 and Group 1, ‡Statistical difference between Group 2 and Group 1. VRR: Volume reduction rate

can interact comfortably with doctors and nurses who sit close to them with short recovery time.[26]

When compared with other energy-based ablation, such as MWA and cryoablation, HIFU has the advantage of noninvasiveness with no need for antenna insertion. Besides, with the HIFU ablation strategy of "dot–line–plane–volume", conformal ablation could be achieved according to the shape of the lesions, which could effectively control the energy delivery so that coagulation necrosis and cavitation occur precisely inside the lesion without damaging surrounding normal tissue, while spherical ablation induced by MWA and cryoablation might damage the normal tissue close to the tumor of irregular shape or leave the margin of the tumor unablated. The safety and efficacy of HIFU for the treatment of breast FA have been demonstrated by several previous studies.[20] Coagulation necrosis was shown in FA cells under different staining after HIFU, and the cells were destroyed with chromatin deconstructed and organelles swollen, damaged, and even disappeared,[18] which indicated that FA could be deactivated effectively by HIFU.

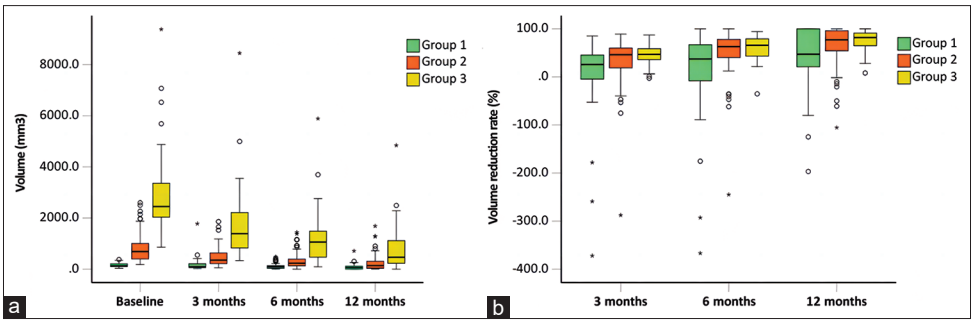

Figure 2: Changes of FA volume and volume reduction rate in different follow-up.(a) Volume change of breast FA in Groups 1-3 at baseline, 3, 6, and 12 months post HIFU.(b) Volume reduction rate of breast FA in Groups 1-3 at 3, 6, and 12 months post-HIFU. FA: Fibroadenoma. HIFU: High-intensity focused ultrasound

