

Original Article

500 Cases of High-intensity Focused Ultrasound (HIFU) Ablated Uterine Fibroids and Adenomyosis

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ABSTRACT

Objective: Clinical outcomes of 500 high-intensity focused ultrasound (HIFU)-treated uterine fibroids and adenomyosis are analyzed and presented.**Materials and methods:** This is a retrospective cross-sectional analysis from a single tertiary medical center. From April 2015 to October 2018, 546 cases were enrolled for the study. After excluding 46 patients with less than 3 months of follow-up period, there were 404 fibroids, 149 adenomyosis and 53 mixed conditions entered for analysis. The patients' uterine fibroids and adenomyosis were treated by HIFU according to Chongqing Haifu protocol, with 12 cm diameter transducer of focal length 10–16 cm at 0.8 or 1.6 MHz T2-weight MRI imaging was rendered prior to and 3 month post treatment to assess lesion volume change using non-perfusion volume, which was the primary outcome. Secondary outcomes including quality of life, subjective satisfaction, adverse events and pregnancy rate were determined using self-reported questionnaires. The mean follow up period ranged from 3 to 38 months with an average of 21 months.**Results:** Three months after HIFU-treated uterine fibroids and adenomyosis, the lesion size reduced 40.2% and 46.3%, respectively. Symptoms all improved with better quality of life for the fibroid group, while those with adenomyosis or combined diseases benefit the most from pain control. Serum CA125 decreased significantly for all studied groups, and LDH only showed improvement for fibroids group. Number of adverse events is comparable to Chongqing data (approximately 10.2%), with mostly mild and self-resolving conditions. No permanent sequelae or death was documented. Twelve pregnancies are reported in this cohort.**Conclusion:** HIFU is safe and effective in treating uterine fibroids and adenomyosis. The results are reproducible if standardized treatment schedules are followed. It is a promising treatment alternative with the advantages of precision, non-invasiveness, rapid recovery and readiness for pregnancy.© 2020 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Uterine fibroids and adenomyosis are common benign pathology condition of the female, especially in childbearing age. The incidence ranges from 20 to 40% in reproductive aged women [1]. For this reason, they may gravely affect the fertility of women and cause cyclic menstruation symptoms such as dysmenorrhea and hypermenorrhea. Although there are various medications available for fibroid treatment including hormonal GnRH treatment and Ulipristal acetate, these methods of control are temporary and

sometimes futile in resistant cases. The counselling of High-intensity Focused Ultrasound (HIFU) ablation for uterine fibroids involve discussions on surgical options, such as open laparotomy or laparoscopic myomectomy. The patient is advised also on the risk of recurrent growth and re-intervention and medications with adverse or undesirable side-effects.

HIFU ablation presents an attractive option to conventional and surgical medicine, as it is non-invasive, requires minimal hospitalization, has no surgical wound, and has good relief and outcome in many patients. Social and economic cost in days lost of work and production are minimized compared to open surgery. Other growing applications of HIFU ablation include liver cancer, osteosarcoma and solid tumors such as the kidney, breast, thyroid and prostate [2,3].

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At Kaohsiung Medical University Hospital (KMUH), after diagnosis of fibroids and adenomyosis of symptomatic women, discussion ensues on the multiple available options for treatment. Usually medical therapy is instituted for symptom relief, although all alternatives including surgery is also discussed. Analgesic medication such as non-steroidal anti-inflammatory drugs (NSAIDs) is given for dysmenorrhea while menorrhagia may be treated with oral contraceptive pills, GnRH agonist or Ulipristal acetate. Patients are made aware that myomectomy may remove the tumor, however recurrence still occurs. Often the women desire uterine preservation and integrity for potential future childbearing, and if medical treatment is futile, many patients prefer minimal-invasive or non-invasive treatment. After consideration of all available options, patients consent to receive ultrasound-guided high-intensity focused ultrasound (USg-HIFU) ablation therapy. HIFU ablation is performed according to the JC tumor therapeutic system, Chongqing Haifu Technology (Chongqing Haifu Medical Co. Ltd, China) [1]. We here report the clinical outcomes of 500 HIFU treated cases for uterine fibroids and/or adenomyosis, demonstrated by lesion volume changes, symptoms relief by questionnaire scores, pregnancy outcomes and adverse events.

Material and methods

From April 2015 to October 2018, 546 patients received HIFU ablation of uterine fibroids and adenomyosis at KMUH. Of the 546 patients, 500 were followed for at least 3 months. Those who were pregnant, younger than 18 years old, unable to communicate, with suspected or known malignancy, infection, unable to lie prone for extended periods, with extensive scar tissue on abdomen or connective tissue disorders or unable to be followed for at least 3 months were excluded (Fig. 1). All remaining patients who opted for HIFU after failed response to conservative medical treatment were included in this retrospective analysis. Patient characteristics, uterus position, lesion details and HIFU procedures were depicted in Table 1. MRI was the main imaging tool for objective assessment of lesion size change before and after HIFU. Uterine fibroids appear with low-signal intensity on T2W images and isointense to the myometrium on T1W images. There are well-defined borders to the surrounding myometrium. Adenomyosis has ill-defined borders with scattered ectopic glandular endometrial tissues embedded, appearing hyperintense on T2W images. The lesion is more diffused with thickened junctional zone to the endometrium. Very often, fibroids and adenomyosis can coexist in the same patients with both above-mentioned features presented. Pre-HIFU symptoms were assessed and listed in Table 2 and Fig. 2. The averaged follow-up duration was 21 months with a range of 3–38 months. The project was approved by KMUH Institutional Review Board (IRB), by which relevant guidelines and regulations were followed accordingly.

