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REVIEW

High intensity focused ultrasound for the treatment of adenomyosis: selection criteria, efficacy, safety and fertility

Running head: HIFU treatment for adenomyosis

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Conflict of interest

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Abstract

Introduction: Adenomyosis is a disorder of uterus in which endometrial glands and stroma are present within the uterine musculature. The main clinical manifestations are dysmenorrhea and menorrhagia. Adenomyosis has a great impact on both the quality of life and fertility of women. The treatment of adenomyosis remains an immense challenge. *Material and methods:* Relevant articles were searched through MEDLINE, Pubmed between 2000 and March 2017. The search terms of adenomyosis, magnetic resonance imaging (MRI) features of adenomyosis, high intensity focused ultrasound (HIFU), Ultrasound-guided HIFU and MRgFUS were used. There were no language restrictions. *Results:* HIFU is a non-invasive local thermal ablation technique which has been used in the treatment of both focal and diffuse adenomyosis. Several case studies have demonstrated that HIFU presents low rate of minor and / or major complications and at the same time long symptom relief period. Multiple factors such as the enhancement type of the adenomyotic lesion, volume of the adenomyotic lesions, number of hyperintense foci on T2WI, location of the uterus, location of adenomyotic lesions, thickness of the abdominal wall and distance from the skin to the adenomyotic lesions contribute to the efficacy of HIFU. Consequently, based on these contributing factors, specific and strict selection criteria have been used in order to achieve higher efficacy. Thus, patients with pelvic endometriosis, adhesions between the bowel and the uterus, or an abdominal surgical scar wider than 10mm, are not suitable for HIFU treatment. Moreover, HIFU treated patients with adenomyosis, who wished to conceive, showed high conception and live birth rate. *Conclusion:* HIFU is a new and promising treatment option for patients with adenomyosis, but its efficacy, safety, cost-effectiveness and fertility outcome must be evaluated by randomised control trials.

Key words:

HIFU, high intensity focused ultrasound; adenomyosis; selection criteria; efficacy; fertility

Abbreviations:

HIFU, high-intensity focused ultrasound;

MRgFUS/MRgHIFU magnetic resonance imaging -guided HIFU

MRI, magnetic resonance imaging;

NPV, non-perfused volume;

NSAIDs, nonsteroidal anti-inflammatory drugs.

SIR Society of Interventional Radiology

USgHIFU ultrasound-guided HIFU

Key Message

High-intensity focused ultrasound (HIFU), a non-invasive technique, has been used to treat either focal or diffuse adenomyosis. Based on a small sample of case studies HIFU seems to be a promising treatment for patients with adenomyosis who wish to conceive. Further randomise control trials are required to determine its efficacy, safety and fertility outcome.

Introduction

Adenomyosis is a benign disorder of uterus. In 1860, German pathologist Carl von Rokitansky found endometrial glands in the myometrium and he provided the first description of this disorder and referred to it as “adenomyoma” (1). In 1972, Bird provided the modern definition of adenomyosis which is characterized by the benign invasion of endometrium into the myometrium. This produces a diffusely enlarged uterus which microscopically exhibits ectopic, non-neoplastic, endometrial glands and stroma surrounded by hypertrophic and hyperplastic myometrium (2). The main symptoms of adenomyosis include dysmenorrhea and menorrhagia; it also has a great impact on

fertility of women of childbearing age (3). Adenomyosis has a major adverse impact on a woman's quality of life, but the treatment for this disorder is still a big challenge.

