NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of ultrasound-guided high-intensity transcutaneous focused ultrasound for symptomatic uterine fibroids

Uterine fibroids are non-cancerous growths on the inside or outside of the womb (uterus). In this procedure, the woman lies face down with an ultrasound scanning device placed on the skin of the abdomen which is immersed in water. This scans the womb to show where the fibroids are. A separate device is used to deliver a precisely focussed dose of high-intensity ultrasound energy through the skin of the abdomen (transcutaneous). This heats the fibroid until most or all of it is destroyed. The woman may have to lie still for up to 3 hours during the procedure. The aim is to reduce symptoms caused by the fibroids.

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Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2018.

Procedure name

- Ultrasound-guided high-intensity transcutaneous focused ultrasound for symptomatic uterine fibroids

Specialist societies

- British Society of Interventional Radiology
- Royal College of Obstetricians and Gynaecologists.

Description of the procedure

Indications and current treatment

Uterine fibroids are benign tumours of the uterine wall. They can be asymptomatic or cause symptoms including menorrhagia, intermenstrual bleeding, pelvic pressure or pain, and urinary incontinence. They can be associated with fertility problems and miscarriage.

Treatment depends on whether the fibroids cause symptoms, and if the person wishes to have children in the future. For symptomatic fibroids, treatment options include medications and surgery. Surgery includes hysterectomy, myomectomy, uterine artery embolisation, endometrial ablation techniques, MRI-guided focussed ultrasound and myolysis.

What the procedure involves

Ultrasound-guided high-intensity transcutaneous focused ultrasound (HIFU) for symptomatic uterine fibroids is done with the patient lying face down, with the abdominal wall immersed in degassed water. Intravenous sedation may be used to help minimise body movement. A urinary catheter is inserted to keep the bladder empty during the procedure. Continuous sonographic imaging is used to identify the fibroid(s) with a real-time diagnostic ultrasound scanner integrated into the centre of a therapeutic ultrasound transducer. After the target fibroid has been confirmed, it is ablated by high-intensity ultrasound energy. The patient may have to lie still for up to 3 hours. Ultrasound-guided HIFU uses grayscale or echogenicity changes to determine the adequacy of ablation. After treatment, imaging (by ultrasound or MRI scan) is used to evaluate the volume of the fibroid ablated.

Outcome measures

Non-perfused volume (NPV) ratio

This is the sum of the non-perfused volume (volume that was not enhanced in the contrast-enhanced MRI) of all treated fibroids divided by the volume of all uterine fibroids, treated and untreated. It is indicative of ablation efficiency.

Efficacy summary

Non-perfused volume (NPV) ratio

In a retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids, the median NPV ratio for patients with uterine fibroids was 85% (interquartile range 75% to 94%).[1]

In a retrospective case series of 9,988 patients with uterine fibroids (7,438 patients) or adenomyosis (2,549 patients), the mean NPV ratio (± standard deviation [SD]) for patients with uterine fibroids was 83.1%±15.6%.[2] In the same study the technical success rate (defined as a NPV ratio over 25% of the tumour volume) in patients with uterine fibroids was 98% (7,319/7,439).[2]

In a prospective non-randomised cohort study of 2,411 patients with fibroids having ultrasound-guided high-intensity focused ultrasound (USgHIFU) (n=1,353), myomectomy (n=586) or hysterectomy (n=472), the mean NPV ratio for USgHIFU was 87%.[3]

In a retrospective comparative study of 442 patients with anteverted (n=221) or retroverted uterus (n=221) having USgHIFU, the mean NPV ratio (±SD) after the procedure was statistically significantly greater in the anteverted uterus group

(87.7% ± 11.8%) compared with the retroverted uterus group (85.2% ± 18.7%, p=0.00).[5]

In a prospective comparative study of 94 patients with symptomatic uterine fibroids treated with USgHIFU or MRI-guided HIFU (MRIgHIFU) there were statistically significantly more patients in the USgHIFU group with an NPV ratio of 100% at 6 months compared with the MRIgHIFU group (43% (22/51) compared with 23% (10/43), p=0.031). In the same study, the proportions of patients with an NPV ratio of 90% to 99% at 6 months were 18% (9/51) compared with 23% (10/43) respectively for USgHIFU and MRIgHIFU and the proportions of patients with an NPV ratio of less than 90% at 6 months were 39% (20/51) compared with 53% (23/43) respectively.[8]

In the prospective case series of 10 patients with uterine fibroids having USgHIFU, the mean NPV ratio (± SD) at 3 months after the procedure was 67.7% ± 39.0% in the treated fibroids (range 2-100%, n=14). Of the 10 patients, 8 had an NPV ratio greater than 80%.[10]

Fibroid volume shrinkage

In a retrospective case series of 189 nulliparous women, the mean uterine fibroid volume shrinkage was 58.0% ± 31.3% after USgHIFU treatment (the findings referred to only the largest fibroid in cases of multiple fibroids).[6]

In the prospective comparative study of 94 women with symptomatic uterine fibroids treated with USgHIFU or MRIgHIFU, the mean fibroid volume reduction at 6 months (for patients with a NPV ratio of 100%) was 52.7% ± 11.4% in the USgHIFU group compared with 59.1% ± 9.0% in the MRIgHIFU group (no statistically significant difference between groups).[8]

In the prospective case series of 10 patients, the mean volume of the 14 treated fibroids was 224.1 cm^3 ± 190.5 cm^3 (range 11.5 cm^3 to 626.3 cm^3) at baseline. The mean volume and mean volume reduction rate (MVR%) of the 14 treated fibroids at 3 months were 172.2 cm^3 ± 152.8 cm^3 (range 5.8 cm^3 to 492.2 cm^3; p<0.01) and 23.3% ± 25.5% respectively. At 12 months, as MRI was not available for all patients, relative to a matched baseline group of mean volume 188.0 cm^3 ± 175.0 cm^3 (range 11.5 cm^3 to 553.9 cm^3, n=8), the mean volume and MVR% were 91.5 cm^3 ± 85.3 cm^3 (range 2.8 cm^3 to 136.8 cm^3; p<0.05) and 49.3 ± 23.7%. At 24 months, relative to a matched baseline group of mean volume 334.0 cm^3 ± 180.4 cm^3 (range 146.0 cm^3 to 626.3 cm^3, n=8, different subset of fibroids), the mean volume and MVR% were 160.4 cm^3 ± 98.3 cm^3 (range 73.4 cm^3 to 355.0 cm^3; p<0.005) and 51.9% ± 11.1%.[10]

Re-intervention rate

In the prospective non-randomised cohort study of 2,411 patients with fibroids having USgHIFU, myomectomy or hysterectomy, the re-intervention rate (defined as any need for recurrent treatment of fibroid-related symptoms, assessed for the HIFU and myomectomy groups only) was 1% (14/1,353) in the USgHIFU group compared with 0% (0/586) in the myomectomy group at 1 year. The re-interventions were: one second HIFU treatment, 12 myomectomies and 1 hysterectomy.[3]

Reduction of uterine fibroid symptoms

In the prospective non-randomised cohort study of 2,411 women with fibroids having USgHIFU, myomectomy or hysterectomy, the mean uterine fibroid symptoms (UFS) scores (scale ranges from 0 to 100 with higher scores indicating more serious symptoms) decreased statistically significantly more in the USgHIFU group than in the myomectomy group at 6 months (difference from baseline: –9.84 ±13.37 compared with –8.23 ± 13.10, p=0.002) and at 12 months (-12.17 ± -9.71 compared with –9.71 ± 13.69, p=0.000).[3]

In the retrospective case series of 189 nulliparous women, 84% (159/189) of women had clinical symptoms before USgHIFU treatment and the symptoms remission rate was 89% (141/189) after treatment.[6]

In a prospective comparative study of 130 patients with symptomatic uterine fibroids having USgHIFU (n=89) or laparoscopic myomectomy (n=41), the mean symptom scores assessing symptom improvement (11-point symptom score ranging from 5 (markedly worse) to +5 (markedly better)) were not statistically significantly different between groups at 1 month (3.3 compared with 3.1) or at 12 months (4.0 compared with 4.3).[7]

In the prospective comparative study of 94 patients with symptomatic uterine fibroids treated with USgHIFU or MRIgHIFU, the mean symptom severity score in the USgHIFU group decreased from 25.3 ± 14.7 before the procedure to 15.1 ± 5.1 at 6 months compared with a change from 26.6 ± 4.3 to 14.6 ± 2.0 in the MRIgHIFU group (no statistically significant difference between groups at 6 months).[8]

In the prospective case series of 10 patients, the mean symptom severity scores (SSS) statistically significantly decreased from 56.5 ± 29.1 before the procedure to 33.4 ± 23.3 ($p<0.01$) at 3 months, 45.0 ± 35.4 ($p<0.05$) at 12 months and 40.6 ± 32.7 ($p<0.01$) at 24 months.[10]

Quality of life

In the prospective non-randomised cohort study of 2,411 women with fibroids having USgHIFU, myomectomy or hysterectomy, the mean quality of life scores

(scale ranges from 0 to 100 with higher scores indicating better quality of life) increased statistically significantly more in the USgHIFU group than in the myomectomy group at 6 months (difference from baseline: 9.61 ± 14.01 compared with 7.42 ± 12.83, p=0.001) and at 12 months (12.89 ± 16.16 compared with 10.50 ± 15.33, p=0.008). [3]

In the prospective comparative study of 130 women with symptomatic uterine fibroids having USgHIFU (n=89) or laparoscopic myomectomy (n=41), the SF-36 scores (from 0 to 100 with higher scores indicating better function) for physical function, physical role, bodily pain, general health, vitality, social function, emotional role and mental health were similar between groups before the procedure. At 1 month, the SF-36 score for physical function had statistically significantly improved from 74.8±24.9 to 88.4±25.4 (p<0.001) in the USgHIFU group only and the SF-36 score for mental health had statistically significantly improved from 61.2±22.4 to 77.4±19.4 (p<0.001) in the myomectomy group only. Only SF-36 scores for emotional role and mental health were statistically significantly different between groups at 1 month (52.4±44.0 compared with 70.3±35.5 [p=0.02] and 66.4±18.0 compared with 77.4±19.4 [p=0.002] respectively). At 12 months, all the SF-36 scores had statistically significantly improved from baseline in the USgHIFU group (p<0.001), and in the myomectomy group, only general health and emotional role did not statistically significantly change from baseline. There were no statistically significant differences in the SF-36 scores between groups at 12 months. [7]

Pregnancy rate

In the prospective non-randomised cohort study of 2,411 women with fibroids having USgHIFU, myomectomy or hysterectomy, the pregnancy rate 1 year after the procedure was 2% (28/1,353) in the USgHIFU group compared with less than 1% (4/586) in the myomectomy group and 0% (0/472) in the hysterectomy group.[3]

In the retrospective case series of 189 nulliparous women, the pregnancy rate was 69% (131/189) after USgHIFU treatment with a mean interval between USgHIFU treatment and pregnancy of 12.3 ± 9.9 months. The spontaneous pregnancy rate was 95 % (125/131) and the pregnancy rate through assisted reproductive technology was 5% (6/131). Among women with a history of infertility, the pregnancy rate after USgHIFU was 20% (9/45). At the time of analysis, the birth rate was 70% (93/133), there were 14% (19/133) ongoing pregnancies and the abortion rate was 16% (21/133) with 13% (17/133) of spontaneous abortions. [6]

Patient satisfaction

In the prospective comparative study of 130 women with symptomatic uterine fibroids having USgHIFU (n=89) or laparoscopic myomectomy (n=41), the willingness rate to recommend treatment to a friend was not statistically significantly different between groups (89% [74/83] compared with 92% [36/39]). [7]

Sexual function

In the prospective RCT of 100 patients who had USgHIFU (n=48) or myomectomy (n=52) for symptomatic uterine fibroids, the rate of sexually active patients 3 months after USgHIFU was 100% compared with 96% after myomectomy and 100% in both groups at 6 months. In the same study, the mean brief index of sexual functioning (BISF) scores (higher score represents more favorable sexual functioning) statistically significantly improved from baseline to 6 months in both groups from 24.64 ± 6.64 to 26.67 ± 5.15 for USgHIFU and from 24.91 ± 6.51 to 26.82 ± 5.72 for myomectomy ($p<0.05$). There was no statistically significant difference between groups at 6 months. [4]

Return to work or daily activities

In the prospective non-randomised cohort study of 2,411 women with fibroids having USgHIFU, myomectomy or hysterectomy, the mean time to return to work was statistically significantly shorter in the USgHIFU group (4 days) than in the myomectomy group (24 days) and in the hysterectomy group (29.5 days); $p<0.001$ for the comparison between USgHIFU and surgery. [3]

In the prospective RCT of 100 patients who had USgHIFU (n=48) or myomectomy (n=52) for symptomatic uterine fibroids, the time to return to normal daily activities was statistically significantly shorter in the USgHIFU group (7 days) compared with the myomectomy group (15 days), $p<0.001$. In the same study, the time to out-of-bed activity was also statistically significantly shorter in the USgHIFU group (1 hour) compared with the myomectomy group (48 hours), $p<0.001$. [4]

In the prospective comparative study of 130 women with symptomatic uterine fibroids having USgHIFU (n=89) or laparoscopic myomectomy (n=41) there were statistically significantly less lost workdays, days late for work, days spent in bed and days without usual activities in the USgHIFU group compared with the myomectomy group ($p<0.001$). [7]

Treatment time

In the prospective comparative study of 94 women with symptomatic uterine fibroids treated with USgHIFU or MRIgHIFU, the treatment time for USgHIFU

was statistically significantly shorter (114.4 ± 39.2 minutes) compared with MRIgHIFU (174.5 ± 42.2 minutes), p=0.021.[8]

Hospital length of stay

In the prospective non-randomised cohort study of 2,411 women with fibroids having USgHIFU, myomectomy or hysterectomy, the mean hospital length of stay was statistically significantly shorter in the USgHIFU group (4 days) than in the myomectomy group (9 days) and in the hysterectomy group (10.5 days); p<0.001 for the comparison between USgHIFU and surgery. [3]

In a prospective RCT of 100 patients who had USgHIFU (n=48) or myomectomy (n=52) for symptomatic uterine fibroids, the hospital length of stay was statistically significantly shorter in the USgHIFU group (1 day) compared with the myomectomy group (4 days), p<0.001. [4]

