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Paul Christopher Lyon, Vic Rai, Natalia Price, Aarti Shah,
Feng Wu, David Cranston

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Intensity Focused Ultrasound
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Clinical Experience**

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Ultrasound-Guided High Intensity Focused Ultrasound Ablation for Symptomatic Uterine Fibroids: Preliminary Clinical Experience

Ultraschallgesteuerte hochintensive fokussierte Ultraschallablation bei symptomatischen Uterusmyomen: Eine vorläufige klinische Erfahrung

Authors

Paul Christopher Lyon^{1,3}, Vic Rai², Natalia Price², Aarti Shah³, Feng Wu¹, David Cranston¹

Affiliations

- 1 Clinical HIFU Unit, Oxford-University-Hospitals NHS Foundation Trust, Oxford, United Kingdom of Great Britain and Northern Ireland
- 2 Department of Obstetrics and Gynaecology, Oxford-University-Hospitals NHS Foundation Trust, Oxford, United Kingdom of Great Britain and Northern Ireland
- 3 Department of Radiology, Oxford-University-Hospitals NHS Foundation Trust, Oxford, United Kingdom of Great Britain and Northern Ireland

Key words

gynecology, high intensity focused ultrasound, HIFU, uterine fibroids, thermal ablation

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Correspondence

Dr. Paul Christopher Lyon

Department of Radiology, Oxford-University-Hospitals NHS Foundation Trust, Churchill-Hospital, Old Road, OX3 7LE Oxford, United Kingdom of Great Britain and Northern Ireland

Tel.: ++44/(0) 30 03 04 77 77

paul.lyon@nhs.net

ABSTRACT

Objective To evaluate the middle-term efficacy and complications of ultrasound-guided high intensity focused ultrasound (USgHIFU) for the treatment of symptomatic uterine fibroids in an NHS population.

Methods A prospective observational single-center study at a single university hospital in Oxford, UK. Patients with symptomatic uterine fibroids who declined standard surgical/radiological intervention and were referred to the HIFU unit were

considered for USgHIFU treatment. Clinical evaluation, adverse event monitoring, uterine fibroid symptoms and health-related quality of life questionnaire (UFS-QOL) and contrast-enhanced pelvic magnetic resonance imaging (MRI) were performed before and at regular intervals after treatment to assess patient outcome.

Results 12 of 22 referred patients underwent one session of USgHIFU ablation of 14 fibroids overall and received a two-year follow-up. No serious adverse events were reported, but a second-degree skin burn was observed in one patient who had a surgical scar from a previous caesarean section. Mean symptom severity scores (SSS-QOL) improved significantly from 56.5 ± 29.1 (SD) at baseline to 33.4 ± 23.3 ($p < 0.01$) at three months, 45.0 ± 35.4 ($p < 0.05$) at one year and 40.6 ± 32.7 ($p < 0.01$) at two years post-treatment. The mean non-perfused volume ratio was $67.7 \pm 39.0\%$ (SD) in the treated fibroids ($n = 14$) within three months of treatment. The mean volume reduction rates of the treated fibroids were $23.3 \pm 25.5\%$ (SD) at 3 months post-treatment ($p < 0.01$, $n = 14$), $49.3 \pm 23.7\%$ at 12 months ($p < 0.05$, $n = 8$), and $51.9 \pm 11.1\%$ at 24 months ($p < 0.005$, $n = 8$).

Conclusion This study demonstrates the clinical efficacy of USgHIFU ablation of uterine fibroids and the low risk of complications. We believe that this noninvasive approach may offer an alternative therapy for women with symptomatic uterine fibroids. While HIFU is fast becoming the standard of care for fibroid ablation in other countries, to our knowledge, this study is the first to present clinical experience of US-guided HIFU ablation of symptomatic uterine fibroids in an NHS population.

Plain Language Summary High intensity focused ultrasound (HIFU) can be used for the noninvasive ablation of symptomatic uterine fibroids, and MR-guided treatment has already gained FDA approval. Ultrasound-guided HIFU has the advantage of offering practicalities in anesthesia and considerable cost-savings over MR-guided treatments. In this prospective study we have demonstrated the middle-term efficacy and favorable safety profile of ultrasound-guided HIFU for the treatment of symptomatic uterine fibroids for the first time in an NHS population.