The diagnosis of adenomyosis is suspected by clinical evaluation and confirmed with ultrasound and magnetic resonance imaging (MRI). The diagnostic criteria include focal or diffuse thickening of the uterine junctional zone or the presence of a low signal intensity myometrial mass with ill-defined borders (4). Pathological analysis showed that adenomyosis was characterized by the invasion of ectopic endometrial glands and stromal cells into the hypertrophic uterine smooth muscle. Because adenomyotic lesions are rich in proliferation of uterine smooth muscle, the lesions are presented as ill-defined low signal intensity areas on T2-weighted images on MRI. Hyperintense foci are another feature of adenomyosis shown on T2-weighted images on MRI. These bright foci correspond to heterotopic endometrium tissue or glands, small cysts, and hemorrhages within the lesion. The ectopic endometrial glands and stromal cells in the lesions does not show significant periodic changes on MRI because the ectopic endometrium is similar to the basal layer of the endometrium which does not respond to hormone stimulation. MRI can clearly show the appearance of adenomyosis with diffuse or focal widening of the junctional zone. Based on the appearance of the lesions on MRI, adenomyosis is defined as diffuse or focal adenomyosis (5).

Traditionally treatment of adenomyosis is medical and/or surgical. Currently, hysterectomy remains the definitive cure for adenomyosis. As the boundary of the adenomyotic lesion is unclear, it is difficult to remove the lesion completely, conservative surgery has proven to be effective only in around 50% of patients and the recurrence rate is very high (6). Over the last decade, uterine artery embolization (UAE) and medical treatments including levonorgestrel-releasing intrauterine device, gonadotropin-releasing hormone analogues (GnRHa), and oral contraceptives, as well as nonsteroidal anti-inflammatory drugs (NSAIDs) have been used in the management of this disorder. However, the side effects of these treatments and the high recurrence after medical therapy cessation have limited the effects of these treatments (7,8). In addition, there is no specific treatment for patients who want to retain their uterus or wish to remain fertile. Thus, it is of great importance to explore new, more effective, safe and less invasive treatment strategies for these patients. In this review, we searched the relevant articles through MEDLINE, Pubmed between 2000 and March 2017. The search terms of adenomyosis, magnetic resonance imaging (MRI) features of adenomyosis, high intensity focused ultrasound (HIFU), Ultrasound-guided HIFU and MRgFUS were used. There were no language restrictions. The aim was to review the benefits and/or harms from clinical studies of HIFU.

High intensity focused ultrasound (HIFU) technology

High intensity focused ultrasound (HIFU) or focused ultrasound surgery is a novel non-invasive local thermal ablation technique. The possibility that HIFU might be developed as a local thermal ablation technique was first introduced by Lynn et al. (9) in the 1940s, but this technique was not developed at that time because there was no adequate targeting method. With the development of diagnostic imaging, HIFU received international attention again in the 1980s. The mechanisms of HIFU treatment involve thermal, cavitational and mechanical effects. The ultrasound beams are produced by a concave shaped extracorporeal transducer (Fig.1). During treatment, the ultrasound beams penetrate through the tissue in the acoustic pathway and is then focused on the target tumor within the body. When the temperature increases to 65□, coagulative necrosis occurs in the target tumor (10). The acoustic focus region of the transducer is 5mm wide and 8mm long, and the treatment is performed under the guidance of ultrasound or MRI.

MRI has excellent anatomic resolution and MRI-based thermal mapping offers real-time temperature monitoring during HIFU treatment; thus it enhances safety and efficacy during HIFU treatment. Ultrasound was the first diagnostic imaging technique introduced to monitor HIFU treatment. Ultrasound offers real-time anatomic imaging and grey scale change during treatment and is thus a reliable indicator in monitoring response to HIFU treatment (11). Ultrasound-guided HIFU (USgHIFU) differs from MRI-guided HIFU (MRgFUS/MRgHIFU) in that it is silent and does not require the patient to be enclosed in a confined space. During treatment the patient lies in cold degassed water which allows for an enhanced acoustic window and simultaneously reduces the risk of skin burn. The patient is in a prone position on the HIFU table and a nurse and a physician are sitting close to the patient. The patient experiences a friendly environment and can comfortably communicate with the nurse or the physician. Compared to MRgFUS/MRgHIFU, USgHIFU is less costly. In China, the total cost of USgHIFU treatment per patient ranges from US$2000-$3000, while the mean cost of MRgFUS per patient is US$15,274 (12).