In the prospective comparative study of 130 women with symptomatic uterine fibroids having USgHIFU (n=89) or laparoscopic myomectomy (n=41), the mean length of hospital stay was statistically significantly shorter in the USgHIFU group (2.9 days) compared with the myomectomy group (6.2 days) (p<0.001). [7]

Safety summary

Skin burn

Skin burn was reported in less than 1% of patients (26/17,402) with uterine fibroids after USgHIFU treatment, in a retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids.[1]

Skin burn was reported in less than 1% (26/9,988) of all patients with uterine fibroids or adenomyosis within 14 days of USgHIFU treatment in the retrospective case series of 9,988 patients.[2]

Second-degree skin burn was reported in less than 1% (3/1,353) of patients in the USgHIFU group and in none of the patients in the surgery group (having myomectomy or hysterectomy) after treatment, in a prospective non-randomised cohort study of 2,411 women with fibroids having USgHIFU (n=1,353), myomectomy (n=586) or hysterectomy (n=472). In the same study, first to second degree skin burn was reported in less than 1% (2/1,353) of patients in the USgHIFU group and in none of the patients in the surgery group. [3]

Skin burn was reported in 25% (12/48) of patients who had USgHIFU compared with none of the patients who had myomectomy (n=52) in a prospective RCT of 100 patients with symptomatic uterine fibroids (p<0.001).[4]

A 'hot' skin sensation was reported in 48% of patients during the USgHIFU procedure in the anteverted uterus group (n=221) compared with 27% of patients in the retroverted uterus group (n=221) in a retrospective comparative study of women (p=0). In the same study, skin burn after the USgHIFU treatment was reported in none of the patients with anteverted uterus and in 2% (5/221) of patients with retroverted uterus (p=0.031); the patients were treated by resection.[5]

Skin burn was reported in 13% (12/89) of patients after USgHIFU and in none of the patients after laparoscopic myomectomy (n=41) in a prospective comparative study of 130 women with symptomatic uterine fibroids having USgHIFU or laparoscopic myomectomy (p<0.001).[7]

In the prospective case series of 10 patients, second-degree skin burn was reported in 1 patient who had a surgical scar from a previous caesarean section. This skin toxicity was treated with a cool pack plus aloe gel and resolved by day 21 without further medication.[10]

In the retrospective case series of 346 patients, skin burn was reported in 1 patient without sacral injury and in none of the patients with sacral injury (p=0.423). This adverse event was classified as Class C and the burnt area needed resection.[11]

Pain

Lower abdominal pain was reported in 2% (225/9,988) of all patients with uterine fibroids or adenomyosis within 7 days of USgHIFU treatments in the retrospective case series of 9,988 patients.[2]

Lower abdominal pain was reported in 69% of patients during the USgHIFU procedure in the anteverted uterus group (n=221) compared with 58% of patients in the retroverted uterus group (n=221) in the retrospective comparative study of 442 women (p=0.012). In the same study, groin pain was reported in 3% of patients during the procedure in the anteverted uterus group compared with 13% of patients in the retroverted uterus group (p=0). After the procedure, lower abdominal was reported in 17% of women with anteverted uterus compared with 20% of women with retroverted uterus (no statistically significant difference between groups).[5]

Mild pain in the lower abdomen was reported in 9% (2/22) of patients with completely ablated fibroids treated with USgHIFU compared with 30% (3/10) of patients treated with MRIgHIFU in the prospective comparative study of

94 women with symptomatic uterine fibroids treated with USgHIFU or MRIgHIFU.[8]

Pain (no further details specified) was reported in 73% (35/48) of patients who had USgHIFU compared with 54% (28/52) of patients who had myomectomy in the prospective RCT of 100 patients with symptomatic uterine fibroids (p=0.048).[4]

Pain or discomfort (no further details specified) was reported in 45% (40/89) of patients after USgHIFU and in 41% (17/41) of patients after laparoscopic myomectomy in the prospective comparative study of 130 women with symptomatic uterine fibroids having USgHIFU or laparoscopic myomectomy (no statistically significant difference between groups).[7]

Leg pain was reported in less than 1% of patients (10/17,402) with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids.[1]

Leg or buttock pain was reported in less than 1% (76/9,988) of all patients with uterine fibroids or adenomyosis within 3 months of USgHIFU treatment in the retrospective case series of 9,988 patients.[2]

Lumbar and sacrum pain was reported in 11% (150/1,353) of patients in the USgHIFU group compared with 13% (134/1,058) of patients in the surgery group in the prospective non-randomised cohort study of 2,411 women with fibroids having USgHIFU, myomectomy or hysterectomy. In the same study, numbness and pain in the lower limbs after treatment was reported in 3% (34/1,353) of patients in the USgHIFU group compared with 2% (18/1,058) of patients in the surgery group. Weakness in lower limb was reported in less than 1% (9/1,353) of patients in the USgHIFU group compared with 6% (62/1,058) of patients in the surgery group.[3]

Transient leg pain was reported in 12% of patients in the anteverted uterus group (n=221) compared with 14% of patients in the retroverted uterus group (n=221) during the USgHIFU procedure in the retrospective comparative study of 442 women (no statistically significant difference between groups). In the same study, sciatic or buttock pain was reported in 39% of patients in the anteverted uterus group compared with 72% of patients in the retroverted uterus group (p=0). After the procedure, leg pain or numbness was reported in none of the patients with anteverted uterus compared with less than 1 % (1/221) of patients with retroverted uterus (no statistically significant difference between groups). Sciatic or buttock pain after the procedure was reported in 5% and 20% of women respectively (p=0.001).[5]

Mild pain in the lower back was reported in 5% (1/22) of patients with completely ablated fibroids treated with USgHIFU compared with none of the patients treated

with MRIgHIFU in a prospective comparative study of 94 women with symptomatic uterine fibroids treated with USgHIFU or MRIgHIFU.[8]

Pain and distension of anus was reported in less than 1 % (11/1,353) of patients in the USgHIFU group compared with 4% (38/1,058) of patients in the surgery group in the prospective non-randomised cohort study of 2,411 women with fibroids having USgHIFU, myomectomy or hysterectomy.[3]

In the retrospective case series of 346 patients, lower abdominal pain (Class B) was reported in 15.6% (33/211) compared with 16.3% (22/135), p=0.871) respectively for the group without injury and the group with injury. In the same study, the proportion of patients with sacrum or buttock pain (Class B) was 0.9% (2/211) compared with 3.7% (5/135), p=0.076) respectively for the group without injury and the group with injury. The proportion of patients with leg numbness, pain, or both (Class B) was 0.5% (1/211) compared with 2.2% (3/135), p=0.138) respectively for the group without injury and the group with injury. Leg pain caused by a temporary sciatic nerve irritation (Class C) was reported in none of patients in the group without injury and 1.5% (2/135) in the group with injury (p=0.076).[11]

Vaginal bleeding or discharge

Vaginal bleeding was reported in less than 1% of patients (6/17,402) with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids.[1]

Vaginal secretion was reported in 9% (874/9,988) of all patients with uterine fibroids or adenomyosis within 1 to 14 days of USgHIFU treatment in the retrospective case series of 9,988 patients.[2]

Vaginal bleeding or abnormal vaginal discharge was reported in 6% (3/48) of patients who had USgHIFU compared with 48% (25/52) of patients who had myomectomy in the prospective RCT of 100 patients with symptomatic uterine fibroids (p<0.001).[4]

Vaginal discharge was reported in 5% of women with anteverted uterus (n=221) after the USgHIFU procedure compared with 7% of women with retroverted uterus (n=221) in the retrospective comparative study of 442 women (p=0.012).[5]

Irregular vaginal bleeding or discharge was reported in 18% (16/89) of patients after USgHIFU and in 15% (6/41) of patients after laparoscopic myomectomy in the prospective comparative study of 130 women with symptomatic uterine fibroids having USgHIFU or laparoscopic myomectomy (no statistically significant difference between groups).[7]

Abnormal vaginal discharge was reported in 14% (3/22) of patients with completely ablated fibroids treated with USgHIFU compared with 20% (2/10) of patients treated with MRIgHIFU in the prospective comparative study of 94 women treated with USgHIFU or MRIgHIFU.[8]

In the retrospective case series of 346 patients, vaginal discharge was reported in 2.4% (5/211) of patients in the group without injury compared with 0.7% (1/135), p=0.258) in the group with injury. These adverse events recovered spontaneously within 3 days.[11]

Heavy vaginal bleeding was reported in 1 patient with a submucosal fibroid in a case reports of 3 patients treated with USgHIFU, 8 months after the procedure. The patient was treated with blood transfusions, ulipristal and an emergency uterine artery embolisation.[9]

Genital tract infection was reported in 12% (11/89) of patients after USgHIFU and in 12% (5/41) of patients after laparoscopic myomectomy in the prospective comparative study of 130 women with symptomatic uterine fibroids having USgHIFU or laparoscopic myomectomy (no statistically significant difference between groups).[7]

Uterine infection or bleeding

Intrauterine infection was reported in less than 1% of patients (2/17,402) with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids. [1]

Uterus bleeding was reported in less than 1% (24/9,988) of all patients with uterine fibroids or adenomyosis within 14 days of USgHIFU treatment in the retrospective case series of 9,988 patients.[2]

Uterine bleeding was reported in 7 % (88/1,353) of patients in the USgHIFU group compared with 21% (222/1,058) of patients in the surgery group in the prospective non-randomised cohort study of 2,411 patients with fibroids having USgHIFU, myomectomy or hysterectomy.[3]

In the prospective case series of 10 patients, haemorrhage into the fibroid was reported in 1 patient.[10]

Urinary retention

Urinary retention was reported in less than 1% of patients (7/17,402) with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids.[1]

Urinary retention was reported in less than 1% (16/9,988) of all patients with uterine fibroids or adenomyosis within 7 days of USgHIFU treatment in the retrospective case series of 9,988 patients.[2]

Urinary retention was reported in less than 1% (2/1,353) of patients in the USgHIFU group compared with 2% (25/1,058) of patients in the surgery group in the prospective non-randomised cohort study of 2,411 patients with fibroids having USgHIFU, myomectomy or hysterectomy.[3]

Irritation sign of bladder or urinary retention was reported in 4% (2/48) of patients who had USgHIFU compared with 21% (11/52) of patients who had myomectomy in the prospective RCT of 100 patients with symptomatic uterine fibroids (p=0.016).[4]

Urinary tract adverse event

Urinary tract adverse event was reported in 22% (20/89) of patients after USgHIFU and in 22% (9/41) of patients after laparoscopic myomectomy in the prospective comparative study of 130 patients with symptomatic uterine fibroids having USgHIFU or laparoscopic myomectomy (no statistically significant difference between groups).[7]

Hyperpyrexia

Hyperpyrexia was reported in less than 1% of patients (5/17,402) with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids. [1]

Fever was reported in less than 1% (4/9,988) of all patients with uterine fibroids or adenomyosis within 7 days of USgHIFU treatment in the retrospective case series of 9,988 patients.[2]

Fever that did not need treatment was reported in less than 1 % (2/1,353) of patients in the USgHIFU group compared with less than 1% (6/1,058) of patients in the surgery group in the prospective non-randomised cohort study of 2,411 patients with fibroids having USgHIFU, myomectomy or hysterectomy.[3]

Temperature of more than 38ºC was reported in 2% (2/89) of patients after USgHIFU and in 10% (4/41) of patients after laparoscopic myomectomy on any 2 days after treatment in the prospective comparative study of 130 patients with symptomatic uterine fibroids having USgHIFU or laparoscopic myomectomy (no statistically significant difference between groups).[7]

Rehospitalisation more than 24 hours after the procedure

Rehospitalisation more than 24 hours after the procedure was reported in 3% (3/89) of patients after USgHIFU and in 2% (1/41) of patients after laparoscopic

myomectomy in the prospective comparative study of 130 patients with symptomatic uterine fibroids having USgHIFU or laparoscopic myomectomy (no statistically significant difference between groups).[7]

Rapid fibroid enlargement

Rapid fibroid enlargement was reported in 2 patients after 12 USgHIFU treatments and 4 years after 1 USgHIFU treatment in a case reports of 3 patients treated with USgHIFU. Both patients were treated with a transabdominal myomectomy.[9]

Other adverse events

The following adverse events were also reported in the literature:

Renal failure was reported in less than 1% of patients (4/17,402) with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids. [1]

Acute cystitis was reported in less than 1% of patients (3/17,402) with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids. [1]

Odynuria or haematuria was reported in less than 1% (52/9,988) of all patients with uterine fibroids or adenomyosis within 7 days of USgHIFU treatment in the retrospective case series of 9,988 patients.[2] Haematuria was reported in less than 1 % (3/1,353) of patients in the USgHIFU group compared with 2% (18/1,058) of patients in the surgery group in the prospective non-randomised cohort study of 2,411 patients with fibroids having USgHIFU, myomectomy or hysterectomy.[3]

Bowel injury was reported in less than 1% of patients (3/17,402) with uterine fibroids 4 to 12 days after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids. The patients were treated by surgery. [1] Intestinal perforation was reported in less than 1% (2/9,988) of all patients with uterine fibroids or adenomyosis between 15 to 30 days of USgHIFU treatment in the retrospective case series of 9,988 patients.[2]

Gastrointestinal adverse event was reported in 21% (19/89) of patients after USgHIFU and in 49% (20/41) of patients after laparoscopic myomectomy in the prospective comparative study of 130 pateints with symptomatic uterine fibroids having USgHIFU or laparoscopic myomectomy ($p<0.001$).[7] Intestinal complication was reported in less than 1% (3/9,988) of all patients with uterine

fibroids or adenomyosis within 8 to 30 days of USgHIFU treatment in the retrospective case series of 9,988 patients.[2]

Deep vein thrombosis was reported in less than 1% of patients (2/17,402) with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids. [1]

Hydronephrosis was reported in 1 patient with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids. [1]

Pubic symphysis injury was reported in 1 patient with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids. [1]

Thrombocytopenia was reported in 1 patient with uterine fibroids after USgHIFU treatment, in the retrospective case series of 27,053 patients including 17,402 patients with uterine fibroids. [1]