ZUSAMMENFASSUNG

Ziel Bewertung der mittelfristigen Wirksamkeit und der Komplikationen des ultraschallgesteuerten hochintensiven fokussierten Ultraschalls (USgHIFU) zur Behandlung von symptomatischen Uterusmyomen in einer NHS-Population.

Material und Methoden Prospektive Beobachtungsstudie an einem Universitätsklinikum in Oxford (Vereinigtes Königreich). Patienten mit symptomatischen Uterusmyomen, die eine chirurgische/radiologische Standardintervention ablehnten und an die HIFU-Einheit überwiesen wurden, wurden für eine Behandlung mit USgHIFU in Betracht gezogen. Zur Beurteilung des Patienten-Outcomes wurden vor und in regelmäßigen Abständen nach der Behandlung klinische Untersuchungen, die Überwachung von Nebenwirkungen, eine Befragung zur Symptomatik der Uterusmyome und zu der gesundheitsbezogenen Lebensqualität (UFS-QOL) sowie eine kontrastverstärkte Magnetresonanztomografie (MRT) des Beckens durchgeführt.

Ergebnisse 12 von 22 überwiesenen Patienten nahmen an einer Sitzung der USgHIFU-Ablation von insgesamt 14 Myomen teil und erhielten eine 2-jährige Nachbeobachtung. Es wurden keine schwerwiegenden unerwünschten Nebenwirkungen berichtet, bei einem Patienten mit einer Operations-

narbe aus einem früheren Kaiserschnitt wurde jedoch eine Hautverbrennung zweiten Grades beobachtet. Die mittleren Schweregrade der Symptome (SSS-QOL) verbesserten sich signifikant von $56,5 \pm 29,1$ (SD) zu Studienbeginn auf $33,4 \pm 23,3$ ($p < 0,01$) nach 3 Monaten, $45,0 \pm 35,4$ ($p < 0,05$) nach 1 Jahr und $40,6 \pm 32,7$ ($p < 0,01$) 2 Jahre nach der Behandlung. Das mittlere nicht perfundierte Volumenverhältnis der behandelten Myome ($n = 14$) lag innerhalb von 3 Monaten nach der Behandlung bei $67,7 \pm 39,0\%$ (SD). Die mittleren Volumenreduktionsraten der behandelten Myome waren 3 Monate nach der Behandlung $23,3 \pm 25,5\%$ (SD) ($p < 0,01$; $n = 14$), $49,3 \pm 23,7\%$ nach 12 Monaten ($p < 0,05$; $n = 8$) und $51,9 \pm 11,1\%$ nach 24 Monaten ($p < 0,005$; $n = 8$).

Schlussfolgerung Diese Studie zeigt die klinische Wirksamkeit der USgHIFU-Ablation von Uterusmyomen und das geringe Risiko von Komplikationen. Wir glauben, dass dieser nichtinvasive Ansatz eine alternative Therapie für Frauen mit symptomatischen Uterusmyomen bieten kann. Während in anderen Ländern die HIFU zur Myom-Ablation immer mehr zum Standard wird, ist diese Studie unseres Wissens die erste, die klinische Erfahrungen mit der US-gestützten HIFU-Ablation von symptomatischen Uterusmyomen in einer NHS-Population zeigt.

Introduction

Uterine fibroids are the most common pelvic tumors with an incidence of up to 70 % of women over the age of 40 worldwide [1]. They are a significant cause of morbidity for women of reproductive age. Although the majority are asymptomatic, significant symptoms such as pelvic pain, menorrhagia, dysmenorrhea, dyspareunia, pelvic fullness, urinary frequency and infertility are reported in approximately 25 % of cases [2]. The burden of the diseased uterus has a major impact on health economics and healthcare resources [3]. In the United States alone, 175 000 hysterectomies are performed annually due to fibroids, at a cost of over \$2 billion [2, 4].