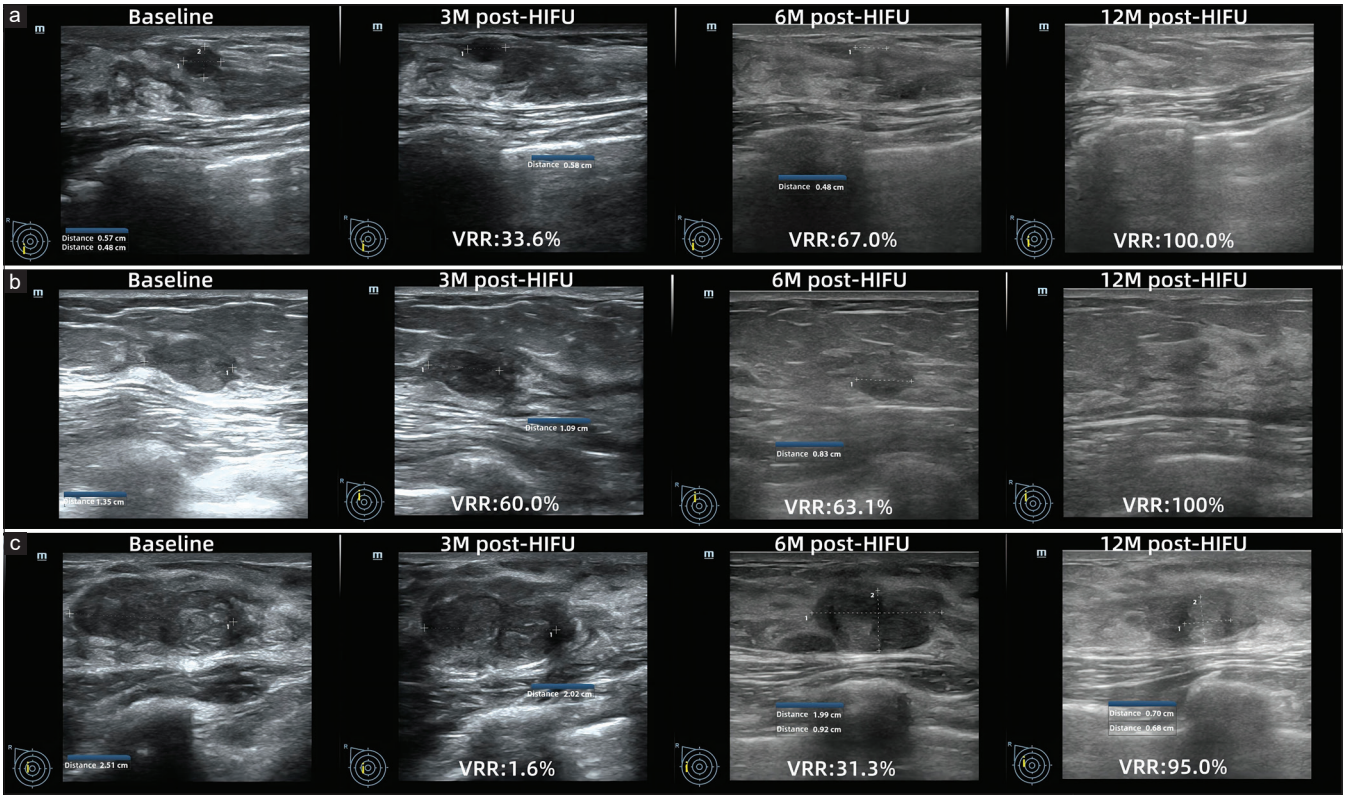

Figure 3: Typical ultrasound images of volume reduction rate in three patients with fibroadenoma (FA) in different sizes.(a) Volume change of FA < 10 mm in a 33-year-old woman; (b) Volume change in a 34-year-old woman with FA of 13.5 mm; (c) Volume change in a 24-year-old woman with FA of 25.1 mm. US: Ultrasound. VRR: Volume reduction rate. HIFU: High-intensity focused ultrasound. M: Months

In this study, we reported the outcomes of 245 FAs in 88 patients after US-guided HIFU ablation and compared the characteristics of FA of different sizes before and after HIFU. To the best of our knowledge, it was the largest cohort study of patients with FA who underwent HIFU at present. For the baseline characteristics of FA, as the longest diameter of FA increased, the distance from the superficial margin of FA to the skin and the distance from the deep margin to pectoralis decreased [Table 1]. Meanwhile, the near-field acoustic pathway type of FA ≤ 2 cm was mainly mixed type, while that of FA > 2 cm was mainly fat type [Table 1]. This might be related to the physiological characteristics of FA and the size of Chinese women's breasts. FA is an expansive benign tumor, and the breast of Chinese women is usually small and dense, mainly composed of breast gland tissue.[27] The growth of FA in a confined space leads to the compression of the mammary gland in the near-field and far-field acoustic pathways. The mammary gland is more compressed in the acoustic pathway of the large FA, thus the distance from the superficial margin of FA to the skin and the distance from the deep margin of FA to the chest wall were shorter in large lesions. For FA > 2 cm, the distance from the superficial margin of FA to the skin was the smallest in the three groups, with the breast mammary gland compressed severely and fat

tissue not compressed in the near-field acoustic pathway, so the acoustic pathway was mainly fat type. Furthermore, with the increase in FA size, the Adler blood flow classification was also accordingly increased [Table 1]. As it is all known, blood vessels are required to provide nutrients and remove metabolites to support the growth of the tumor. Therefore, FA with more abundant blood supply tends to grow larger.