Blurred vision was reported in less than 1% (2/9,988) of all patients with uterine fibroids or adenomyosis within 7 days of USgHIFU treatment in the retrospective case series of 9,988 patients.[2] Blurred vision was reported in less than 1% (10/1,353) of patients after treatment in the USgHIFU group compared with none of the patients in the surgery group in the prospective non-randomised cohort study of 2,411 patients with fibroids having USgHIFU, myomectomy or hysterectomy.[3]

Hernia in the abdominal wall was reported in 1 patient out of 9,988 patients with uterine fibroids or adenomyosis more than 90 days after USgHIFU treatment in the retrospective case series of 9,988 patients.[2]

Respiratory tract infection was reported in less than 1% (1/1,353) of patients in the USgHIFU group compared with less than 1% (9/1,058) of patients in the surgery group in the prospective non-randomised cohort study of 2,411 patients with fibroids having USgHIFU, myomectomy or hysterectomy.[3]

Nausea and vomiting were reported in 2 % (21/1,353) of patients in the USgHIFU group compared with 15% (158/1,058) of patients in the surgery group in the prospective non-randomised cohort study of 2,411 patients with fibroids having USgHIFU, myomectomy or hysterectomy.[3]

Dizziness and headache were reported in less than 1 % (2/1,353) of patients in the USgHIFU group compared with less than 1% (1/1,058) of patients in the surgery group in the prospective non-randomised cohort study of 2,411 patients with fibroids having USgHIFU, myomectomy or hysterectomy.[3]

Neurological symptoms were reported in 15% (7/48) of patients who had USgHIFU compared with 4% (2/52) of patients who had myomectomy in the prospective RCT of 100 patients with symptomatic uterine fibroids (p=0.083).[4] Nervous system adverse event was reported in 4% (4/89) of patients after USgHIFU and in 15% (6/41) of patients after laparoscopic myomectomy in the prospective comparative study of 130 patients with symptomatic uterine fibroids having USgHIFU or laparoscopic myomectomy (p=0.02).[7]

Cardiovascular system adverse event was reported in 4% (4/89) of patients after USgHIFU and in 7% (3/41) of patients after laparoscopic myomectomy in the prospective comparative study of 130 patients with symptomatic uterine fibroids having USgHIFU or laparoscopic myomectomy (no statistically significant difference between groups).[7]

Sciatic nerve injury

In the retrospective case series of 346 patients, sciatic nerve injury was reported in none of patients in the group without injury compared with 1.5% (2/135), p=0.076) of the group with injury, with the pain being relieved after 3 months with NSAIDs.[11]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers did not list any anecdotal or theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to ultrasound-guided high-intensity transcutaneous focused ultrasound for symptomatic uterine fibroids. The following databases were searched, covering the period from their start to 25 March 2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with symptomatic uterine fibroids.
Intervention/test	Ultrasound-guided high-intensity transcutaneous focused ultrasound.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 28,565 patients from 1 RCT[4], 4 non-randomised comparative studies[3,5,7-8], 5 case series[1,2,6,10,11] and 1 case reports[9].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on ultrasound-guided high-intensity transcutaneous focused ultrasound for symptomatic uterine fibroids

Study 1 Liu Y C (2018)

Details

Study type	**Retrospective case series**
Country	China (19 centres)
Recruitment period	2011-2017
Study population and number	n=**27,053 (17,402 with uterine fibroids)** patients with benign uterine disease
Age and sex	Median 42 years; 100% female Median BMI: 22.5 kg/cm^2
Patient selection criteria	Inclusion criteria: confirmed diagnosis, patients agreed to have pre-HIFU and post-HIFU MRI evaluation, patients could communicate with physicians during the procedure of HIFU treatment. Exclusion criteria: the lesion could not be visualised, pregnancy or lactation, suspected or confirmed uterine malignant diseases.
Technique	All patients needed to have bowel preparation before HIFU treatment. On the morning of the treatment day, the skin from the umbilicus level to the upper margin of the pubic symphysis was shaved, degreased and degassed before HIFU. JC or JC200 models of focused ultrasound tumour therapeutic system (Chongqing Haifu Medical Technology, Co., Ltd) were used. Real-time monitoring was done using My-Lab70 type B ultrasonic equipment (Esaote Group).
Follow-up	**1 month**
Conflict of interest/source of funding	Lian Zhang is a senior consultant to Chongqing Haifu. This work was partially supported by the National Basic Research Programme of China, the National Natural Science Fund by the National Science Foundation of China and the National Key Technology R&D Program.

Analysis

Study design issues: The severity of adverse effects was evaluated according to the SIR classification system for complications by outcome: (1) Class A: no therapy, no consequence; (2) Class B: nominal therapy, no consequence; (3) Class C: require therapy, minor hospitalization (<48 h); (4) Class D: required major therapy, unplanned increase in level of care, prolonged hospitalisation (>48 h); (5) Class E: permanent adverse sequelae; (6) Class F: death.

Study population issues: Among the 27,053 patients, 17,402 had uterine fibroids, 8434 had adenomyosis, 876 had caesarean scar pregnancy, and 341 had placenta accreta. In the patients with uterine fibroids, 12,342 had a solitary fibroid and 5060 had multiple fibroids.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **27,053 (17,402 with uterine fibroids)** **NPV ratio** (for patients with uterine fibroids; median [interquartile range]): 85% (75% to 94%)	**SIR classification of adverse effects after USgHIFU treatment in <u>all patients</u> (n=27,053)**

SIR classification	Adverse effects	Number of events	Incidence rate (%)
Class A	Mild lower abdominal pain	8,263	30%
	Sacrococcygeal pain	2,833	10%
	Abnormal vaginal discharge	1,270	5%
	Lower limb paraesthesia	188	<1%
	Nausea and vomiting	108	<1%
	Erythema on skin	86	<1%
	Fever	79	<1%
	Haematuria	24	<1%
	Total	12,851	48%
Class B	Lower abdominal pain	113	<1%
	Sacrococcygeal pain	33	<1%
	Abnormal vaginal discharge	27	<1%
	Skin blisters	20	<1%
	Lower limb paresthesia	19	<1%
	Fever	3	<1%
	Total	215	<1%
Class C	Skin burns	38	<1%
	Leg pain	17	<1%
	Vaginal discharge or bleeding	13	<1%
	Urinary retention	8	<1%
	Hyperpyrexia	7	<1%
	Acute cystitis	4	<1%
	Intrauterine infection	3	<1%
	Total	90	<1%
Class D	Bowel injury	4	<1%
	Acute renal failure	4	<1%
	Deep vein thrombosis	2	<1%
	Pubic symphysis injury	1	<1%
	Post-HIFU thrombocytopenia	1	<1%
	Sciatic nerve injury	1	<1%
	Hydronephrosis	1	<1%
	Total	14	<1%
Class E and F		0	0%

Incidence of major complications (class C and D of the SIR classification) after USgHIFU treatment in patients with uterine fibroids

Complications	Incidence % (number of patients) n=17,402
Skin burns	0.1494 (26)
Leg pain	0.0575 (10)
Urinary retention	0.0402 (7)
Vaginal bleeding	0.0345 (6)
Hyperpyrexia	0.0287 (5)
Renal failure	0.0230 (4)
Acute cystitis	0.0172 (3)
Bowel injury*	0.0172 (3)
Intrauterine infection	0.0115 (2)
Deep vein thrombosis	0.0115 (2)
Hydronephrosis	0.0057 (1)
Pubic symphysis injury	0.0057 (1)
Thrombocytopenia	0.0057 (1)
TOTAL	0.4080

The incidence rates of the major complications among patients with uterine fibroids, adenomyosis and placenta accrete were not statistically significantly different.

*This occurred between 4 and 12 days after the procedure and the patients were treated by surgery.

Abbreviations used: BMI, body mass index; HIFU, high-intensity focused ultrasound; NPV, non-perfused volume; SIR, society of interventional radiology; USgHIFU, ultrasound-guided HIFU.

Study 2 Chen J (2015)

Details

Study type	**Retrospective case series**
Country	China (16 centres)
Recruitment period	2006-2007
Study population and number	n=**9,988** patients with uterine fibroids (**7,438**) or adenomyosis (2,549)
Age and sex	Mean 40 years; 100% female
Patient selection criteria	Inclusion criteria: age>18, no pregnancy desire in the near future; clinically diagnosed with uterine fibroids or adenomyosis with symptoms like dysmenorrhea and menorrhagia; uterine fibroids or adenomyosis confirmed by enhanced MRI examinations; clear imaging of the lesion by ultrasound monitor built in the HIFU treatment system, and ultrasound focal point able to be located inside the lesions with its focal region covering most of the lesion; no bone or cannot move gas-containing organ found in the ultrasonic path; no allergy to contrast agent or contraindication for MRI examination; free from cognitive impairment, and able to communicate therapeutic experience with the medical staff; consent to ultrasound ablation therapy and having signed the informed consent form; consent to the use of their clinical data and imaging date for medical study and publication. Exclusion criteria: patients with scars in their lower abdomen that could cause obvious sound attenuation or having a history of radiation therapy; suspected of or confirmed as uterine malignancy; acute infectious pelvic disorders.
Technique	The ultrasound ablation procedure was done with an USgHIFU tumour therapeutic system [JC or JC200, Chongqing Haifu (HIFU) Tech Co., Ltd]. The device features the built-in B-mode ultrasound (Esaote MyLab70) that provides real-time visualisation during the treatment. Prophylactic antibiotics were prescribed orally for 3 days.
Follow-up	**Minimum 6 months**
Conflict of interest/source of funding	Wen-Zhi Chen is a shareholder and a consultant for Chongqing Haifu Medical Technologies Inc. Lian Zhang and Ke-Quan Li are consultants to Chongqing Haifu Medical Technologies Inc. Other authors have no conflicts of interest. The study was supported by the National Key Technology Research and Development Program.

Analysis

Study design issues:

- 42 doctors did the procedure.
- The severity of adverse effects was evaluated according to the SIR classification system for complications by outcome: (1) Class A: no therapy, no consequence; (2) Class B: nominal therapy, no consequence; (3) Class C: require therapy, minor hospitalization (<48 h); (4) Class D: required major therapy, unplanned increase in level of care, prolonged hospitalisation (>48 h); (5) Class E: permanent adverse sequelae; (6) Class F: death.

Study population issues:

- 6,545 patients had a solitary uterine fibroid, 818 had multiple uterine fibroids, and 76 had fibroids complicated with adenomyosis.
- There were mainly 3 types of fibroids: submucous myoma in 89 patients (12%), intramural myoma in 5,059 patients (68%) and subserosal myoma in 1,478 patients (20%).
- Fibroids location: 3,496 fibroids were found in the anterior wall (47%), 2,306 in the posterior wall (31%), 447 in the lateral wall (6%), and 1,190 in fundus (16.0%).
- The median volume of the dominant fibroid tumour was 67.5 cm^3 (interquartile range, 38.1 to 134.5 cm^3).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **9,988 patients with uterine fibroids (7,438) or adenomyosis (2,549)**

For uterine fibroids only

Technical success rate (NPV ratio over 25% of the tumour volume)**:** 98% (7,319/7,439)

Volume of ablation (median [1/4, 3/4]): 78.5 cm^3 (53.1, 129.4)

NPV rate (%, mean): 83.1 ± 15.6 (range 25.0 to 100.0)

Safety

Adverse reactions after HIFU (all patients, N=9,988)

Description	% patients (n)	1-7 days	8-14 days	15-30 days	31-90 days	>90 days
Vaginal secretion	9% (874)	768	106	0	0	0
Lower abdominal pain	2% (225)	225	0	0	0	0
Leg or buttock pain	<1% (76)	55	12	7	2	0
Odynuria or haematuria	<1% (52)	52	0	0	0	0
Uterus bleeding	<1% (24)	20	4	0	0	0
Blurred vision	<1% (2)	2	0	0	0	0
Skin burns	<1% (26)	22	4	0	0	0
Urinary retention	<1% (16)	16	0	0		0
Fever	<1% (4)	4	0	0	0	0
Intestinal	<1% (3)	0	2	1	0	0
Intestinal perforation	<1% (2)	0	0	2	0	0
Hernia in abdominal wall	<1% (1)	0	0	0	0	1
Total	1305	89% (1164/1305)	10% (128/1305)	<1% (10/1305)	<1% (2/1305)	<1% (1/1305)

No permanent injury or fatal complication occurred.

Adverse reactions according to SIR classification

SIR classification	% of adverse reactions	% of patients
Class A	94% (1228/1305)	12% (1228/9988)
Class B	3% (45/1305)	<1% (45/9988)
Class C	2% (24/1305)	<1% (26/9988)
Class D	<1% (8/1305)	<1% (6/9988)
Class E	0	0
Class F	0	0

Abbreviations used: HIFU, high-intensity focused ultrasound; NPV, non-perfused volume; SIR, society of interventional radiology; USgHIFU, ultrasound-guided HIFU.

Study 3 Chen J (2017)

Details

Study type	**Prospective non-randomised cohort study**
Country	China (20 centres)
Recruitment period	2011-2013
Study population and number	n= **2,411 (1,353 USgHIFU versus 586 myomectomy versus 472 hysterectomy)** women with symptomatic fibroids
Age and sex	USgHIFU: Mean 41 years; mean BMI: 23 Hysterectomy: Mean 47 years; mean BMI: 24 Myomectomy: Mean 41 years; mean BMI: 23
Patient selection criteria	Inclusion criteria: Premenopausal women who had completed their planned family (and had no recent plan for a further pregnancy). Imaging-confirmed diagnosis of symptomatic fibroids with any of the following indications for hysterectomy: (a) enlarged uterus; (b) menorrhagia or secondary anaemia; (c) pelvic pain, urinary frequency, or constipation. For patients with multiple fibroids, no more than 3 fibroids with minimal diameters of 2 cm based on abdominal ultrasound present. Fibroids clearly imaged by abdominal ultrasound. For patients with abdominal surgical scars, the width of image blurring because of acoustic attenuation had to be <10 mm. Exclusion criteria: Patients with uterine adenomyosis. Previous myomectomy. Concurrent pregnancy. Pedunculated subserous or submucosal fibroids. Any single fibroid >10 cm maximum diameter. Acute pelvic inflammation or uncontrolled systemic disease. Patients unable to communicate adequately with physicians, or unwilling to sign informed consent.
Technique	USgHIFU: A single session of HIFU ablation was done using the JC (JC200) Focused Ultrasound Therapeutic Unit for Tumour (Chongqing Haifu Medical Technology Co., Ltd). Treatment was monitored by real-time ultrasonography. After the procedure, patients lay prone for 2 hours under observation. Surgical procedures: The surgical route of hysterectomy or myomectomy was left to the discretion of the attending gynaecologist.
Follow-up	**1 year**
Conflict of interest/source of funding	No conflict of interest declared. This project was funded by the National Key Technology R&D Program.