Surgery remains the default position for the clinical management of symptomatic fibroids [5]. The advancement of laparoscopic and hysteroscopic instruments has allowed for minimally invasive removal of modest-sized fibroids. High intensity focused ultrasound (HIFU) generates tightly focused energy deposition with resultant tissue heating at depth within the body. This results in controlled and precise ablation of the target without damage to the surrounding tissue. As a noninvasive approach, HIFU therapy has played an increasing role in the treatment of symptomatic uterine fibroids [6–8]. In order to better understand the feasibility of recruiting fibroid patients into a HIFU trial and to develop recruitment strategies for a large-scale multicenter trial in the UK, we conducted a preliminary pilot study of HIFU treatment for patients with symptomatic uterine fibroids in Oxford, UK. During the 2-year follow-up period we also assessed the safety, feasibility and efficacy of ultrasound-guided HIFU (USgHIFU) in the treat-

ment of patients with symptomatic uterine fibroids, for the first time in an NHS population.

Methods

Patients

From January 2011 to December 2014, 22 patients with symptomatic uterine fibroids were referred to a single-center multidisciplinary team consisting of gynecologists, radiologists and clinical HIFU specialists. This pilot study was approved by the Technology Advisory Group of Oxford University Hospitals NHS Foundation Trust. Patients were over 18 years of age and had fibroid-related symptoms without any major medical comorbidities. Patients discussed various treatment options with gynecologists and those who declined standard surgical management but had interest in HIFU were considered. A written patient information sheet, which described the intervention, its benefits and risks, and anticipated recovery time, was sent to suitable patients.

Pre-HIFU screening included a medical and gynecological assessment, a validated uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL) [9], and a pelvic MRI with gadolinium. All patients required trans abdominal ultrasound (US) examination to ensure that suitable fibroids could be visualized with a clear margin. When patients had multiple uterine fibroids, the fibroid(s) most likely to be correlated with the patient's symptoms were determined as the dominant fibroid(s) on MRI and targeted for treatment. No patients received gonadotropin-releasing

hormone therapy (GnRH) before treatment. All patients underwent written informed consent prior to HIFU.

HIFU Treatment

Treatment was performed using a CE-marked extracorporeal USgHIFU device (Model-JC200 HIFU System, Haifu Medical, Chongqing, China), with a 200 mm diameter, 145 mm focal length single element HIFU transducer driven at a frequency of 0.97 MHz. The concave treatment transducer has a central aperture containing an integrated B-mode US imaging probe for real-time imaging. Patients received treatment under intravenous sedation with remifentanyl and propofol. During the HIFU procedure patients were positioned prone on the treatment bed over a water bath containing cooled degassed water.

Clinical Evaluation

At baseline, between one to three months, and at one and two years post-treatment, patients were asked to complete the symptom severity score (SSS) of the UFS-QOL questionnaire, which was specific to uterine fibroids and their treatment. In the questionnaire, eight items were linked to the SSS. Each item was scored from 1 (no symptoms) to 5 (major symptoms). The overall SSS scores were calculated for each patient. For the SSS higher scores indicated worse symptoms.

Radiological Evaluation

Patients underwent a contrast-enhanced pelvic MRI scan to assess the treated fibroids at the same time points as for the UFS-QOL questionnaires. In order to estimate fibroid volume, the orthogonal long axis and short axis of the treated fibroids were measured on T2-weighted images in the sagittal view, together with a left-right measurement in the axial-oblique view. Using the equation for the volume of an ellipsoid ($V = 4\pi/3 \times r_1 \times r_2 \times r_3$, where r_i represents an orthogonal radius), the volumes of the treated fibroids were estimated at 3, 12 and 24 months post-treatment. The fibroid volume reduction rate was calculated by subtracting the measurement of the fibroid volume at the follow-up MRI from the pretreatment volume and dividing the result by the pretreatment fibroid volume. Using the same measurement technique, the non-perfused volume (NPV) was determined on contrast-enhanced T1-weighted fat-suppressed images within three months post-treatment. The NPV ratio was calculated by dividing the post-treatment NPV by the pretreatment fibroid volume.