Selection criteria for HIFU treatment of adenomyosis

In clinical practice the following inclusion criteria have been proposed for the selection of women with adenomyosis suitable for HIFU treatment: (10,13): (1) patients present with dysmenorrhea and /or menorrhagia; (2) diagnosis of adenomyosis confirmed by MRI; (3) size of the adenomyotic lesion thicker than 3 cm; (4) patients agree to undergo pre- and post-HIFU MRI; (5) patients able to communicate with physicians.

Exclusion criteria: (1) menstruating, pregnant or breastfeeding women; (2) patients with suspected or confirmed uterine malignancy; (3) patients with pelvic endometriosis; (4) patients with abdominal surgical scar width greater than 10mm; (5) patients with bowel adhesions to the uterus or the abdominal wall.

Efficacy and safety of HIFU treatment for adenomyosis

The history and development of HIFU as a treatment for adenomyosis has proven that hypertrophic uterine smooth muscle tissue in the adenomyotic lesion is sensitive to HIFU and thus HIFU is an ideal way to treat adenomyosis (14). The initial study of HIFU treatment for adenomyosis was performed during laparoscopic surgery, using a hand-held focused ultrasound transducer, followed by hysterectomy(15). Seven patients with focal adenomyosis who gave their consent to undergo hysterectomy were enrolled to investigate the feasibility of HIFU treatment. Histological examination of the resected uteri from the seven patients confirmed that coagulative necrosis occurred in every adenomyotic lesion. 2,3,5-triphenyltetrazolium chloride staining showed clear boundaries between the treated and the non-treated regions; the cells in the treated region were found to be non-viable. This study suggests that HIFU could accurately ablate adenomyotic lesions.

In 2007, Fan et al.(10) commenced a study to assess the safety and efficacy of HIFU treatment for adenomyosis. Ten patients with symptomatic adenomyosis were treated with MRgHIFU under conscious sedation. All the patients completed HIFU treatment and the post-HIFU MRI evaluation showed that an average non-perfused volume ratio of 62.5±21.6% was achieved. All patients experienced symptom relief and no complications occurred. Fukunishi et al. (16) treated 20 patients with adenomyosis using MRgFUS and the results showed that all patients had symptom relief during 6 months follow-up. At the same time, Zhou et al. (17) treated 78 adenomyosis patients who complained of both dysmenorrhea and menorrhagia, using USgHIFU. Sixty nine attended follow-up for at least 18 months. With an average of 24.2 months follow-up, significant symptom relief was observed in 62 patients (89.9%). An MRI evaluation 1 day after HIFU showed coagulation necrosis in 60 adenomyotic lesions in 69 patients, with an non-perfused volume (NPV) ratio, which was defined as the non-perfused volume divided by the adenomyotic volume, higher than 50% in 47 lesions and a ratio lower than 50% in 13 lesions. Although MRI did not show any changes in the lesions in 9 patients, during the follow-up period 6 of them reported symptom relief. During HIFU treatment 66 patients complained of pain in the treated region, with a pain score ranging from 0 to 4. The patients tolerated the treatment well and no severe complications occurred. Over the last few years, 346 patients with adenomyosis have been treated with USgHIFU in Incheon Christian Hospital, Korea. Lee et al. retrospectively analyzed the treatment results and reported that the shrinkage rate of the uterus at 3, 6, and 12 months after HIFU was

43.99%, 47.01%, and 53.98%, respectively. The reduction rate of the symptom severity score at 3, 6, and 12 months after HIFU was 55.61%, 52.38%, and 57.98%, respectively. The quality of life of these patients has been significantly improved after HIFU treatment (18). These studies suggest that HIFU can be used for treatment of adenomyosis but further studies are needed, especially if HIFU is superior to other treatment options, i.e. intrauterine device with progestogen.