Analysis

Follow-up issues:

- Follow-up visits were scheduled at 6 months and 12 months post-procedure.
- At 12-month follow-up, the rate of patients lost to follow-up were 7% (89/1,353) in the USgHIFU group, 5% (32/586) in the myomectomy group and 3% (13/472) in the hysterectomy group.

Study design issues:

- The main objective of the study was to evaluate the clinical outcomes of USgHIFU and surgery in treating uterine fibroids, and prepare for a randomised trial.
- Patients were given written information describing the potential risks and benefits associated with each procedure, including the likely effects on fertility and the risk of recurrence of symptom. Patients made the choices according to their preference after being informed of all 3 options.
- To adjust for the effects of inequalities between treatment groups, multiple regression modelling was done to identify the influence of preselected covariates on the dependent variable. This process was carried out for the total UFS and QoL scores.

Study population issues: The mean age of the USgHIFU group was lower than that of the surgery group (myomectomy plus hysterectomy). Other group differences included BMI, uterine volume and UFS score.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **2,411 (1,353 USgHIFU versus 586 myomectomy versus 472 hysterectomy)**

Mean NPV score for USgHIFU: 87%

Re-intervention rate at 1 year (defined as any need for recurrent treatment of fibroid-related symptoms, assessed for the HIFU and myomectomy groups only):

- USgHIFU group: 1% (14/1,353)
- Myomectomy group: 0% (0/586)

The re-interventions were: one second HIFU treatment, 12 myomectomies and 1 hysterectomy.

Pregnancy rate at 1 year:

- USgHIFU group: 2% (28/1,353)
- Myomectomy group: 0.7% (4/586)
- Hysterectomy group: 0% (0/472)

UFS-QoL score (mean ± SD) - Both scales range from 0 to 100, but high scores indicate better QoL but more serious symptoms on the UFS scale

Parameter	**UFS-QoL score or change in score**			
	HIFU group (n = 1353)	**Myomectomy group (n = 586)**	**p (unadjusted)**	**p (adjusted)**
UFS				
Baseline	19.89 ± 14.29	15.34 ± 13.34	**0.000**	
At 6 months	10.20 ± 10.18	7.09 ± 8.25	**0.000**	
At 12 months	7.73 ± 9.65	5.77 ±7.77	**0.000**	
Absolute difference at 6 months	–9.84 ±13.37	–8.23 ± 13.10	**0.002**	**0.034**
Absolute difference at 12 months	-12.17 ± -9.71	–9.71 ± 13.69	**0.000**	**0.001**
QoL				
Baseline	72.75 ± 16.33	72.85 ± 14.46	0.532	

Safety

Adverse events allocated to treatment

Adverse event	**HIFU group (n = 1353)**	**Surgery group (myomectomy or hysterectomy, n = 1058)**	**Myomectomy group (n = 586)**
Minor adverse event	25% (335)	68% (719)	68% (397)
Abdominal distension	0	<1% (4)	<1% (3)
Lumbar and back (sacrum) pain	11% (150)	13% (134)	11% (64)
Shoulder and back pain	0	1% (11)	2% (11)
Numbness and pain in lower limb	3% (34)	2% (18)	2% (11)
Weakness in lower limb	<1% (9)	6% (62)	5% (30)
Pain and distension of anus	<1% (11)	4% (38)	3% (18)
Subcutaneous emphysema	0	<1% (5)	<1% (5)
Uterine bleeding	7% (88)	21% (222)	26% (150)
Urinary retention	<1% (2)	2% (25)	1% (7)
Haematuria	<1% (3)	2% (18)	1% (7)
Fever (no therapy)	<1% (2)	<1% (6)	<1% (3)
Respiratory tract infection	<1% (1)	<1% (9)	<1% (4)
Fat liquefaction of incision	0	<1% (4)	<1% (3)
Incision infection	0	<1% (1)	0
Skin burn (1st to 2nd degree)	<1% (2)	0	0
Nausea and vomiting	2% (21)	15% (158)	14% (80)

At 6 months	82.49 ± 12.94	80.44 ± 12.41	**0.000**	
At 12 months	85.84 ± 12.22	83.45 ± 11.28	**0.000**	
Absolute difference at 6 months	9.61 ± 14.01	7.42 ± 12.83	**0.001**	**0.001**
Absolute difference at 12 months	12.89 ± 16.16	10.50 ± 15.33	**0.008**	**0.002**

The UFS-QoL cannot be used appropriately after hysterectomy.

Hospital length of stay (mean)

- USgHIFU group: 4 days
- Myomectomy group: 9 days
- Hysterectomy group: 10.5 days

p<0.001 for the comparison between USgHIFU and surgery.

Time to return to work (mean)

- USgHIFU group: 4 days
- Myomectomy group: 24 days
- Hysterectomy group: 29.5 days

p<0.001 for the comparison between USgHIFU and surgery.

Dizziness and headache	<1% (2)	<1% (1)	0
Blood pressure unsteadiness	-	<1% (1)	-
Blurred vision	<1% (10)	0	0
Choking sensation in chest	0	<1% (1)	<1% (1)
Stomach pain	0	<1% (1)	-
Major adverse events	<1% (3)	13% (133)	10% (60)
Intraoperative massive haemorrhage (≥ 400 ml)	0	1% (11)	1% (7)
Intraoperative blood transfusion	0	9% (96)	7% (41)
Fever (>38°C)	0	<1% (3)	<1% (2)
Pelvic abdominal infection	0	<1% (5)	<1% (3)
Incision infection	0	<1% (3)	<1% (1)
Second-degree skin burn	<1% (3)	0	0
Respiratory tract infection	0	<1% (2)	<1% (1)
Readmission	0	<1% (3)	0
Deep venous thrombosis (lower limbs)	0	<1% (2)	<1% (1)
Vaginal cuff bleeding	0	<1% (1)	0
Vaginal cuff infection	0	<1% (1)	0
Drainage-site infection	0	<1% (1)	<1% (1)
Pelvic haematoma (drainage)	0	<1% (1)	<1% (1)
Pelvic abscess (drainage)	0	<1% (1)	<1% (1)
Bladder injury	0	<1% (1)	0

	Abdominal distension and vomiting (indwelling gastric tube)	0	<1% (1)	0
	Arrhythmia (emergency)	0	<1% (1)	<1% (1)

Abbreviations used: BMI, body mass index; NPV, non-perfused volume; QoL, quality of life; SD, standard deviation; UFS, uterine fibroid symptoms score; USgHIFU, ultrasound-guided HIFU

Study 4 Wang X (2013)

Details

Study type	**Prospective RCT**
Country	China (1 centre)
Recruitment period	2010-2011
Study population and number	n= **100 (48 USgHIFU versus 52 myomectomy)** premenopausal patients with symptomatic uterine fibroids
Age and sex	USgHIFU: Mean 39 years; 100% (48/48) female; mean BMI: 22 Myomectomy: Mean 38 years; 100% (52/52) female; mean BMI: 22
Patient selection criteria	Inclusion criteria: premenopausal; clinically diagnosed with symptomatic uterine fibroids (as confirmed by ultrasonography) and presenting with operation indications and no wish to conceive. Exclusion criteria: submucous fibroids or pedunculated subserous fibroids; presence of other gynecological disorders, including vaginitis, pelvic inflammation, ovarian tumour, endometriosis, cervical dysplasia or symptomatic prolapse; menstruating, pregnant or breastfeeding women; or abnormal liver or renal function. Patients with submucous fibroids or pedunculated subserous fibroids.
Technique	USgHIFU: patients were treated with JC-focused ultrasound cancer treatment system under the guidance of real-time ultrasound. All patients received the maximum power of 400 W, except 1 patient who received 415 W. Myomectomy: the same group of surgeons did the procedures. Endotracheal intubation and general anaesthesia were administered to all patients. All steps were done using conventional surgical techniques and instruments via an abdominal transverse incision.
Follow-up	**6 months**
Conflict of interest/source of funding	None. This study was supported by the Grants from the National Natural Science Foundation of China and the Scientific and Technological Project of Chongqing.

Analysis

Follow-up issues: 110 patients were first randomised to the USgHIFU or to the myomectomy group using a computer-generated sequence and each group included 55 patients. In the USgHIFU group, 2 patients withdrew their consent and 5 patients were lost to follow-up. In the Myomectomy group, 3 patients were lost to follow-up. The total proportion of patients lost to follow-up was 10 %.

Study design issues:

- The purpose of this study was to evaluate the changes in sexual life associated with USgHIFU treatment compared with surgical treatment. The brief index of sexual functioning (BISF-W) was used to evaluate changes in sexual function. Differences in the outcome were calculated for each individual before treatment and at 3 and 6 months after treatment, and changes were compared between groups.
- The BISF-W questionnaire has 22 questions in 7 dimensions investigating all aspects of sexual life. The possible range of total score is -16 to +75.Higher scores indicate a higher quality of sexual function, except for 1 dimension (problems affecting sexual function).
- The BISF-W was only completed by patients who had been sexually active in the 4 weeks before administration of the questionnaire.
- Power analysis of the difference of the dimension scores at follow-up indicated that all patients from each group were needed to detect a clinically relevant 20 % difference between the groups ($\alpha = 0.05$ and power $(1–\beta) = 0.8$).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **100 (48 USgHIFU versus 52 myomectomy**

Operative results

Characteristic	USgHIFU	Myomectomy	p values
Hospital stay, day	1 (1, 2)	4 (4, 6)	**<0.001***
Time of out-of-bed activity, hour	1 (0.17, 5)	48 (24, 72)	**<0.001***
Time to return to normal daily activities, day	7 (2, 60)	15 (7, 60)	**<0.001***

*From the Mann–Whitney U test

Sexual activity (% of sexually active patients)

	USgHIFU	Myomectomy	p values
Pre-operation	100%	100%	
1 month	81%	17%	**<0.001**
3 months	100%	96%	
6 months	100%	100%	

Patients after myomectomy were advised not to have sexual activity during the month after surgery, while UsgHIFU patients were advised to resume sexual activity depending on their physical condition without any special restraint.

BISF-W total scores compared with baseline at different time points (mean±SD)

Total scores**	USgHIFU	Myomectomy	p values
Pre-operation	24.64 ± 6.64	24.91 ± 6.51	0.933
3 months	25.04 ± 4.54	24.83 ± 4.99	0.701
6 months	26.67 ± 5.15***	26.82 ± 5.72***	0.605

** A higher score represents more favorable sexual functioning

***Statistically significant difference from baseline within group (p<0.05)

Safety

Adverse reactions and complications

Characteristic	USgHIFU	Myomectomy	p values
Adverse reactions	88% (42/48)	79% (41/52)	0.263[a]
Pain	73% (35/48)	54% (28/52)	**0.048[b]**
Burning of skin	25% (12/48)	0	**<0.001[a]**
Vaginal bleeding/abnormal vaginal discharge	6% (3/48)	48% (25/52)	**<0.001[a]**
Irritation sign of bladder/urinary retention	4% (2/48)	21% (11/52)	**0.016[a]**
Vomiting/abdominal distension	0	15% (8/52)	**<0.001[a]**
Neurological symptoms	15% (7/48)	4% (2/52)	0.083[a]
Others	8% (4/48)	13% (7/52)	0.529[a]
Complications	0	27% (14/52)	**<0.001[a]**
Postoperative complication	0	13% (7/52)	**0.013[a]**
Transfusion	0	2% (1/52)	>0.999[a]
Hospital readmission time (>24 h)	0	0	-
Anaesthesia-related complications	0	12% (6/52)	**0.027[a]**
Severe complications	0	0	-
Death	0	0	-

[a] From Fisher's exact test

[b] From Pearson's Chi-squared test

Abbreviations used: BISF-W, brief index of sexual functioning; BMI, body mass index; HIFU, high-intensity focused ultrasound; SD, standard deviation; USgHIFU, ultrasound-guided HIFU

Study 5 Zhang W (2016)

Details

Study type	**Retrospective comparative study**
Country	China
Recruitment period	2011-2015
Study population and number	n= **442 (221 anteverted versus 221 retroverted uterus)** women with a single uterine fibroid
Age and sex	Mean 42 years
Patient selection criteria	Inclusion criteria: patients were premenopausal and at least 18 years of age, patients agreed to have MRI examinations before and after USgHIFU treatment, patients had solitary uterine fibroids and the fibroids presented with hypointensity on T2WI of an MRI. Exclusion criteria: patients with uterine fibroids presenting as isointensity or hyperintensity on T2WI, patients with multiple fibroids, patients with suspected or confirmed malignant diseases.
Technique	USgHIFU ablation was performed using an ultrasound compatible HIFU tumour therapeutic system (JC200, Haifu VR Technology, Chongqing).
Follow-up	**Immediately post-treatment**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: NPV of the fibroid (defined as the volume that was not enhanced in the contrast-enhanced MRI) was measured post-HIFU treatment.

Study design issues:

- The aim of the study was to compare the treatment outcomes of USgHIFU for uterine fibroids in patients with an anteverted uterus compared with a retroverted uterus.
- Two senior radiologists evaluated all MR images independently.