Except for the baseline features, we also compared the treatment response of FA of different sizes. The sonication energy gradually increased with the longest diameter of FA, and so did the sonication time and treatment time [Table 2]. Baker *et al*. have found that each interface in the acoustic pathway causes absorption, reflection, and scattering of ultrasonic beams.[28] More energy was needed in the deeper lesion to achieve the same volume of coagulation necrosis compared with the superficial lesions.[29] In addition, as this study found, large lesions had abundant blood flow, and blood flow could carry heat away more quickly,[22] making it difficult for local temperatures to reach the threshold that leads to tumor necrosis, so more energy was required for large FA. Hence, the sonication time and treatment time were increased correspondingly. EEF was lower in the larger lesions than in the smaller ones. When the size of FA becomes large, degeneration such as infarction, calcification, and transparency may occur, which could promote the deposition of ultrasonic energy and make it easy to cause coagulation necrosis in focus.[21] Once the coagulation necrosis was induced, in the process of ultrasonic energy deposited into the target area, the acoustic environment of the tissue around the focus was dynamically affected by the expansion of the coagulation necrosis area and the increase of the focus temperature, which could facilitate further deposition of the ultrasonic energy.[30] It was consistent with the results of *in vitro* experiments which showed that the EEF required for "volume ablation" was lower than that for "slice ablation", while the EEF required for "slice ablation" was lower for "dot ablation."[31] Since all the patients in each group experienced only mild pain during HIFU and no adverse event was found, it indicated that FA of different sizes could be treated by HIFU with good patient tolerance.

To explore the VRR change of FA of different sizes after HIFU, the follow-up results of FA after US-guided HIFU ablation were compared. It was found that the VRR of FA > 1 cm was greater than that of FA < 1 cm [Table 3]. The reasons were complicated. First of all, the large lesions received longer sonication time and more energy and were more susceptible to coagulation necrosis. Second, the larger-sized FA had a larger contact surface with surrounding normal breast tissue. Since the blood supply was abundant in the surrounding normal tissue, the necrotic tissue in the larger-sized FA could be absorbed more quickly with a larger contact surface. Finally, EEF was found to be higher in the smaller FA [Table 3], and EEF in group 1 (22.5 J/mm^3) was much higher than the other two groups (10.4 J/mm^3 and 5.8 J/mm^3). It might imply that small FA, especially with the size <1 cm, might be overtreated and the excessive energy deposition would cause tissue carbonization, which could affect the VRR. Therefore, the VRR was higher in larger FA. It was worth noting that although the VRR of large ones was greater than that of small lesions, the absolute residual volume was larger for large lesions than for small lesions due to the larger baseline volume. A previous study pointed out that 25.6% of the lesions completely disappeared at 12 months post-HIFU.[19] Similar findings were found in this study, with a median VRR of 75.9% (48.4%, 94.7%) at 12 months, suggesting that most of the FA might still be present but impalpable to patients at 12-month follow-up. Concerns and questions may arise about the regrowth of the mass and the long-term efficacy of HIFU in the treatment of FA. Therefore, the long-term clinical outcomes of HIFU for treating FA need to be further investigated to provide evidence for the efficacy of HIFU in the future.

This study preliminarily explored the efficacy of FA of different sizes and tried to assist doctors during the training of HIFU technology in selecting suitable patients and accumulating treatment experience. Xiao *et al*. found that the learning curve could be completed after 60–65 tumors were treated by doctors.[32] The skills of HIFU treatment for FA could be improved by treating different patients with different levels of difficulty according to the stage of the learning curve of HIFU doctors.[33] In our clinical experience, when treating FA with a diameter of 1–2 cm, the distance in the near-field and far-field acoustic pathway was moderate, the sonication time and treatment time were not too long, and the postoperative NPVR and the VRR were mostly satisfactory, so this size of FA was suitable for the beginners. For FA of 2–3 cm, it was too close to the pectoralis and rich in blood supply, which might increase the difficulty of HIFU treatment with longer treatment time, more sonication energy, and higher risk of side effects, while for FA <1 cm, the positioning time might be long and the VRR was relatively low. Therefore, FA of 2–3 cm and <1 cm might be more suitable for HIFU doctors with some experience, and the treatment plan should be adjusted appropriately according to the features of FA with different sizes and locations.

There are some limitations to our study. First, this is a retrospective study. The number of lesions varied among the three groups, which might lead to bias in the results and not fully capture the discrepancy between the three groups. Second, FA larger than 3 cm was not included in this study. Thus, the efficacy of US-guided HIFU for lesions larger than

3 cm needs to be further investigated. Finally, our study was conducted in a single center with a relatively short follow-up period. In the future, a multi-center study with a large sample size and long follow-up period is needed to evaluate the long-term outcome of HIFU treatment for FA.