Recently, several centers further investigated the middle and long-term efficacy of HIFU treatment for adenomyosis (Table 1). Studies have shown that the non-perfused volume ratio of adenomyosis is related to the long-term efficacy of the treatment. Liu et al.(19) investigated the clinical predictors of long-term success in the HIFU treatment of adenomyosis. In that study, 230 patients with adenomyosis who had dysmenorrhea and/or menorrhagia were treated using USgHIFU. The average NPV ratio calculated immediately after HIFU was 57.4±24.4%. Among the treated patients, 208 attended follow-up with a median time of 40 months (range: 18-94 months). 83.2% of treated patients reported varying degrees of symptomatic relief of dysmenorrhea based on the visual analog scale (VAS) scores and 71.0% of the patients were asymptomatic during follow-up. Dysmenorrhea recurred in 45 patients at the median of 12 months after HIFU. The results were further analyzed and it was found that older patients with a higher NPV ratio were more likely to achieve long-term clinical success. From October 2010 to December 2011, 350 patients with symptomatic adenomyosis were treated with HIFU in Suining Central Hospital of Sichuan, Three Gorges Central Hospital of Chongqing, and Fuling Central Hospital of Chongqing. All patients underwent an MRI one day after HIFU, achieving an NPV ratio average of 72.7 ± 18.0% (range：5.0%–99.0%). Among them, 224 patients completed a 2 year follow-up; the relief rate of dysmenorrhea at 2 years was 82.3%, and the relief rate of menorrhagia was 78.9% (10). The re-intervention rate was lower in patients with a higher NPV ratio. Zhang et al. further compared the efficacy of HIFU treatment for focal and diffuse adenomyosis (20). The follow-up results showed that the patients with diffuse adenomyosis had significantly less relief from dysmenorrhea at 3-months, but no other significant difference was observed between the two groups. The post-HIFU MRI examination showed no significant difference in NPV ratio between the two groups. The NPV ratio for focal and diffuse adenomyotic lesions were 71.7±19.3% and 71.6 ±19.1%, respectively. Therefore, HIFU treatment is effective for both focal and diffuse adenomyosis.

The safety of HIFU treatment has been demonstrated in many studies. Common severe adverse effects or complications of HIFU treatment of adenomyosis include skin burns and nerve injury. In the initial stages of this noninvasive technique, skin burns and leg pain were frequently reported (16,17). The growth in gynaecologists' experience and the improvement in technology has resulted in a reduction in the rate of complications.

Recently, Liu et al. and Shui et al. reported that common adverse effects after HIFU treatment include pain in the treated region, vaginal discharge, and mild sacral pain. Skin burns, leg pain, or numbness of the lower limbs were reportedly seen in less than 1% of the treated patients (18,19). Based on the Society of Interventional Radiology (SIR) classification system, most of these adverse effects or complications were classified as class A or B and subsided within two weeks without any treatment. From 2011 to 2015, 10310 patients with adenomyosis were treated with the JC model of USgHIFU in China (Fig. 2). When the adverse effects were retrospectively reviewed it was found that a total of 2367 patients (23.0%) presented with 4136 adverse effects (Table 2). In these patients, the most common adverse effect was lower abdominal pain, which accounted for 21.9% (2253/10310) of the adverse effects; another frequent adverse effect was minimal vaginal discharge, which accounted for 11.0% (1136/10310); sacrococcygeal pain was reported by 712 out of 10310 patients, which accounted for 6.9% of the adverse effects. The adverse effects of lower abdominal pain, vaginal discharge, and sacrococcygeal pain were classified as class A based on the SIR classification system and these adverse effects subsided in most of the patients without any further treatment, within 7 days. Among these patients, 13 (0.1%) complained of leg pain or numbness after HIFU which lasted from two weeks to two months. This adverse effect was classified as class B. The rest of the adverse effects, including skin burns in 21(0.2%) patients, and bowel injury in 2 (0.02%) patients, were classified as class C or class D. During HIFU treatment procedure, a degassed water balloon is used to compress the abdominal wall and displace the bowel from the acoustic pathway; inadequate coupling between the abdominal wall and the degassed water balloon results in heat generation which causes skin burns. Among the 21 patients with skin burns, 7 cases had superficial second degree skin burn; 14 patients with second or third degree skin burns had surgical resection to remove the burnt tissue. A previous study has shown that the rate of skin burns related to HIFU was significantly higher in patients with abdominal surgical scars which may be as a result of denervated tissue. These patients may thus not have felt pain when the scars were heated (21). Therefore, poor skin preparation, less blood supply in scar tissue, and skin sensory loss could explain the increased number and severity of skin burns in the patients with abdominal surgical scars. By regularly checking the skin or moving the transducer down in the water tank, the rate of these skin complications can be further decreased. In comparison to earlier studies, the rate of leg pain or numbness of the leg related to HIFU decreased dramatically;the reason for the leg pain or the numbness of the leg was because of temporary sacral nerve irritation. By taking NSAIDs this pain generally subsided within two weeks.