Study population issues: There were statistically significant differences between groups in the sonication power (lower for the retroverted uterus group) and in the total energy used (less energy used in the retroverted uterus group) ($p<0.05$).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **442 (221 anteverted versus 221 retroverted uterus)**

Volume of fibroids (mean ± SD)

Variables	Anteverted uterus (n=221)	Retroverted uterus (n=221)	p
Post-HIFU lesion volume (cm^3)	31.0 ± 38.1	29.1 ± 35.3	0.111
NPV (cm3)	27.1 ± 33.9	25.1 ± 33.1	0.212
NPV ratio (%)	87.7 ± 11.8	85.2 ± 18.7	**0.00**

Safety

Incidence rates of adverse effects during the USgHIFU procedure

Variable	Anteverted uterus (n=221)	Retroverted uterus (n=221)	p
Transient leg pain	12%	14%	0.331
Sciatic/buttock pain	39%	72%	**0**
Lower abdominal pain	69%	58%	**0.012**
Skin 'hot' sensation	48%	27%	**0**
Groin pain	3%	13%	**0**

Incidence rates of adverse effects and complications immediately after USgHIFU treatment.

Variable	Anteverted uterus (n=221)	Retroverted uterus (n=221)	p
Fever	0%	0%	1
Lower abdominal pain	17%	20%	0.312
Sciatic/buttock pain	5%	14%	**0.001**
Leg pain/numbness	0%	<1% (1/221)	0.5
Vaginal discharge	5%	7%	0.214
Skin burn	0%	2% (5/221)*	**0.031**

*Resection was done in 2 patients.

Abbreviations used: HIFU, high-intensity focused ultrasound, SD, standard deviation; T2WI, T2 weighted imaging, USgHIFU, ultrasound-guided HIFU

Study 6 Li J S (2017)

Details

Study type	**Retrospective case series**
Country	China (1 centre)
Recruitment period	2010-2015
Study population and number	n= **189** nulliparous women with uterine fibroids who had USgHIFU treatment
Age and sex	Mean 31 years; 100% (189/189) female
Patient selection criteria	Inclusion criteria: aged 20–42 years, desire to maintain fertility, have normal sexual life without contraception after USgHIFU, women with uterine fibroids who never had a delivery history before USgHIFU. Exclusion criteria: underwent re-interventions including hysterectomy or bilateral oophorectomy after HIFU.
Technique	Treatment was administered using the Model JC Focused Ultrasound Tumour Therapeutic System (Chongqing Haifu Medical Technology Co. Ltd.) with the microwave emission output power set to 200–400 W under continuous real-time ultrasound guidance at 3.5 MHz. The effect of therapy was determined by color doppler ultrasound and contrast-enhanced ultrasound (SonoVue). After USgHIFU patients were told to use contraceptives for 3 months and abstain from sex until after 1 menstruation.
Follow-up	**Median 3 years**
Conflict of interest/source of funding	No competing interests declared. This study was supported by the National Basic Research Program of China, the National Natural Science Fund by the Chinese National Science Foundation and the National Instrumentation Program.

Analysis

Follow-up issues:

- All the patients were advised to return for ultrasound examination at 3 months, 6 months, and 12 months, and then once a year thereafter.
- All the nulliparous women were enrolled and called for follow up. An obstetrician and gynaecologist did the telephone interviews with patients and filled out the case follow-up form. Telephone follow-up information included menstruation, symptoms of uterine fibroids, sexual life, pregnancy, outcome of pregnancy, pregnancy process, and delivery information. The complications during pregnancy and delivery were acquired from the prenatal ultrasound examination report and medical discharge records.
- Loss to follow-up was determined when the doctor failed to reach the patient by telephone after more than 3 attempts over the course of several days. We noted the number of patients who successfully completed telephone follow-up and those patients who were lost to follow-up.

Study design issues:

- The main objective of the study was to evaluate the impact of USgHIFU treatment for uterine fibroids on pregnancy and pregnancy outcomes in women.
- During the study period, 1,232 women had USgHIFU treatment for uterine fibroids. Of these women, 311 patients met the inclusion criteria and follow-up data was obtained for 255 women. 66 women were excluded from the analysis because of no sexual life, use of contraception or hysterectomy.

Study population issues: Twenty women (11%) were more than 35 years old. Of the 189 women, 131 (69%) had a single fibroid and 58 (31%) had multiple fibroids when they were treated with USgHIFU.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **189**

Symptom remission rate and fibroid volume

Variables	Value
Clinical symptoms before USgHIFU (n, %)*	84% (159/189)
Symptoms remission after USgHIFU (n, %)*	89% (141/189)
Volume before HIFU (cm^3, mean±SD) †	81.2 ± 80.6
Volume after HIFU (cm^3, mean±SD) †	34.2 ± 48.3
Volume shrinkage (%, mean±SD)†	58.0 ± 31.3

*Whether clinical symptoms were relieved according to the patient's subjective evaluation.

†In cases of multiple myomas, these findings refer to only the largest myoma.

Pregnancy after USgHIFU

Variables	Value
Pregnancy rate	69% (131/189)
Mean interval between USgHIFU treatment and pregnancy	12.3 ± 9.9 months
Spontaneous pregnancy rate	95% (125/131)
Pregnancy rate through assisted reproductive technology	5% (6/131)
Pregnancy rate of women with a history of infertility	20% (9/45)

Pregnancy outcomes after USgHIFU (n = 133)

Pregnancy outcomes	Cases (n)
Delivery mode	70% (93/133)
Caesarean section*	72% (67/93)
Vaginal delivery	28% (26/93)
On-going pregnancy	14% (19/133)
Abortion	16% (21/133)
Spontaneous abortion	13% (17/133)
Induced abortion	3% (4/133)
Pregnancy complications	11% (10/93)
Labour complications	8% (7/93)

*Including 6 cases (4.5%) termination pregnancy in premature for obstetric factors.

Neonates characteristics (n = 94)

Variables	Value
Male/female (n)	49/45
Number of pregnancy (n)	93
Single pregnancy (n)	99% (92/93)
Twin pregnancy (n)	1% (1/93)
Pregnancy length (weeks)	37.5 ± 1.0
Birth weight (Kg)	3.3 ± 0.4
Low birth weight infants	4

Full term deliveries	94% (88/94)
Preterm deliveries	6% (6/94)

Characteristics between pregnancy group and non-pregnancy group

Variables	Pregnancy group	Non-pregnancy group	p values
Cases (n)	131	68	-
Age (years)	30.3 ± 4.0	33.8 ± 4.2	**0.000**
Infertility history (n, %)	7% (9/131)	62% (36/58)	**0.000**
Number of myomas ablated (n)	1.2 ± 0.8	1.6 ± 1.0	**0.008**
Clinical symptoms before HIFU (n, %)*	84% (110/131)	84% (49/58)	0.874
Symptoms remission after HIFU (n, %)*	98% (108/110)	67% (33/49)	**0.000**
Volume shrinkage (%)†	60.0 ± 30.8	52.3 ± 32.7	0.094

*Whether clinical symptoms were relieved according to patient's subjective evaluation.

†In cases of multiple myomas, these findings refer to only the largest myoma.

Multivariate regression analysis was performed for the comparisons that were found to be statistically significant. Multivariate analysis indicated that age and a history of infertility were the factors that statistically significantly affected pregnancy after treatment ($p < 0.01$).

Abbreviations used: HIFU, high-intensity focused ultrasound; SD, standard deviation; USgHIFU, ultrasound-guided HIFU

Study 7 Wang F (2014)

Details

Study type	**Non-randomised prospective comparative study**
Country	China (single centre)
Recruitment period	2010-2011
Study population and number	n= **130 (89 USgHIFU versus 41 laparoscopic myomectomy)** women with symptomatic uterine myomas
Age and sex	Mean 38 years Mean BMI: 22
Patient selection criteria	Inclusion criteria: premenopausal status; age≥18 years; and presence of symptomatic uterine myomas, with no more than 3 myomas located intramurally or subserosally and the largest myoma <10 cm in diameter. Exclusion criteria: presence of asymptomatic uterine myomas, submucous or pedunculated myomas, pregnancy, contraindication for MRI or gadolinium injection solution, suspected or confirmed malignant uterine tumour, pelvic acute inflammatory disease, and systemic disease. In the USgHIFU group, patients were excluded if they had type 3 uterine myomas identified on the signal intensity of T2-weighted images.
Technique	For the USgHIFU procedure, the USgHIFU tumour therapeutic system (model JC HIFU; Chongqing Haifu Technology Co., Ltd) and B-mode ultrasound (MyLab70; Esaote SpA) were used. In the surgical group, laparoscopic myomectomy was done according to the method of Mais et al. If technical difficulty occurred and the surgery could not be finished using laparoscopy, the procedure was converted to conventional laparotomy. All surgical procedures were done by the same 2 experienced gynaecologists.
Follow-up	**1 year**
Conflict of interest/source of funding	The study was supported by a grant from the Health Ministry of Chongqing, China.

Analysis
Follow-up issues: In the HIFU group, 89 women were enrolled and treated, and 83 completed the 2 follow-up visits. In the surgical group, 41 were allocated to have laparoscopic myomectomy. Two procedures were converted to laparotomic myomectomy because of serious pelvic adhesions and 2 patients were lost to follow-up.
Study design issues:

- The main objective was to assess the quality of life of women at 1 and 12 months after USgHIFU treatment as compared with laparoscopic myomectomy for treatment of symptomatic uterine myomas.
- Patients were assigned to either the HIFU or the surgical group according to their preference.

Study population issues: The only significant difference in baseline characteristics between groups was that the largest mean myoma diameter in the HIFU group was 6.0 cm compared with 6.9 cm in the surgical group (p=0.02).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **130 (89 USgHIFU versus 41 laparoscopic myomectomy)**

SF-36 score (mean [SD]) at admission and at 1 and 12 months after treatment. Scores range from 0 to 100 and higher scores indicate better function.

Variable	USgHIFU Group	Surgical Group	p Value
At admission	n=89	n=41	-
Physical function	74.8 (24.9)	77.6 (23.8)	NS
Physical role	46.5 (42.4)	49.2 (41.3)	NS
Bodily pain	53.4 (23.9)	51.3 (29.5)	NS
General health	64.8 (20.8)	69.5 (18.9)	NS
Vitality	43.1 (24.1)	40.3 (24.5)	NS
Social function	66.1 (29.4)	62.5 (28.3)	NS
Emotional role	64.4 (40.9)	65.4 (43.6)	NS
Mental health	66.4 (19.1)	61.2 (22.4)	NS
At 1 month	n=88	n=41	-
Physical function	**88.4 (25.4) (p<.001)**	86.9 (24.7) (NS)	NS
Physical role	51.9 (33.4) (NS)	44.5 (29.6) (NS)	NS
Bodily pain	53.9 (26.6) (NS)	55.7 (27.3) (NS)	NS
General health	62.9 (20.8) (NS)	64.4 (19.9) (NS)	NS
Vitality	48.7 (26.4) (NS)	49.0 (25.4) (NS)	NS
Social function	61.4 (28.8) (NS)	63.5 (22.8) (NS)	NS
Emotional role	52.4 (44.0) (NS)	70.3 (35.5) (NS)	**0.02**
Mental health	66.4 (18.0) (NS)	**77.4 (19.4) (p<0.001)**	**0.002**
At 12 months	n=83	n=39	
Physical function	**91.2 (20.4) (p<0.001)**	**89.9 (22.8) (p=0.02)**	NS
Physical role	**73.9 (33.4) (p<0.001)**	**72.5 (39.8) (p=0.01)**	NS

Safety

Significant clinical complications and adverse events

Variable	USgHIFU Group (n=89)	Surgical Group (n=41)	p Value
Significant clinical complications			
Total number	19% (17)	27% (11)	NS
Skin burn	13% (12)	0	**<0.001**
Temperature >38ºC on any 2 post-treatment days	2% (2)	10% (4)	NS
Transfusion	0	2% (1)	NS
Unintended surgical procedures related to treatment	0	5% (2)	NS
Rehospitalisation within >24 hour	3% (3)	2% (1)	NS
Anaesthesia related complication	0	7% (3)	**0.006**
Life-threatening event	0	0	NS
Death	0	0	NS
Total significant clinical complications except skin burn	6% (5)	27% (11)	**<0.001**
Adverse events			
Pain/ discomfort	45% (40)	41% (17)	NS
Genital tract	28% (25)	22% (9)	NS
Irregular vaginal bleeding/ discharge	18% (16)	15% (6)	NS
Infection	12% (11)	12% (5)	NS
Urinary tract	22% (20)	22% (9)	NS
Gastrointestinal tract	21% (19)	49% (20)	**<0.001**
Nervous system	4% (4)	15% (6)	**0.02**
Cardiovascular system	4% (4)	7% (3)	NS
Respiratory tract	0	2% (1)	NS
Other	2% (2)	5% (2)	NS

Bodily pain	**75.3 (25.8) (p<0.001)**	**79.0 (27.3) (p <0.001)**	NS
General health	**74.9 (20.3) (p<0.001)**	76.8 (21.9) (NS)	NS
Vitality	**65.6 (25.5) (p<0.001)**	**64.9 (20.8) (p<0.001)**	NS
Social function	**85.7 (25.2) (p<0.001)**	**83.3 (26.3) (p<0.001)**	NS
Emotional role	**82.5 (35.4) (p<0.001)**	80.9 (32.4) (NS)	NS
Mental health	**80.4 (19.1) (p<0.001)**	**79.0 (23.4) (p<0.001)**	NS

p values in parentheses denote comparison of SF-36 scores at admission versus at 1 or 12 months after treatment.

Effect of treatment on symptoms, willingness to recommend the treatment, hospital stay, and disability assessment (mean [SD])

Variable	USgHIFU Group	Surgical Group	p Value
Symptom score at 1 month*	3.3 (1.8) (n=89)	3.1 (2.2) (n=41)	NS
Symptom score at 12 months*	4.0 (2.3) (n=83)	4.3 (2.4) (n=39)	NS
Willingness to recommend treatment to a friend	89% (74/83)	92% (36/39)	NS
Hospital stay (day)	2.9 (1.5)	6.2 (2.7)	**<0.001**
Disability assessment			
Lost workdays	3.9 (2.4)	8.8 (4.0)	**<0.001**
Days late for work	2.6 (1.4)	4.7 (1.9)	**<0.001**
Days spent in bed	1.9 (0.8)	4.3 (2.0)	**<0.001**
Days without usual activities	4.5 (1.5)	10.9 (3.8)	**<0.001**

*Symptom score assessing symptom improvement: 11-point symptom score ranging from -5 (markedly worse) to +5 (markedly better).