Statistical Analysis

All data were collected in accordance with Good Clinical Practice guidelines. Results were expressed as mean \pm standard deviation (SD). Using the Student's t-test and Wilcoxon sum ranked test, the statistical significance for quality of life was evaluated by comparing the difference between SSS values at baseline and at follow-up visits. Paired Student's t-tests were also used for statistical comparison of mean fibroid volumes pre- and post-treatment. A value of $p < 0.05$ was considered to indicate a significant difference.

► **Table 1** Baseline characteristics of the patients (n = 10).

characteristics	mean \pm SD (range), where specified
age (years)	42.2 \pm 8.7 (35 – 65)
menopausal status	
▪ premenopausal	9
▪ postmenopausal	1
number of fibroids	
▪ 1	2
▪ 2 – 5	5
▪ > 10	3
abdominal scar	2
patient symptoms	
▪ heavy menstrual bleeding	8
▪ pain during menstruation	6
▪ pressure on pelvic area	6
▪ bladder pressure	5
symptom severity score (SSS)	56.5 \pm 29.1 (13 – 100)

Results

Patient Characteristics

12 of the 22 fibroid patients referred for HIFU during the study period were deemed clinically suitable for intervention and the remaining 10 were either unsuitable (n = 6) or reconsidered (n = 4) and were referred back to the gynecology team for subsequent management. The reasons for exclusion from the trial were predominately related to technical difficulties such as unclear margins of fibroid on US imaging (n = 2), the presence of un-manueverable bowel between the fibroid and anterior abdominal wall (n = 2) and submucosal fibroid distorting the uterine cavity (n = 1). The remaining patient had simultaneous endometriosis, which may have also been contributing to her symptoms, and it was felt that HIFU was not in her best interest. Of the 12 treated patients, one patient was lost to follow-up due to geographical relocation. A further patient was excluded from radiological and SSS analysis as the baseline MRI demonstrated a significant volume of intra-fibroid hemorrhage, presumed responsible for her symptoms before treatment, and was thought not to be representative of the fibroid morphology of the other treated fibroids. The remaining 10 patients who were included in analysis all underwent one session of HIFU ablation, treating a total of 14 fibroids, and received a two-year follow-up after treatment. The characteristics of the patients and dominant fibroids are summarized in ► **Table 1, 2.**

HIFU Treatment

A morning or afternoon session of HIFU treatment was performed to treat 14 uterine fibroids in 10 patients, including 7 patients

► **Table 2** Characteristics of HIFU-treated dominant uterine fibroids (n = 14).

characteristics	mean ± SD (range), where specified
largest diameter of the uterus (cm)	13.1 ± 3.1 (9 – 18)
number of dominant fibroids	14
largest dominant fibroid diameter (cm)	7.7 ± 2.8 (3.5 – 12.3)
dominant fibroid volume (cm ³)	193.2 ± 193.1 (11.5 – 626.3)
dominant fibroid T2-weighted intensity	
▪ low/low mixed	11
▪ intermediate/intermediate mixed	3
location of dominant fibroids in the uterus	
▪ anterior wall	10
▪ posterior wall	3
▪ side wall	1
type of dominant fibroids	
▪ intramural	11
▪ subserosal	3

treated for a single fibroid, 2 for 2 fibroids and 1 for 3 fibroids. Of 10 patients, 9 had complete treatment of the intended fibroid(s) and the remaining 1 had partial treatment because of an unexpected skin burn which occurred during HIFU exposure, after which intervention was prematurely halted (see adverse events). Up to three fibroids were treated in any one HIFU treatment session and no patients underwent more than one session.

Treatment parameters included acoustic power, HIFU exposure time, acoustic energy, and treatment duration (HIFU procedure duration excluding patient positioning, imaging, targeting and planning). All HIFU treatments were performed in continuous wave without a duty cycle. The mean acoustic power used for treatment was 274.6 ± 53.5 W (range: 185 – 369 W). The mean HIFU exposure time was 29.5 ± 11.9 minutes (range: 11.4 – 46.6 minutes), and the mean acoustic energy was 444.7 ± 182.7 kJ (range: 184 – 734 kJ). The mean treatment duration was 113.3 ± 41.2 minutes (range: 49 to 171 minutes).