Bowel injury is a rare complication that can occur in HIFU treatment. Of 10,310 adenomyosis patients treated with HIFU, two (0.02%) patients developed an intestinal perforation at 10 days and 20 days respectively; these were repaired surgically. After a

thorough review of these two cases it was found that both patients did not follow the protocol for bowel preparation and excessive energy was deposited in the lesions. Care should be taken to avoid this two situations.

Based on evidence from the literature and the large number of patients treated in China, it was found that the development of this noninvasive technique has resulted in a lowering of the rate of adverse effects when treating adenomyosis (22,23). The complication rate is low and thus USgHIFU can be used safely and effectively to treat patients with adenomyosis. Certain studies found that some patients with adenomyosis were difficult to treat and presented with adverse effects (16,19). It is therefore important to to optimize the selection criteria which can indicate patients with adenomyosis suitable for treatment with HIFU. Gong et al. investigated the factors that affect the ablative efficiency of HIFU treatment for adenomyosis (24). They retrospectively reviewed 245 patients with adenomyosis who underwent USgHIFU and found that the enhancement type of the adenomyotic lesion, the thickness of the abdominal wall, the volume of the adenomyotic lesions, the number of hyperintense foci on T2WI, the location of the uterus, and the location of adenomyotic lesions all had a significant relationship to the NPV ratio. The distance from the skin to the adenomyotic lesions and the factors listed above all had a linear relationship with the energy efficiency factor (EEF, which was defined as the amount of energy which is needed for ablating 1 cubic millimeter (mm^3) of the adenomyotic lesion). This study indicated that multiple factors are related to the efficacy of HIFU treatment. Based on the results, if we select patients with a poor blood supply to adenomyotic lesions, thinner abdominal walls, larger lesion volume, less hyperintense foci on T2WI, and lesions located in the anterior wall of the uterus, it is easier to achieve a larger NPV ratio. Therefore using these factors to select patients for HIFU is crucial in ensuring the success of the treatment.

In clinical practice it was observed that some cases did not achieve symptom relief, even if the adenomyotic lesions had been successfully ablated. It is thus assumed that the symptoms of menorrhagia and dysmenorrhea are not only caused by adenomyosis, but also by pelvic endometriosis. Because endometriotic lesions are small, HIFU could not be used successfully. Therefore, patients with adenomyosis and pelvic endometriosis are contraindicated for HIFU. Further studies will have to be executed in this regard.

Another important factor affecting the use of HIFU ablation for adenomyosis is abdominal surgical scars. Scar tissue is more fibrotic and less vascular than normal tissue; it is thus more difficult for ultrasound to penetrate scars. Ultrasound energy is readily absorbed by scar tissue, resulting in thermal damage to skin. This might consequently affect the efficacy and safety of HIFU treatment. Xiong et al. (21) retrospectively reviewed 534 patients with adenomyosis and compared the therapeutic efficacy and safety

of USgHIFU treatment for adenomyotic patients with or without prior abdominal surgical scars. Among 534 patients, 118 had scars. The average width of the scar was 5.6 ± 2.2mm, the length 125.3 ± 26.5mm. MRIs executed on the day following HIFU showed an average NPV ratio of 74.8±27.8% in patients without abdominal scars; the ratio was 75.6±22.3% in patients with scars. However, the incidence rate of skin burns was significantly higher in patients with scars than that in the group without scars (2.5% vs. 0.2%, $P<0.05$). Three cases of second or third degree skin burns occurred in the group of patients with scars; two patients had scar width greater than 10mm. Thus, if the width of the scar is greater than 10mm, the patient is not suitable for HIFU treatment.