Abbreviations used: BMI, body mass index; HIFU, high-intensity focused ultrasound; NS, not statistically significant; QoL, quality of life; USgHIFU, ultrasound-guided HIFU

Study 8 Wang Y (2018)

Details

Study type	**Non-randomised prospective comparative study**
Country	China (single centre)
Recruitment period	2012-2013
Study population and number	n=**94 (51 USgHIFU [68 fibroids] versus 43 MRIgHIFU [44 fibroids])** women with symptomatic uterine fibroids
Age and sex	USgHIFU: Mean 39 years MRIgHIFU: Mean 42 years
Patient selection criteria	Inclusion criteria: no more than 2 fibroids in each patient, determined by MRI; all fibroids hypo-intense on pre-treatment T2-weighted imaging
Technique	Each patient had only 1 session of MRgHIFU or USgHIFU treatment. The USgHIFU procedure was conducted with a JC-200 clinical extracorporeal USgHIFU system (Chongqing Haifu Tech Co, Ltd.), which was equipped with a diagnostic ultrasound (MyLab70; Esaote, Genoa, Italy) for real-time guidance. The MRgHIFU procedure was conducted with the clinical extracorporeal JM 5100 MRgHIFU system (Chongqing Haifu Tech Co, Ltd) fully integrated into a 1.5T Magnetom Avanto MRI scanner (Siemens Medical Systems) to provide a real-time temperature mapping for treatment control.
Follow-up	**6 months**
Conflict of interest/source of funding	The devices used for the procedures were provided by Chongqing Haifu Technical Limited Company.

Analysis

Follow-up issues: After treatment, only the patients with completely ablated fibroids (defined as 100% NPV ratio with no residual portion) were selected for further analysis.

Study design issues:

- The purpose of this study was to compare efficacy, sonication energy efficiency, treatment time and safety of MRgHIFU and USgHIFU for ablation of uterine fibroids.
- All MRgHIFU and USgHIFU procedures were conducted by 1 interventional radiologist with more than 10 years of experience in image-guided tumour ablation therapy.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **94 (51 USgHIFU [68 fibroids] versus 43 MRIgHIFU [44 fibroids])**

NPV ratio and NPV at 6 months

	USgHIFU Group (% patients)	MRIgHIFU Group (% patients)	p
NPV ratio			
100%	43% (22/51) 28 fibroids	23% (10/43) 13 fibroids	**0.031**
90% to 99%	18% (9/51) 14 fibroids	23% (10/43) 12 fibroids	-
Less than 90%	39% (20/51) 26 fibroids	53% (23/43) 26 fibroids	-
NPV for completely ablated fibroids (NPV ratio=100%)			
NPV (cm^3)*	118.9 ± 55.0	127.8 ± 70.2	0.632

*Sum of fibroid's NPV in each patient.

All patients restored normal activities within 2 hours after the procedure.

Fibroid volume reduction and SSS at 6 months

Variable	USgHIFU Group (n=22)	MRIgHIFU Group (n=10)	p
Mean fibroid volume reduction	52.7 ± 11.4%	59.1 ± 9.0%	NS
Mean SSS at baseline	25.3 ± 14.7	26.6 ± 4.3	
Mean SSS at 6 months	15.1 ± 5.1	14.6 ± 2.0	NS

Treatment time (mean ± SD)

- USgHIFU : 114.4 ± 39.2 minutes
- MRIgHIFU: 174.5 ± 42.2 minutes

p=0.021

Safety

Adverse events and complications in patients with completely ablated fibroids

Variable	USgHIFU Group (n=22)	MRIgHIFU Group (n=10)
Abnormal vaginal discharge	14% (3/22)	20% (2/10)
Mild pain in the lower abdomen	9% (2/22)	30% (3/10)
Mild lower back pain	5% (1/22)	0

Abbreviations used: HIFU, high-intensity focused ultrasound; MRIgHIFU, MRI-guided HIFU; NPV, non-perfused volume; NS, not statistically significant; SD, standard deviation; SSS, symptom severity score; USgHIFU, ultrasound-guided HIFU

Study 9 Kim H-K (2015)

Details

Study type	**Case report**
Country	Korea
Recruitment period	2011-2014
Study population and number	n= **3** women with huge uterine fibroids
Age and sex	Mean 38 years
Patient selection criteria	Women with huge uterine myoma who want to preserve fertility.
Technique	USgHIFU
Follow-up	**Not reported**
Conflict of interest/source of funding	None. This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **3** No efficacy outcomes reported.	**Rapid myoma enlargement** Patient 1: The initial MRI before HIFU ablation showed a 15-cm-sized well-defined hypointense mass in the posterior wall of the uterine body and fundus on T2- weighted imaging. However, the follow-up MRI after 12 HIFU ablation showed a 20-cm-sized heterogeneous myoma, extending to the renal hilum level superiorly, with a large area of non-enhancing portion in T2-weighted and post-gadolinium images, suggesting degenerative change. The patient was treated with a transabdominal myomectomy. Patient 3: The patient was referred to hospital complaining of abdominal discomfort due to an oversized uterine myoma. She had a history of myomectomy 10 years ago and another intramural myoma measuring 12-cm 4 years later, for which she had one time of USgHIFU ablation. Two years after the HIFU, a repeated sonogram showed marked interval increase in the size of the uterine myoma with extensively cystic degeneration. A pelvic MRI taken showed a 16-cm-sized heterogeneous mass on the anterosuperior aspect of uterine wall and a 6.8-cm-sized subserosal myoma along the left lateral wall of the uterine body. The patient was treated with a transabdominal myomectomy. **Heavy vaginal bleeding** Patient 2: The patient had an USgHIFU ablation to remove a 5.5-cm-sized uterine submucosal myoma showing menorrhagia. However, 8 months after the procedure, her unusual vaginal bleeding was not resolved and her laboratory tests showed anaemia with a low hemoglobin level (5.0 mIU/L). The follow-up MRI after HIFU showed 6.1-cm–sized bulging mass with heterogeneous enhancement in the anterior wall of the uterus. The patient was treated with blood transfusions, ulipristal and an emergency uterine artery embolization.
Abbreviations used: HIFU, high-intensity focused ultrasound; USgHIFU, ultrasound-guided HIFU	

Study 10 Lyon (In press)

Details

Study type	Prospective case series
Country	UK (single centre in the NHS)
Recruitment period	2011- 2014
Study population and number	n=**10** women with symptomatic uterine fibroids; 14 uterine fibroids (7 patients treated for a single fibroid, 2 for 2 fibroids and 1 for 3 fibroids)
Age and sex	Mean 42 years; 100% (10/10) female
Patient selection criteria	Inclusion criteria: age over 18 years; had fibroid-related symptoms without any major medical comorbidities; declined standard surgical management but had interest in HIFU; had suitable fibroids with a clear margin on US imaging; for those with multiple uterine fibroids, the fibroid(s) most likely to be correlated with patient's symptoms were targeted as dominant fibroid(s) for treatment; did not have gonadotropin-releasing hormone therapy before treatment; and gave written consent. Exclusion criteria: patients with unclear margins of fibroid on US imaging; presence of un-manoeuvrable bowel between the fibroid and anterior abdominal wall; submucosal fibroid distorting the uterine cavity; and simultaneous endometriosis.
Technique	Under intravenous sedation with remifentanyl and propofol, all patients had a morning or afternoon session (113.3 minutes ± 41.2 minutes) of HIFU treatment which was done using a CE-marked extracorporeal USgHIFU device (Model-JC200 HIFU System, Haifu Medical, Chongqing, China). The concave treatment transducer has a central aperture containing an integrated B-mode US imaging probe for real-time imaging.
Follow-up	**2 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Of the 12 treated patients, 2 were excluded from analysis. One patient was lost to follow-up due to geographical relocation, and the other was due to the fact that the baseline MRI showed a significant volume of intra-fibroid haemorrhage, which was thought not to be representative of the fibroid morphology of the other treated fibroids.

Study design issues:

- Eligible patients were referred to a single-centre multidisciplinary team consisting of gynaecologists, radiologists and HIFU specialists, however, there was no information about the operator(s) training and experiences of carrying out the procedure.
- Of the 10 patients, 9 had a complete treatment of the intended fibroid(s) and 1 had a partial treatment due to an unexpected skin burn during the HIFU exposure.
- Of the 10 patients, 2 were further excluded from the analysis as one underwent a hysterectomy at 12 months and the other had a myomectomy at 18 months.

Study population issues:

- Of the 10 patients, 2 patients had a single fibroid, 5 had 2 to 5 fibroids, and 3 had more than 10 fibroids.
- Of the 14 treated uterine fibroids, the dominant fibroids were intramural (n=11) and subserosal (n=3).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **10 patients with uterine fibroids (14)**

Mean NPV ratio (±SD) at 3 months: 67.7% ± 39.0% (range 2% to 100%)

Mean volume (cm^3, mean±SD) and fibroid volume reduction (%, mean±SD) at 3 months, 12 months, and 24 months

	n	Matched baseline volume	Post-HIFU volume	p	Post-HIFU volume reduction
3 months	10	224.1 ± 190.5	172.2 ± 152.8	<0.01	23.3 ± 25.5
6 months**	8	188.0 ± 175.0	91.5 ± 85.3	<0.05	49.3 ± 23.7
12 months***	8	334.0 ± 180.4	160.4 ± 98.3	<0.005	51.9± 11.1

*From paired student's *t*-tests for the comparison of mean fibroid volumes pre- and post-treatment.

**MRI was only available for 8 patients.

*** MRI was only available for 8 patients, with different subset of fibroids.

Mean SSS at baseline, 3 months, 12 months and 24 months – SSS includes 8 items linked with symptom severity score and each item is scored from 1 (no symptom) to 5 (major symptoms), the higher scores indicate worse symptoms

Follow-up	Mean ± SD	p
Baseline	56.5 ± 29.1	
3 months	33.4 ± 23.3	<0.01
12 months	45.0 ± 35.4	<0.05
24 months	40.6 ± 32.7	<0.01

****From student's *t*-tests and Wilcoxon sum ranked test for the comparison of SSS scores at baseline and at follow-up visits.

Safety

Adverse events after HIFU (all patients, n=10).

Skin burns: 10% (1/10)

This patient had a surgical scar from a previous caesarean section. This skin toxicity was treated with cool-pack plus aloe gel and resolved by day 21 without further medication.

Haemorrhage: 10% (1/10)

Need for non-HIFU treatments: 20% (2/10)

One patient had a hysterectomy at 12 months because of symptom persistence after the procedure and the other had a myomectomy at 18 months because of symptom recurrence, which was caused by the growth of untreated fibroids.

Abbreviations used: NPV, non-perfused volume; SD, standard deviation; SSS, symptom severity score.

Study 11 Cun J P (2019)

Details

Study type	**Retrospective case series**
Country	China
Recruitment period	2012- 2017
Study population and number	N=**346 (211 without sacral injury versus 135 with sacral injury after USgHIFU)** women who had USgHIFU ablation to treat a single uterine fibroid.
Age and sex	Mean 38 years; 100% (346/346) female
Patient selection criteria	Inclusion criteria: patients were treated for a single fibroid using USgHIFU and signed informed consent
Technique	USgHIFU treatment was done with a Model-JC 200 focused ultrasound tumor therapeutic system (Chongqing HIFU Technology Inc., Chongqing, China), and the system was connected to a B-model untrasound scanner (MyLab 70, Esaote, Italy) for monitoring the target area and adjacent structures. All patients completed preoperative preparation (lower abdominal skin preparation included degreasing and degassing, and a cleansing enema; the patient's bladder was filled with normal saline using a Foley catheter to control volume and prevent intentional injury.
Follow-up	**Immediately post-treatment**
Conflict of interest/source of funding	None

Analysis

Study design issues:

- The aim of the study was to analyse the factors that influence sacral injury from USgHIFU and to evaluate the relationships between sacral injury and the features of fibroids.
- The severity of adverse events were evaluated according to the Society of Interventional Radiology (SIR) classification system: (1) Class A: no therapy, no consequence; (2) Class B: nominal therapy or no consequence, including overnight admission for observation only; (3) Class C: require therapy, minor hospitalisation (<48 h); (4) Class D: needed major therapy, including unplanned increased in level of care, or prolonged hospitalisation (>48 h); (5) Class E: permanent adverse sequelae; (6) Class F: death.
- There was no information about the operator(s) and their training and experiences of carrying out the procedure.
- There was no information about the mean duration of each USgHIFU session.

Key efficacy and safety findings

Safety

Number of patients analysed: **346 (211 without sacral injury and 135 with sacral injury)**

Features of fibroids associated with sacral injury at baseline

Characteristics	Without injury (n=211)	With injury (n=135)	*p*
Volume of fibroids (cm^3, mean±SD)	77.37 ± 70.41	93.12 ± 65.81	0.038*
Maximal diameter of fibroids (cm, mean±SD)	5.40 ± 1.60	5.83 ± 1.46	0.012*
Fibroid dorsal side to sacrum (cm, interquartile range)	0.77 (0.69, 0.86)	0.74 (0.63, 0.83)	0.000**
Type of fibroids			0.002***
Intramural (n, %)	111 (32.1%)	61 (17.6%)	
Subserosal (n, %)	45 (13.0%)	16 (4.6%)	
Submucosal (n, %)	30 (8.7%)	23 (6.6%)	
Tansmural (n, %)	25 (7.2%)	35 (10.1%)	
Degree of enhancement			0.003***
Slight (n, %)	41 (11.9%)	27 (7.8%)	
Intermediate (n, %)	94 (27.2%)	72 (20.8%)	
Progressive (n, %)	76 (22.0%)	36% (10.4%)	

*From the independent sample t test

**From the 2-sided rank sum test

***From the X^2 test

Multivariable binary logistic regression analysis showed that the degree of enhancement was an independent risk factor for sacral injury during the USgHIFU procedure ($p<0.05$), while the distance from the fibroid's dorsal side to the sacrum was a protective factor ($p<0.001$). Intramural and subserosal types were also protective factors for sacral injury ($p<0.05$).