During HIFU procedure the tissue reactions to thermal ablation were monitored with real-time B-mode US imaging, which showed instantaneous hyperechoic grayscale changes within the targeted fibroids when the ablative power threshold was reached. These changes were clearly demonstrated on US imaging in 9 of 10 patients, as illustrated in ► **Fig. 1**. They occurred in the targeted region immediately after each HIFU exposure, became gradually less evident and sometimes disappeared within a few minutes, while in many cases they persisted for the duration of the treatment. In previous studies, the hyperechoic zone has corresponded mainly to the extent of the coagulation necrosis [10 – 16], thus this

imaging change was used to assess tissue response to HIFU treatment at the time of intervention.

Adverse Events

No serious adverse events were reported during the HIFU procedure or throughout the follow-up period. A second-degree skin burn was observed in one of two patients who had a surgical scar from a previous caesarean section. It occurred on the surface of the scar, and the extent was around 1.0 × 0.5 cm in the cross-section. This skin toxicity was treated with a cool pack plus aloe gel and resolved by day 21 without further medication. In one patient hemorrhage into the fibroid occurred, but this was not a safety concern.

Clinical Outcomes

The mean SSS at baseline was 56.5 ± 29.1, indicating that fibroid-related symptoms had significantly affected the patients' quality of life before treatment. However, 3 months after treatment there was significant symptom reduction to a mean of 33.4 ± 23.3 ($p < 0.01$). As shown in ► **Fig. 2**, the mean SSS continued to reduce to 45.0 ± 35.4 ($p < 0.05$) at 12 months and 40.6 ± 32.7 ($p < 0.01$) at 24 months. During the two-year follow-up period, two of three patients who previously had more than ten fibroids received additional non-HIFU treatments for their fibroids. Of them, one underwent hysterectomy at 12 months as a result of symptom persistence after treatment. The other had myomectomy at 18 months after treatment due to symptom recurrence, which was caused by the growth of untreated fibroids. These two patients were excluded from analysis at time points after the surgical intervention.