Bowel injury during HIFU treatment for adenomyosis is a rare complication but the consequences can be devastating (22). Adenomyosis and endometriosis can cause pelvic adhesions and if the bowel adheres to the uterus or the abdominal wall it will significantly increase the risk of bowel injury. Thus, these patients are not indicated for HIFU.

Fertility following HIFU treatment of adenomyosis.

The association between infertility and adenomyosis is not yet fully understood. Many studies have shown that adenomyosis affects fertility negatively. Thus treatment for adenomyosis could improve fertility (3, 25,26). However, there is no consensus on the treatment of patients with adenomyosis who wish to have children (27). Fertility has always been a main consideration in the development of HIFU treatment for patients with adenomyosis. HIFU treatment is performed under guidance of ultrasound or MRI; the lesion can be precisely ablated, thereby preserving surrounding myometrium and endometrium and ensuring less damage to the uterus (Fig. 3). By that way and because of the lack of scar on uterus wall patients can attempt to conceive much sooner than after surgical treatment. Moreover, the risk of uterine rupture during pregnancy or delivery is lower than following surgical treatment (28).

In 2006, Ricabinovi et al. reported a 36-year-old patient with an 84 cm^3 focal adenomyotic lesion who had difficult conceiving (29). After one session of MRgFUS treatment, a non-perfused volume of 33 cm^3 was achieved. The patient reported a significant reduction in menorrhagia and a remarkable decrease in size of the lesion was found 6 weeks after treatment. The patient conceived spontaneously and delivered a healthy term infant via vaginal delivery. Zhou et al.(30) recently completed a follow-up of 68 HIFU treated adenomyosis patients who wished to conceive. Of these 68 patients, 54 conceived at a median of 10 months (range: 1 to 31 months) post-HIFU, and of these 21 delivered healthy babies. No uterine rupture occurred during gestation or delivery. During a follow-up of 52 adenomyosis patients who wanted to conceive treated with HIFU from April 2011 to February 2016 (Chongqing, China), 20 conceived at a median of 8.75 months after HIFU, and 11 delivered healthy babies at term. No uterine rupture occurred during gestation or delivery. Although the sample size is small, preliminary results

showed that HIFU treatment does not increase the risk of complications during pregnancy and delivery. In addition, it was observed that patients with adenomyosis and primary infertility, conceived spontaneously after HIFU treatment and delivered term babies. The results suggested that HIFU seems to be a safe treatment option for patients who wish to conceive, however, there is an urgent need for randomized clinical trials (RCTs) comparing HIFU to other treatment options such as hormone intrauterine device etc.

In summary, HIFU, a non-invasive technique, has been used more frequently in the treatment of adenomyosis. HIFU can be used for the treatment of either focal or diffuse adenomyosis. Long-term symptom relief is dependent on a high NPV ratio although many other factors may affect the efficiency of HIFU treatment of adenomyosis. Patients with pelvic endometriosis, adhesions, or scars greater than 10mm in width are contraindicated for HIFU. HIFU seems to be a viable option for adenomyosis patients but its indications, efficacy, safety, cost-effectiveness and fertility outcome must be evaluated by randomised control trials before applying it widely in clinical practice.

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Legends

Figure 1. JC model of ultrasound-guided high-intensity focused ultrasound tumor therapeutic system.

Figure 2. The number of patients with adenomyosis treated using JC model of USgHIFU in China over the last five years.