Conclusion

This was the first study to comprehensively compare the baseline, treatment characteristics, and follow-up results for FA of different sizes after HIFU ablation. It was found that HIFU was an effective and safe treatment for breast FA of different sizes. The VRR of FA >1 cm was significantly higher than that of FA ≤1 cm. The findings of our study could help choose suitable FA patients for HIFU doctors at different stages when learning this noninvasive technique.

Author contributions

Xiuying Wu drafted this manuscript and Lei Yang analyzed the data. Zi Li's main contribution was data acquisition. Heng Yin performed the HIFU procedure for FA patients. Wenzhi Chen revised the manuscript critically for important intellectual content. Cai Zhang conceived and designed this study. All authors have read and agreed to the final version of the manuscript.

Data availability statement

All data generated or analyzed during this study are included in this published article and its Supplementary Information Files.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Material

Table 1: Basic characteristics of all the patients with FA

Variables	Data (*N*=88, *n*=245)
Age (years)	26.5 (22.0, 34.0)
BMI (Kg/m^2)	20.8 (19.0, 23.4)
Type of FA	
Single FA	31 (12.7%)
Multiple FAs	57 (87.3%)
History of breast surgery	
Open surgery	14 (77.8%)
Vacuum-assisted breast biopsy	4 (22.2%)
Types of near-field acoustic pathway	
Mainly fat type	99 (40.4%)
Mixed type	133 (54.3%)
Mainly mammary glandular type	13 (5.3%)
CDFI pattern	
Grade 0	98 (45.2%)
Grade I	95 (43.8%)
Grade II	19 (8.8%)
Grade III	5 (2.3%)
Longest diameter of FA (mm)	14.3 (10.4, 18.1)
FA volume (mm^3)	653.2 (280.4, 1389.1)

FA: fibroadenoma. *N*: number of patients; *n*: number of FA lesions.
BMI: Body mass index. CDFI: color Doppler flow imaging

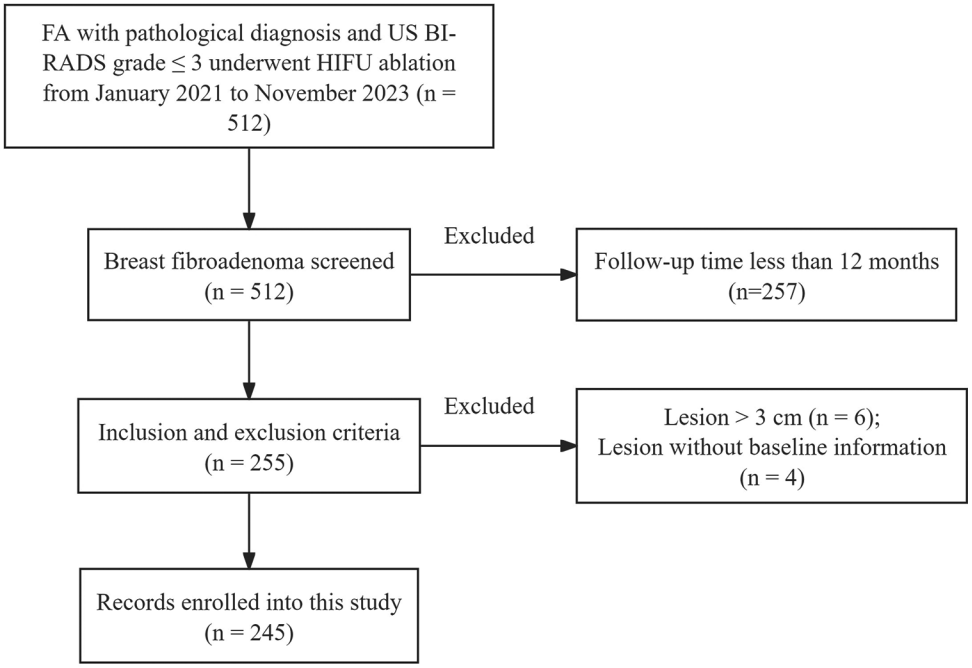

Figure S1: Flow chart for inclusion of FA lesions. FA: fibroadenoma