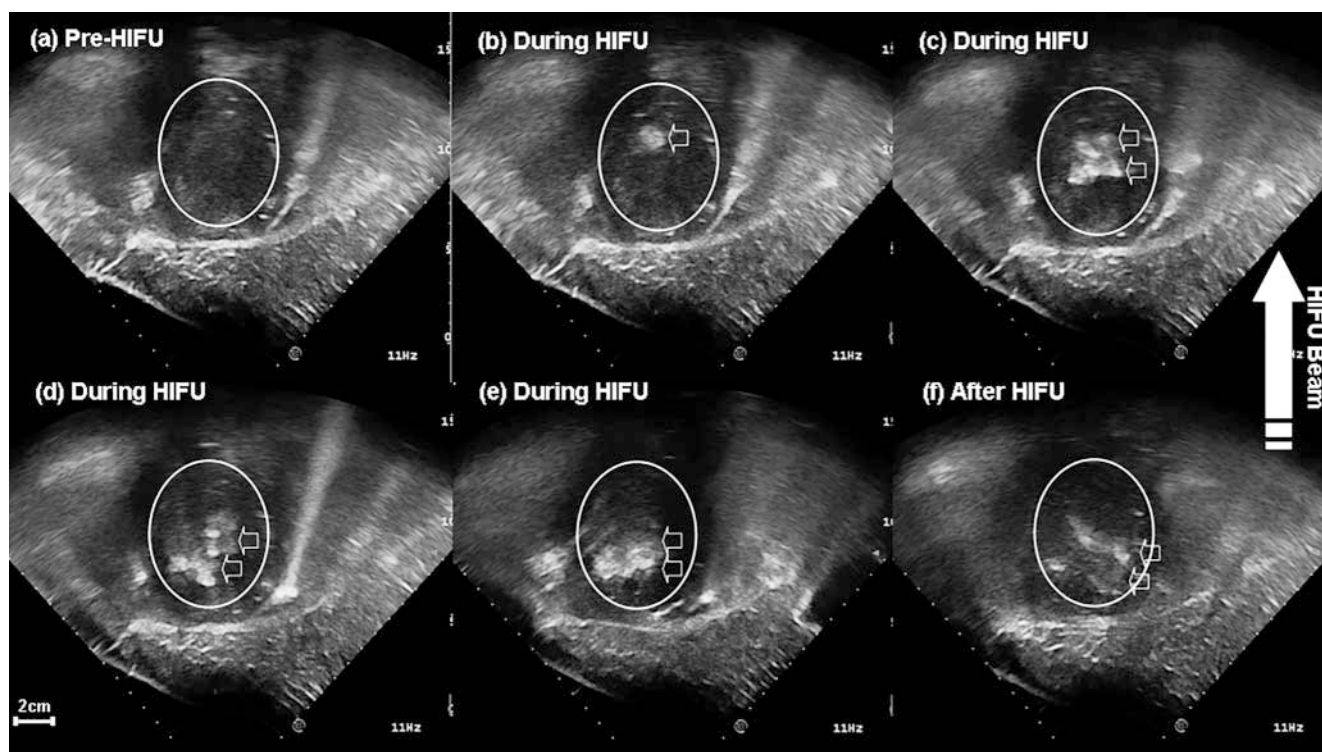
Radiological Outcomes

Non-Perfused Volume (NPV) Ratio

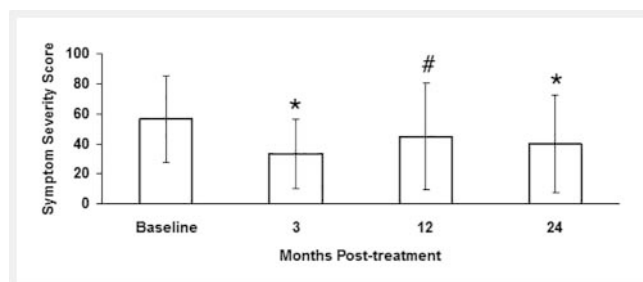
Using the T1 fat-suppressed contrast-enhanced MRI sequences, the NPV ratio was estimated. The post-treatment mean NPV ratio, measured within three months of treatment, was 67.7 ± 39.0 % (SD) in the treated fibroids (range: 2 – 100 %, n = 14). The NPV distribution is displayed in ► **Table 3**. Eight of ten patients demonstrated a greater than 80 % NPV ratio.

Fibroid Volume Reduction

The mean baseline volume of the 14 treated fibroids of the 10 patients available for follow-up was 224.1 ± 190.5 cm³ (range: 11.5 – 626.3). ► **Fig. 3** illustrates significant shrinkage of the treated fibroid of one patient during the follow-up period by MRI. As shown in ► **Fig. 4**, the mean volume and mean volume reduction rate (MVR%) of the 14 treated fibroids at 3 months were 172.2 ± 152.8 cm³ (range 5.8 – 492.2; $p < 0.01$) and 23.3 ± 25.5 % respectively. At 12 months follow-up, MRI was not available for all patients. However, relative to the matched baseline group of mean volume 188.0 ± 175.0 cm³ (range 11.5 – 553.9, n = 8), the mean volume and MVR% were 91.5 ± 85.3 cm³ (range: 2.8 – 136.8; $p < 0.05$, n = 8) and 49.3 ± 23.7 %. At 24 months, relative to the matched baseline group of mean volume 334.0 ± 180.4 cm³ (range 146.0 – 626.3, n = 8, different subset of fibroids), the mean volume and MVR% were 160.4 ± 98.3 cm³ (range: 73.4 – 355.0; $p < 0.005$, n = 8) and 51.9 ± 11.1 %.