Figure 3. Contrast MRI obtained from a 32-year-old patient with adenomyosis. A. Sagittal view of MRI before HIFU treatment showed the adenomyotic lesion located on the anterior wall of the uterus and contrast enhancement was observed in the lesion. B. Sagittal view of MRI obtained 1- day after HIFU showed the adenomyotic lesion located on the anterior wall of the uterus was ablated without damage to the surrounding myometrium.

Table 1. Evaluation of treatment efficacy of patients with dysmenorrhea after high-intensity focused ultrasound (HIFU).

Table 2. Society of Interventional Radiology (SIR) classification of adverse effects of 10310 patients with adenomyosis treated with ultrasound-guided high-intensity focused ultrasound (USgHIFU).

Tables

Table 1. Evaluation of treatment efficacy of patients with dysmenorrhea after high-intensity focused ultrasound (HIFU).

Authors (Reference)	Interventions	No. of cases	Follow-up time (m)	Effective rate
Fukunishi H. et al. (2008) (10)	MRgFUS	20	6	100%
Zhou M. et al. (2011) (11)	USgHIFU	69	24.2	89.9%
Shui L. et al. (2015) (14)	USgHIFU	203	24	82.3%
Liu X. et al. (2016) (13)	USgHIFU	208	40	83.2%

Note:Dysmenorrhea was scored in accordance with the standards of Visual Analogue Scale (VAS). USgHIFU ultrasound-guided HIFU. MRgFUS, magnetic resonance imaging -guided HIFU; USgHIFU, ultrasound-guided HIFU.

Table 2. Society of Interventional Radiology (SIR) classification of adverse effects of 10310 patients with adenomyosis treated with ultrasound-guided high-intensity focused ultrasound (USgHIFU).

SIR class	Description	No. of effects	Incidence rate	Adverse effects
A	No therapy, no consequences	2253 1136 712	21.9% 11.0% 6.9%	Lower abdominal pain Vaginal discharge Sacrococcygeal pain
B	Nominal therapy, observation, no consequences	13	0.1%	Leg pain or numbness
C	Required therapy, minor hospitalization (<48 h)	21	0.2%	Skin burns
D	Major therapy, unplanned increase in level of care, prolonged hospitalization (>48 h)	2	0.05%	Bowel injuries
E-F	Permanent adverse sequelae; Death	0	0	

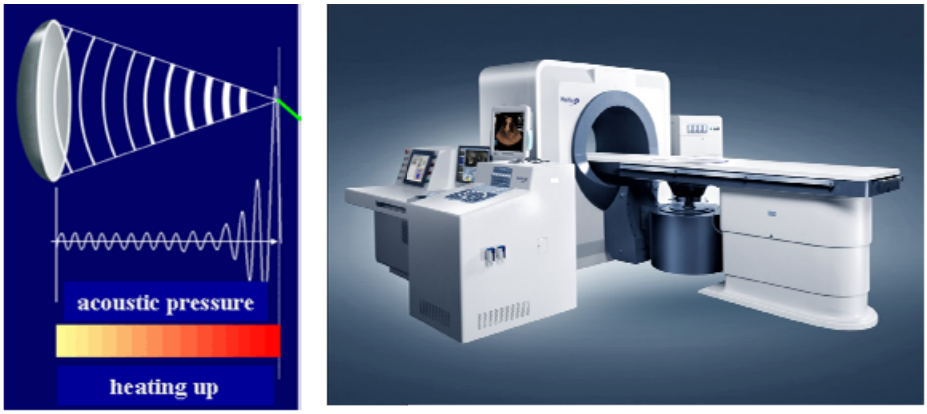

Figure 1. JC model of ultrasound-guided high-intensity focused ultrasound tumor therapeutic system.