Treatment parameters associated with sacral injury

Variable	Without injury (n=211)	With injury (n=135)	Statistics	*p*
TD (J)	419271.73 ± 3.34534E5	587140.24 ± 3.45960E5	T=-4.493	0.000*
EEF (J/mm^3)	6.69 ± 5.31	8.55 ± 6.03	T=-3.014	0.003*
NPV ratio (%)	2.70 (1.90, 4.10)	1.90 (1.30, 2.80)	Z=-2.151	0.031**

*From the independent sample t test

**From the 2-sided rank sum test

Multivariate analysis showed that EEF and TD were risk factors for sacral injury ($p<.05$), indicating that the higher the EEF or TD, the more easily the sacrum was injured. The NPV ratio had no significant relationship with sacral injury in the multivariate analysis.

SIR classification of adverse events after the USgHIFU procedure in all patients (n=346)

SIR	Adverse events	Without injury (n=211)	With injury (n=135)	*p*
Class A	Lower abdominal pain	92 (43.6%)	63 (46.7%)	0.576
	Sacrum/buttock pain	21 (9.5%)	19 (14.1%)	0.242
	Vaginal discharge	5 (2.4%)	1 (0.7%)	0.258

	Leg numbness/pain	6 (2.8%)	7 (5.2%)	0.264
	Erythema on skin	8 (3.8%)	7 (5.2%)	0.535
	Total	229 (61.9%)[a]		
Class B	Lower abdominal pain	33 (15.6%)	22 (16.3%)	0.871
	Sacrum/buttock pain	2 (0.9%)	5 (3.7%)	0.076
	Leg numbness/pain	1 (0.5%)	3 (2.2%)	0.138
	Erythema on skin	3 (1.4%)	2 (1.5%)	0.964
	Total	71 (19.1%)[b]		
Class C	Skin burns	1 (0.5%)[c]	0	0.423
	Leg pain	0	2 (1.5%)[d]	0.076
	Total	3 (0.9%)		
Class D	Sciatic nerve injury	0	2 (1.5%)[e]	0.076
	Total	2 (0.6%)		
Class E&F	-	0	0	-

[a]229 adverse events recovered spontaneously within 3 days.

[b]71 adverse events subsided within 1 week without any specific treatment.

[c]The burnt area necessitated resection.

[d]This was caused by a temporary sciatic nerve irritation.

[e]The pain was relieved after 3 months with NSAIDs

Abbreviations used: EEF, energy efficiency factor; NPV, non-perfused volume; NSAIDs, nonsteroidal anti-inflammatory drugs; SIR, Society of Interventional Radiology; TD, therapeutic dose.

Validity and generalisability of the studies

- In Study 2, the adverse events were reported for all patients having uterine fibroids or adenomyosis.
- There was 1 RCT (study 4) included in Table 2. It compared USgHIFU with myomectomy.
- All the studies came from China apart from Study 9 which was from Korea and Study 10 from the UK.
- The main objective of study 6 was to evaluate the impact of USgHIFU treatment for uterine fibroids on pregnancy and pregnancy outcomes in women.
- Study 8 compared USgHIFU with MRIgHIFU.
- Study 11 was to investigate the risk factors influencing MR changes associated with sacral injury from USgHIFU ablation for uterine fibroids.
- The longest follow-up was a median of 3 years in Study 6.

Existing assessments of this procedure

- The European Menopause and Andropause Society (EMAS) published a position statement on the management of uterine fibroids in 2014[10]. It says:

  ''8.2 Ultrasound-guided high-intensity focused ultrasound

  Ultrasound-guided HIFU ablation is a new non-invasive treatment of uterine fibroids. The technique allows a check on the immediate efficacy of the procedure; then, if viable residualtissue is detected, there is the option to repeat the ablation immediately. Heterogeneous and markedly homogeneous hyperintense fibroids, as classified by MR, may be treated with ultrasound-guided HIFU. Contrast-enhanced ultrasonography may also be used to monitor gradual shrinkage of the treated fibroids or later growth.

Large-scale clinical trials are needed to assess the role and limitations of these techniques.''

- The Society of Obstetricians and Gynaecologists of Canada (SOGC) published a clinical practice guideline on the management of uterine leiomyomas in 2015[11]. It says:

  ''Focused Energy Delivery Systems

  A number of focused energy delivery systems have been tested in the past decade including those based upon radiofrequency electricity, supercooled cryoprobes, and most recently, MRg-FUS or high frequency ultrasound guided transcutaneous focused ultrasound ablation. A major disadvantage of all systems and techniques used to desiccate or ablate fibroids may be that they treat one fibroid at a time and they target the centre of fibroids, while fibroids have been shown to grow mostly from their periphery.

  These technologies are relatively new and although many are promising, they often lack long-term data, which interferes with our ability to present all risks and benefits with assurance. Ongoing research and data collection are required to assess the relative merit of newer options as the technology continues to expand.''

- The College National des Gynecologues et Obstetriciens Francais published updated guidelines on the therapeutic management of uterine fibroid tumours in 2012[12]. It says:

  ''MRI- or ultrasound-guided focused ultrasound treatment is a new possibility, and current results are encouraging, after the learning curve. Rigorous selection of patients is essential with treatment of a single fibroid or two at the most, anterior, between 5 and 12 cm, with a T2-weighted hypointense signal T2 on MRI; approximately 10% of fibroids are accessible to this technique to obtain devascularization greater than 45%, which is correlated with intermediate-term symptom relief in the order of 60–70% (LE3). On the other hand, the reduction of fibroid volume seems less substantial (15–40%) than with the other techniques (LE4). None of the current techniques can be recommended for myolysis; the technique that is most advanced, least aggressive and monitored most effectively seems to be focused ultrasound. Clinical research into these techniques must continue, with trials comparing them to surgery or uterine artery embolization, to obtain an evidence level sufficient to justify a recommendation. Patients treated with these techniques must be included in research protocols. As of today, no publication provides evidence to justify either allowing or proscribing myolysis in women who wish to become pregnant.''

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Hysteroscopic morcellation of uterine leiomyomas (fibroids). NICE interventional procedures guidance 522 (2015). Available from http://www.nice.org.uk/guidance/ipg522
- Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids. NICE interventional procedures guidance 413 (2011). Available from http://www.nice.org.uk/guidance/ipg413
- Magnetic resonance (MR) image-guided percutaneous laser ablation of uterine fibroids. NICE interventional procedures guidance 30 (2003). Available from http://www.nice.org.uk/guidance/ipg30

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Advisor Questionnaires for ultrasound-guided high-intensity transcutaneous focused ultrasound for symptomatic uterine fibroids were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE received 1 completed questionnaire. The patient commentator' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

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Company engagement

A structured information request was sent to 3 companies who manufacture a potentially relevant device for use in this procedure. NICE did not receive any completed submission.

Issues for consideration by IPAC

Ongoing studies
Directed Ablation of Uterine Fibroids Using a Noninvasive Approach (DIANA). NCT03219385. Not yet recruiting. Case series. Estimated study completion date: September 2022. Estimated enrolment: 180 patients. USA.

Prospective, Muti-institute, Single Arm, Confirmative Trial Evaluating Efficacy and Safety of High Intensity Focused Ultrasound Device (RODIN) in Women With Symptomatic Uterine Leiomyoma NCT03328260. Active. Not Recruiting. Case series. Estimated study completion date: February 2019. Actual enrolment: 34 patients. Republic of Korea.

References

1. Liu Y C, Zhang W W, He M et al. (2018) Adverse effect analysis of high-intensity focused ultrasound in the treatment of benign uterine diseases, International Journal of Hyperthermia, 35(1), 56-61, DOI: 10.1080/02656736.2018.1473894
2. Chen J, Chen W, Zhang L et al. (2015) Safety of ultrasound-guided ultrasound ablation for uterine fibroids and adenomyosis: A review of 9988 cases. Ultrasonics Sonochemistry 27, 671-676
3. Chen J, Li Y, Wang Z, et al. (2017) Evaluation of high-intensity focused ultrasound ablation for uterine fibroids: an IDEAL prospective exploration study. BJOG: An International Journal of Obstetrics & Gynaecology 125(3), 354-364
4. Wang X, Qin J, Wang L et al. L (2013) Effect of high-intensity focused ultrasound on sexual function in the treatment of uterine fibroids: comparison to conventional myomectomy. Archives of Gynecology & Obstetrics 288(4), 851-8
5. Zhang W, He M, Huang G et al. (2016) A comparison of ultrasound-guided high intensity focused ultrasound for the treatment of uterine fibroids in patients with an anteverted uterus and a retroverted uterus. International Journal of Hyperthermia 32(6), 623-9
6. Li J S, Wang Y, Chen J Y et al. (2017) Pregnancy outcomes in nulliparous women after ultrasound ablation of uterine fibroids: A single-central retrospective study. Scientific Reports 7(1), 3977
7. Wang F, Tang L, Wang L et al. (2014) Ultrasound-guided high-intensity focused ultrasound vs laparoscopic myomectomy for symptomatic uterine myomas. Journal of Minimally Invasive Gynecology 21(2), 279-84
8. Wang Y, Wang Z B, and Xu Y H (2018) Efficacy, efficiency, and safety of magnetic resonance-guided high-intensity focused ultrasound for ablation of uterine fibroids: Comparison with ultrasound-guided method. Korean Journal of Radiology 19(4), 724-732
9. Kim H-K, Kim D, Lee M-K et al. (2015) Three cases of complications after high-intensity focused ultrasound treatment in unmarried women. Obstetrics & Gynecology Science 58(6), 542-6.
10. Lyon et al. (In press) Ultrasound-guided High Intensity Focused Ultrasound Ablation for Symptomatic Uterine Fibroids: A Preliminary Clinical Experience. European Journal of Ultrasound.
11. Cun J P, Fan H J, Zhao W et al. (2019) Factors influencing MR changes associated with sacral injury after high-intensity focused ultrasound ablation of uterine fibroids. International Journal of Hyperthermia 36(1), 21-28.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	25/03/2019	Issue 3 of 12, March 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	25/03/2019	Issue 3 of 12, March 2019
HTA database (CRD website)	25/03/2019	n/a
MEDLINE (Ovid)	25/03/2019	1946 to March 22, 2019
MEDLINE In-Process (Ovid)	25/03/2019	1946 to March 22, 2019
MEDLINE Epubs ahead of print (Ovid)	25/03/2019	March 22, 2019
EMBASE (Ovid)	25/03/2019	1974 to 2019 March 22

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search
-

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Uterine Neoplasms/
2 Leiomyoma/
3 Myofibroma/
4 Myoma/
5 (uter* adj4 (neoplasm* or tumour* or tumor* or growth*)).tw.
6 (fibroma* or myofibroma* or leiomyoma* or leimyoma* or angioleiomyoma* or angiomyoma* or myoma*).tw.
7 (fibromyoma* or fibroleiomyoma).tw.
8 ((fibroid* or myoma*) adj4 (tumour* or tumor* or uter* or submucos* subseros* or intramural* or pedunculated or cervical or cervix or womb)).tw.
9 or/1-8
10 Ultrasonic Therapy/
11 High-Intensity Focused Ultrasound Ablation/
12 (((high* adj4 intensit*) or "high* intens*" or high?-intens*) adj4 focus* adj4 ultrasound*).tw.
13 HIFU.tw.
14 or/10-13
15 9 and 14
16 (Haifu and (JC or JC200)).tw.
17 (Mirabilis adj4 System).tw.
18 (ALPIUS adj4 "900").tw.
19 (exAblate* adj4 "2000").tw.
20 or/15-19
21 animals/ not humans/
22 20 not 21
23 limit 22 to english language

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Cheung V Y, Lam T P, Jenkins C R et al. (2016) Ovarian Reserve After Ultrasound-Guided High-Intensity Focused Ultrasound for Uterine Fibroids: Preliminary Experience. Journal of Obstetrics & Gynaecology Canada: JOGC 38(4), 357-61	Case series n=12 FU=1 year	Ovarian reserve does not seem to be affected by ultrasound-guided HIFU in the treatment of uterine fibroids.	Studies with more patients or longer follow-up are included.
Cho J Y, Kim S H, Kim S Y et al. (2013) Efficacy and safety of daily repeated sonographically guided high-intensity focused ultrasound treatment of uterine fibroids: preliminary study. Journal of Ultrasound in Medicine 32(3), 397-406	Case series n=24 FU=3 months	Daily repeated USgHIFU treatment of uterine fibroids may be a useful and safe method and can be used as a different option for HIFU treatment in patients who prefer treatment without anaesthesia or sedation.	Studies with more patients or longer follow-up are included.
Fruehauf J H, Back W, Eiermann A et al. (2008) High-intensity focused ultrasound for the targeted destruction of uterine tissues: experiences from a pilot study using a mobile HIFU unit. Archives of Gynecology & Obstetrics 277(2), 143-50	Case series n=12 FU=none	This study shows that a mobile ultrasound source can be used safely and effectively to destroy uterine tissues, such as fibroids, without major side effects.	Studies with more patients or longer follow-up are included.
He M, Jacobson H, Zhang C et al. (2018) A retrospective study of ultrasound-guided high intensity focussed ultrasound ablation for multiple uterine fibroids in South Africa. International Journal of Hyperthermia 34(8), 1304-1310	Retrospective case series n=81 FU=6 months	USgHIFU is safe and effective in treating patients with multiple uterine fibroids.	Studies with more patients or longer follow-up are included.
Lee J S, Hong G Y, Lee K H et al. (2017) Changes in anti-mullerian hormone levels as a biomarker for ovarian reserve after ultrasound-guided high-intensity focused ultrasound	Prospective case series	USgHIFU ablation for uterine fibroid and adenomyosis was effective without affecting ovarian reserve.	Studies with more patients or longer follow-up are included.

treatment of adenomyosis and uterine fibroid. BJOG: An International Journal of Obstetrics & Gynaecology 124 Suppl 3, 18-22	n=45 patients with uterine fibroids FU=1 year		
Lee J S, Hong G Y, Park B J et al. (2015) Ultrasound-guided high-intensity focused ultrasound treatment for uterine fibroid & adenomyosis: A single center experience from the Republic of Korea. Ultrasonics Sonochemistry 27, 682-687	Case series n=272patients with uterine fibroids FU=1 year	USgHIFU treatment for uterine fibroid and adenomyosis is an effective non-invasive therapy via the assessment of fibroid volume reduction, symptom improvement, UFS-QOL score increase, and acceptable level of side effects. Although preliminary experience of HIFU is encouraging, well-designed prospective trials and more clinical experiences are needed to ascertain the efficacy and safety of this new treatment.	Studies with more patients or longer follow-up are included.
Leung J H, Yu S C, Cheung E C et al. (2014) Safety and efficacy of sonographically guided high-intensity focused ultrasound for symptomatic uterine fibroids: preliminary study of a modified protocol. Journal of Ultrasound in Medicine 33(10), 1811-8	Case series n=20 FU=3 months	Sonographically guided high-intensity focused ultrasound using a modified protocol may be safe and effective for symptomatic uterine fibroids in selected patients to avoid skin burns.	Studies with more patients or longer follow-up are included.
Liu Y, Ran W, Shen Y et al. (2017) High-intensity focused ultrasound and laparoscopic myomectomy in the treatment of uterine fibroids: a comparative study. BJOG: An International Journal of Obstetrics & Gynaecology 124 Suppl 3, 36-39	Non-randomised comparative study n=166 (99 USgHIFU versus 67 laparoscopic myomectomy) FU=1 year	USgHIFU can be as efficacious as laparoscopic myomectomy (LM) and effectively improve patients' quality of life in the treatment of uterine fibroids, with fewer adverse effects and complications, shorter hospital stays, and quicker postoperative recovery compared with LM.	Studies with more patients or longer follow-up are included.
Luo J, Ren X, and Yu T (2015) Efficacy of extracorporeal ultrasound-guided high intensity focused ultrasound: An evaluation based on controlled trials in China. International Journal of Radiation Biology 91(6), 480-5	Review n=518	USgHIFU should be curtailed in resectable cases and be an alternative in inoperable cases; a combination regimen should not be recommended. The Response Evaluation Criteria in Solid Tumors can be applied to HIFU.	Studies with more patients or longer follow-up are included.
Meng X, He G, Zhang J et al. (2010) A comparative study of fibroid ablation rates using radio frequency or high-intensity focused ultrasound. Cardiovascular & Interventional Radiology 33(4), 794-9	RCT n=100 (USgHIFU versus 50 RFA) FU=1 week	Radiofrequency can be applied for the majority of fibroids. As a noninvasive therapy, USgHIFU could be the preferred method for the treatment of small, hypovascular fibroids.	Studies with more patients or longer follow-up are included.