► **Fig. 1** Grayscale changes of a treated dominant uterine fibroid visualized on real-time US images in axial-slice during USgHIFU procedure. **a** US image obtained before HIFU shows a large uterine fibroid indicated by a white circle. **b–e** US images obtained during HIFU procedure show progressive hyperechogenicity in the treated area of the fibroid (arrows). **f** US images obtained immediately after HIFU procedure show persisting (but somewhat reduced) hyperechogenicity of the treated fibroid (arrows).



► **Fig. 2** Bar chart shows the improvement of mean symptom severity score (SSS) in patients with symptomatic uterine fibroids during two-year follow-up period. SSS significantly decreased after treatment with an important symptomatic reduction. Compared with the baseline (pretreatment): * $p < 0.01$; # $p < 0.05$.

Discussion

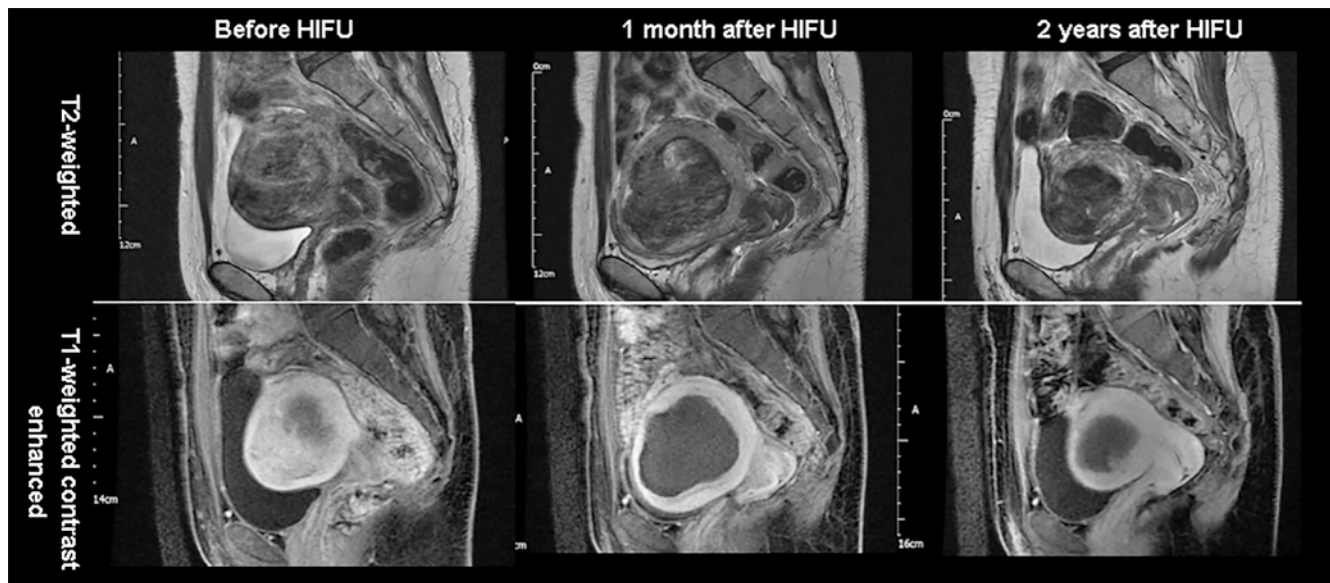
USgHIFU therapy has been increasingly used as a noninvasive approach to treat symptomatic uterine fibroids in China. Recently, Chen and colleagues reported a large non-randomized study in which patients with symptomatic fibroids were treated across 20 Chinese hospitals [8]. Of the 2411 women recruited, 1353 underwent USgHIFU, 472 had hysterectomy and 586 had myomectomy. Statistical analysis showed that both the SSS and QOL score improved more rapidly after HIFU than after surgery at six months. Major adverse events were significantly lower in HIFU relative to surgery (0.2% vs. 12.6%).

► **Table 3** Distribution of non-perfused volume ratio within 3 months after treatment.