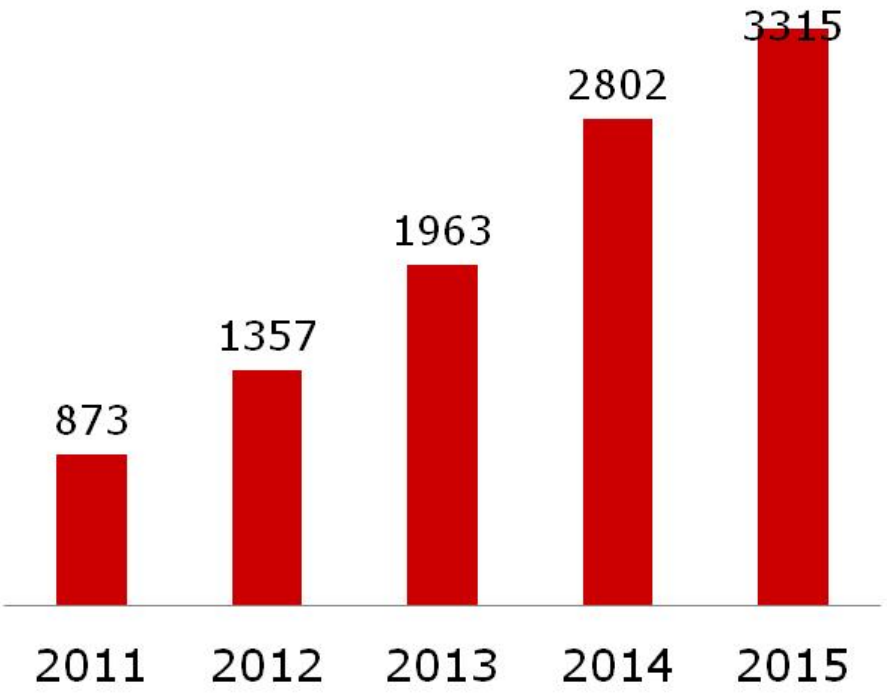

Figure 2. The number of patients with adenomyosis treated using JC model of USgHIFU in China over the last five years.

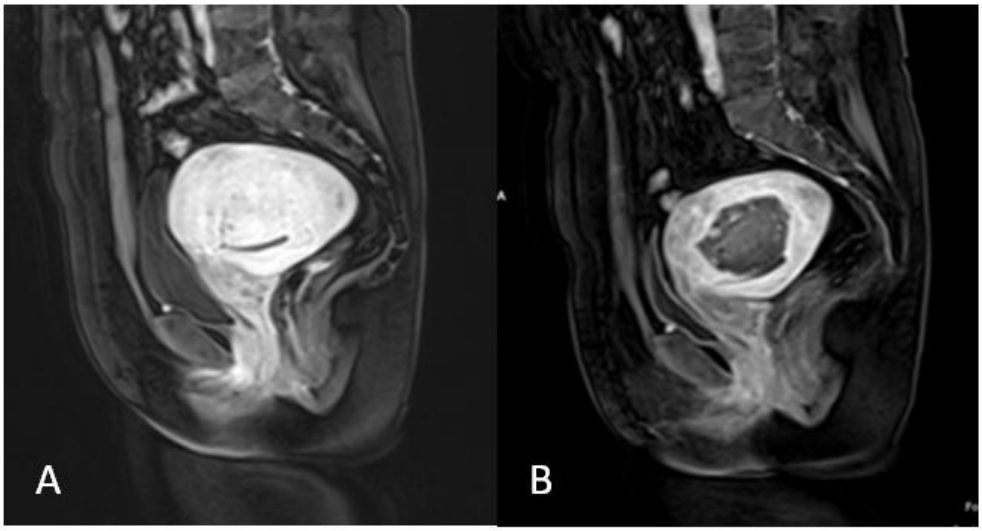

Figure 3. Contrast MRI obtained from a 32-year-old patient with adenomyosis. A. Sagittal view of MRI before HIFU treatment showed the adenomyotic lesion located on the anterior wall of the uterus and contrast enhancement was observed in the lesion. B. Sagittal view of MRI obtained 1- day after HIFU showed the adenomyotic lesion located on the anterior wall of the uterus was ablated without damage to the surrounding myometrium.