Orsi F, Monfardini L, Bonomo G et al. (2015) Ultrasound guided high intensity focused ultrasound (USgHIFU) ablation for uterine fibroids: Do we need the microbubbles?. International Journal of Hyperthermia 31(3), 233-9	RCT n=33 (17 contrast-enhanced ultrasound [CEUS] + USgHFU versus 16 USgHIFU only) FU=1 year	CEUS was safe and effective in enhancing US guidance during HIFU ablation of uterine fibroids. Moreover, the use of CEUS during HIFU sonication increased the ablation efficacy, leading to a more relevant fibroid volume reduction at 1 and 3 months. This gap disappeared after 6 months, when there were no differences between the 2 groups of patients at MRI. However, USgHIFU represented a very effective method for the treatment of uterine fibroids, and the use of CEUS during HIFU procedure reduced the treatment time and treatment repetitions for incomplete fibroid ablation.	Studies with more patients or longer follow-up are included.
Parsons J E, Lau M P. H, Martin P J et al. (2017) Pilot Study of the Mirabilis System Prototype for Rapid Noninvasive Uterine Myoma Treatment Using an Ultrasound-Guided Volumetric Shell Ablation Technique. Journal of Minimally Invasive Gynecology 24(4), 579-591	Prospective case series n=73 FU=6 months	USgHIFU ablation with the prototype device demonstrated an excellent safety profile and produced clinically relevant NPVs in a mean total treatment time of under 4 minutes using the final validated treatment settings. Short-term clinical efficacy metrics assessed in subsets of patients were encouraging, and larger studies should be conducted to confirm these results.	Studies with more patients or longer follow-up are included.
Peng S, Hu L, Chen W et al. (2015) Intraprocedure contrast enhanced ultrasound: the value in assessing the effect of ultrasound-guided high intensity focused ultrasound ablation for uterine fibroids. Ultrasonics 58, 123-8	Case series n=68 FU=post treatment	CEUS clearly showed the size of fibroids and the non-perfused areas of the fibroid. Results from CEUS correlated well with results obtained from MRI.	Studies with more patients or longer follow-up are included. There were no comparisons between pre- and post-treatment results.
Peng S, Xiong Y, Li K et al. (2012) Clinical utility of a microbubble-enhancing contrast ("SonoVue") in treatment of uterine fibroids with high intensity focused ultrasound: a retrospective study. European Journal of Radiology 81(12), 3832-8	Retrospective non-randomised comparative study n=291 (162 USgHIFU + Sonovue versus 129 USgHIFU only) FU=post-treatment	SonoVue may enhance the outcome of HIFU ablation and can be used to assess the extent of treatment.	Studies with more patients or longer follow-up are included.

Qin J, Chen J Y, Zhao W P et al. (2012) Outcome of unintended pregnancy after ultrasound-guided high-intensity focused ultrasound ablation of uterine fibroids. International Journal of Gynaecology & Obstetrics 117(3), 273-7	Retrospective case series n=24 pregnancies FU=1 year	Pregnancy within 1 year after USgHIFU ablation of uterine fibroids appears safe; however, large scale studies are needed to confirm these data.	Studies with more patients or longer follow-up are included.
Ren X L, Zhou X D, Zhang J et al. (2007) Extracorporeal ablation of uterine fibroids with high-intensity focused ultrasound: imaging and histopathologic evaluation. Journal of Ultrasound in Medicine 26(2), 201-12	Case series n=119 FU=1 year	Imaging and histopathologic evidence directly validate USgHIFU ablation as an effective treatment of uterine fibroids.	Studies with more patients or longer follow-up are included.
Wang Y, Wang W, and Ye H (2014) Contrast-enhanced ultrasonography assessment of therapeutic efficacy for ultrasound-guided high-intensity focused ultrasound ablation of uterine fibroids: Comparison with contrast-enhanced magnetic resonance. Journal of Medical Ultrasound 22(1), 22-28	Case series n=67 FU=not reported	CEUS may be used as a convenient alternative to contrast-enhanced magnetic resonance (CEMR) in the assessment of therapeutic efficacy for USgHIFU ablation of uterine fibroids.	Studies with more patients or longer follow-up are included.
Wang Y-J, Zhang P-H, Zhang R et al. (2018) Predictive Value of Quantitative Uterine Fibroid Perfusion Parameters From Contrast-Enhanced Ultrasound for the Therapeutic Effect of High-Intensity Focused Ultrasound Ablation. Journal of Ultrasound in Medicine 04, 04	Case series n=263 FU=1 day	Quantitative parameters from CEUS are potentially useful for evaluating the therapeutic effect of HIFU ablation for uterine fibroids.	Studies with more patients or longer follow-up are included.
Wang X, Qin J, Chen J et al. (2013) The effect of high-intensity focused ultrasound treatment on immune function in patients with uterine fibroids. International Journal of Hyperthermia 29(3), 225-33	RCT n=120 (60 USgHIFU versus 60 myomectomy) FU=1 day	Short-term post-operative immune function is better preserved after USgHIFU treatment. Better preserved immune function may reflect a reduction in tissue trauma after USgHIFU treatment and contribute to reduced post-operative complications.	The main aim of this study was to evaluate the effect of USgHIFU on immune function in patients with uterine fibroids.
Wang W, Wang Y, Wang T et al. (2012) Safety and efficacy of US-guided high-intensity focused ultrasound for treatment of submucosal fibroids. European Radiology 22(11), 2553-8	Case series n=76 FU=median 30 months	USgHIFU ablation may be a safe and effective treatment for submucosal fibroids. Further studies are warranted to observe its influence on fertility.	Studies with more patients or longer follow-up are included.

Yin N, Hu L, Xiao Z B et al. (2018) Factors influencing thermal injury to skin and abdominal wall structures in HIFU ablation of uterine fibroids. International Journal of Hyperthermia 34(8), 1298-1303	Retrospective case series n=892 FU=not reported	Multiple logistic regression analysis revealed that abdominal wall thickness, total energy and abdominal wall scar were the most significant influencing factors that influenced minimal thermal injury of abdominal wall structures in USgHIFU ablation of uterine fibroids.	Studies with more patients or longer follow-up are included.
Zhang C, Jacobson H, Ngobese Z E et al. (2017) Efficacy and safety of ultrasound-guided high intensity focused ultrasound ablation of symptomatic uterine fibroids in Black women: a preliminary study. BJOG: An International Journal of Obstetrics & Gynaecology 124 Suppl 3, 12-17	Case series n=26 FU=post-treatment	USgHIFU is feasible and safe to use to treat symptomatic uterine fibroids in Black women.	Studies with more patients or longer follow-up are included.
Zhao W-P, Zhang J, Han Z-Y, et al. (2017) A clinical investigation treating different types of fibroids identified by MRI-T2WI imaging with ultrasound guided high intensity focused ultrasound. Scientific Reports 7(1), 10812	Retrospective case series n=172 FU=1 year	USgHIFU ablation of all types of fibroids were safe and effective.	Studies with more patients or longer follow-up are included.
Zhao W P, Chen J Y, and Chen W Z (2016) Dynamic contrast-enhanced MRI serves as a predictor of HIFU treatment outcome for uterine fibroids with hyperintensity in T2-weighted images. Experimental and Therapeutic Medicine 11(1), 328-334	Retrospective case series n=131 FU=post-treatment	Hyperintense uterine fibroids with slight and irregular enhancement in the arterial phase of dynamic contrast-enhanced MRI are suitable for USgHIFU treatment. By contrast, uterine fibroids with regular enhancement were associated with the lowest treatment efficacy and safety.	Studies with more patients or longer follow-up are included.
Zhao W P, Han Z Y, Zhang J et al. (2015) A retrospective comparison of microwave ablation and high intensity focused ultrasound for treating symptomatic uterine fibroids. European Journal of Radiology 84(3), 413-417	Retrospective comparative study n=73 (42 USgHIFU versus 31 MWA) FU=6 months	The safety and effectiveness of percutaneous MWA and USgHIFU in the treatment of uterine fibroids were similar; however, the median treatment time of PMWA was shorter than that of USgHIFU.	Studies with more patients or longer follow-up are included.
Zhao W P, Chen J Y, Zhang L et al. (2013) Feasibility of ultrasound-guided high intensity focused ultrasound ablating uterine fibroids with hyperintense on T2-weighted MR imaging. European	Retrospective case series n=282 FU=1 month	The heterogeneous and markedly homogeneous hyperintense fibroids were suitable for USgHIFU, and only the slightly homogeneous hyperintense fibroids should be excluded.	Studies with more patients or longer follow-up are included.

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Zhou X D, Ren X L, Zhang J et al. (2007) Therapeutic response assessment of high intensity focused ultrasound therapy for uterine fibroid: utility of contrast-enhanced ultrasonography. European Journal of Radiology 62(2), 289-94	Case series n=64 FU=1 year	CEUS is potentially useful for evaluating the early therapeutic effect of percutaneous HIFU ablation for uterine fibroids.	Studies with more patients or longer follow-up are included.
Zou M, Chen L, Wu C et al. (2017) Pregnancy outcomes in patients with uterine fibroids treated with ultrasound-guided high-intensity focused ultrasound. BJOG: An International Journal of Obstetrics & Gynaecology 124 Suppl 3, 30-35	Retrospective case series n=78 FU = 18 months	USgHIFU treatment can effectively treat patients with uterine fibroids who wish to have children; it could significantly reduce the preparation period for pregnancy after the operation. It can also improve the fertility of patients with a history of infertility and abnormal pregnancy and child-bearing, with no additional obstetric risks.	Studies including pregnancy outcomes after USgHIFU are already included.
Dimitrov D, Zhou K, Karamanliev M et al. (2018) Introducing clinical protocol for ultrasound-guided high-intensity focused ultrasound ablation of uterine fibroids in patients in Europe, provided from experienced Chinese center-prospective comparative. Biomedical Research (India) 29(17), 3378-3384	Comparative case series n=75 (26 Bulgarian vs 49 Chinese) patients (87 fibroids) Follow-up=1 year	The initial results of our study showed that contrast enhanced ultrasound clinical protocol for real time monitoring of efficacy and quality of the USgHIFU for uterine fibroid treatment that had been used in • Chinese centres may also be applicable for European patients.	Studies with more patients or longer follow-up are already included.
Fan H-J, Cun J-P, Zhao W et al. (2018) Factors affecting effects of ultrasound guided high intensity focused ultrasound for single uterine fibroids: a retrospective analysis. International Journal of Hyperthermia 35(1), 534-540	Retrospective case series n=207 patients Follow-up=post-procedure	The effect of ultrasound guided high intensity focused ultrasound treatment for single uterine fibroids is affected by multiple factors, and the uterine fibroids of hypointense on T2 weighted image, large size, mild enhancement on T1 weighted image and anteverted uterus can be easily ablated with high ablation efficiency.	Overall efficacy/safety were not the main outcomes of the study which aimed to explore factors associated with success. And larger case series already included.
Lee J S, Kim T E, Kim J H et al. (2018) Unintended pregnancies with term delivery following ultrasound-guided high-intensity focused ultrasound (USgHIFU) ablation of uterine fibroid and adenomyosis. Clinical and	Case series n=23 (11 uterine fibroids and 12 adenomyosis) Follow-up not reported	USgHIFU seems to have the effectiveness to precisely treat adenomyosis and uterine fibroid, allowing for normal reproduction. Well-designed prospective trials are needed to ascertain the safety of this treatment with pregnancy due	A study including more patients and reporting on the same outcomes is already

Experimental Obstetrics and Gynecology 45(6), 842-844		to the lack of large-scaled study.	included in Table 2.
Liu X, Xue L, Wang Y et al. (2018) Vaginal delivery outcomes of pregnancies following ultrasound-guided high-intensity focused ultrasound ablation treatment for uterine fibroids. International Journal of Hyperthermia 35(1), 510-517	Prospective case series n=174 patients Follow-up=mean 76 months	Ultrasound-guided HIFU ablation could be considered a promising clinical treatment for women with uterine fibroids and plans for future pregnancy, and vaginal delivery after ultrasound-guided HIFU ablation treatment appear to be feasible and safe.	A study including more patients and reporting on the same outcomes is already included in Table 2.