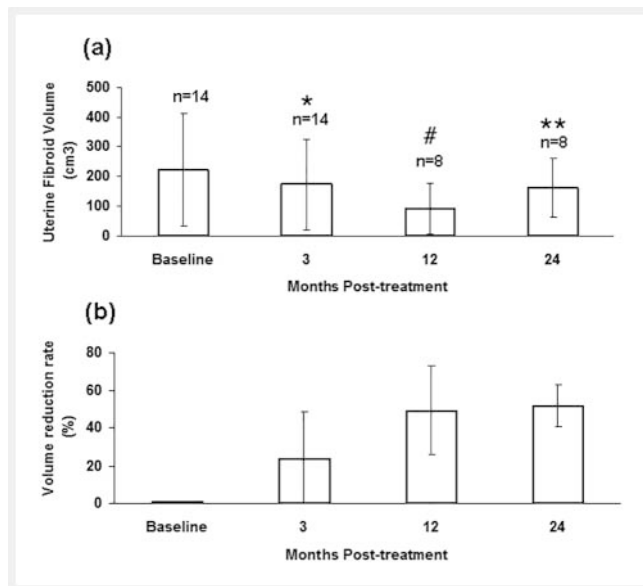
non-perfused volume ratio (%)		no. of fibroids
range	mean \pm SD	
0 – 25	6.4 \pm 3.8	3
25 – 50	40.1 \pm 0.1	2
50 – 75	–	0
75 – 100	94.2 \pm 8.4	9

To our knowledge, this single center study is the first clinical experience of USgHIFU in an NHS population of women with symptomatic uterine fibroids. A low rate of adverse effects was observed in our study. Only one patient experienced a minor skin burn overlying an existing cesarean section scar that resolved with topical cream. Therefore, patients with any significant previous surgical scar located in the US beam pathway are likely to be excluded from HIFU therapy in our future multicenter clinical trial.

Analysis of SSS assessment revealed that nine of ten women experienced considerable relief in fibroid-related clinical symptoms after HIFU treatment. A mean SSS reduction of 23 points was observed within three months after treatment and remained low throughout the two-year follow-up period. However, two of



► **Fig. 3** Sagittal MR images before and after USgHIFU treatment in a 46-year-old woman with a dominant intramural fibroid during two-year follow-up period. T2-weighted image shows a time-dependant decrease in size of the treated fibroid, with 68 % volume reduction two years post-treatment. T1-weighted contrast-enhanced fat-suppressed image obtained 1 month after treatment shows more than 90 % non-perfused volume ratio in the treated fibroid.



► **Fig. 4** Bar chart shows mean volume change **a** and mean volume reduction rate change **b** in the treated fibroids during two-year follow-up period. They present a significant volume reduction from the pre-treatment volume. Compared with the baseline (pre-treatment): ** $p < 0.005$; * $p < 0.01$; # $p < 0.05$.

the three patients who had > 10 fibroids went on to receive a hysterectomy as a result of persistent symptoms or growth of untreated fibroids, suggesting that patients with a large number of uterine fibroids may not be suitable for HIFU.

Our results show that 8/10 patients had an NPV ratio greater than 80% in the treated fibroids, coincident with a statistically significant decrease in the mean volume at 3–24 months compared to baseline (23.3 % at three months, 49.3 % at one year, and 51.9 %

at two years). The MVR% at two years is likely underestimated in our series, as the two dominant fibroids demonstrating the highest volume reduction rates at one year (69–75 %) were removed at subsequent surgery in these two patients with over 10 fibroids. As expected, no significant volume reduction was observed in non-treated fibroids, although these metrics were not statistically quantified.

In conclusion, our study indicates that noninvasive uterus-sparing USgHIFU therapy is safe, feasible and effective for symptom relief in patients with uterine fibroids with an expected volume reduction of around 50 % at 1–2 years. HIFU may be a particularly attractive option for women considering future pregnancy. Our study is limited by the small size of the single-center study group and lack of control group receiving an alternative treatment for uterine fibroids. A multicenter randomized trial comparing USgHIFU with conventional treatments for uterine fibroids, including surgery and uterine artery embolization, would be of great utility in the future, and may lead to guidelines as to which patient characteristics and fibroid anatomy best suits which therapy.

Conflict of Interest

The authors declare that they have no conflict of interest.

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