Pre-HIFU preparations included electrocardiogram (EKG), Chest X-ray (CXR), a 3-day clear liquid diet and laboratory tests for complete blood count (CBC), renal function, liver function, coagulation profile, serum lactate dehydrogenase (LDH), cancer antigen 125 (CA125), urine routine, urine pregnancy test. The patient was admitted the day before operation and fasted 12 h prior. Abdomen skin was prepared by shaving below the umbilicus and down to the perineal area. HIFU ablation was performed using the JC USg-HIFU tumor therapeutic system (Chongqing Haifu Medical Co. Ltd., China). The 20 cm diameter piezoelectric transducer has a focal length 10–16 cm operating at 0.8 or 1.6 MHz with a focal region of $1.5 \times 1.5 \times 10$ mm. The built-in B-mode ultrasound (Esoate MyLab70, Genoa, Italy) provided real-time imaging. After patients were comfortable in prone position, the intravenous conscious anesthesia was administered by an anesthesiologist to maintain Ramsay level 3–4 sedation. A water balloon was positioned anterior to the abdomen to push the intestines away from the sonication treatment pathway and water bag infusion instilled accordingly. Oxytocin (Oriental Chemical Works Inc., New Taipei, Taiwan) infusion of 80 Units in 500 ml saline water was infused for uterine vessel contraction, thereby decreasing vascularity.

After targeting the lesion and composing the treatment plan, HIFU proceeded noting any discomfort. The protocol of ablation started from the tumor center with point by point circumferentially outward leaving a 1.5 cm margin to the surrounding normal tissue or serosal layer of the uterine corpus. Ablation treatment was given to achieve massive grey scales changes or coagulative necrosis on ultrasound. Resting intervals for several seconds occurred after every 100 s of ablation. After HIFU, the patient was instructed to stay prone for at least 2 more hours with urinary bladder still distended allowing sufficient cooling time. Symptom-relieving medications such as NSAIDs, steroids and vitamin B12 for neural protection or antibiotics were prescribed as needed. Urine output, urine color, post-procedure renal functions were surveyed. Patients were usually discharged the next day.

Patients were followed up 1 week, 3 months, 6 months and every 6 months afterwards after HIFU to assess efficacy and tumor reduction, evaluated by repeated MRI (Fig. 3). Self-reported symptom scores were accessed at 3 months post-HIFU using multiple questionnaires: uterine fibroid symptom health-related quality of life (UFS-QOL) [4], visual analogue score (VAS) [5], international consultation on incontinence modular questionnaire-short form (ICIQ-SF) [6], pelvic organ prolapse distress inventory 6 (POPDI-6) [7], urogenital distress inventory-6 (UDI-6) [8], incontinence impact questionnaire-7 (IIQ-7) [8], overactive bladder symptom scores (OABSS) [9] and female sexual function index (FSFI) [10]. Serum LDH and CA 125 changes were also investigated. Pregnancy cases were recorded. These results were compiled in Table 2.

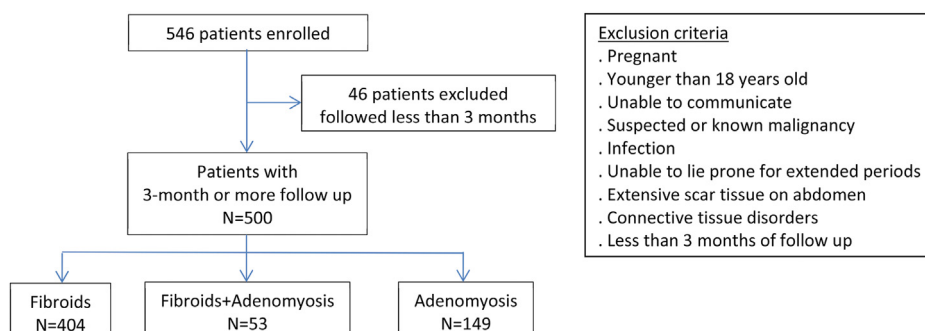


Fig. 1. Case numbers of fibroids only, adenomyosis only and combined disease.

Table 1
Patient characteristics, lesion and treatment details.

Characteristics	Uterine fibroids	Adenomyosis
No. of patients	404	149
Age range (years old)	40.7 ± 5.9	41.7 ± 5.3
Body mass index (kg/m ²)	22.7 ± 3.8	23.2 ± 4.5
Position of uterus		
Ante-verted (%)	71.1 (287/404)	72.5 (108/149)
Retro-verted (%)	18.5 (75/404)	21.5 (32/149)
Neutral (%)	10.4 (42/404)	6.0 (9/149)
Position of lesion		
Posterior wall (%)	34.7	53.1
Anterior wall (%)	35.7	35.2
Fundal (%)	8.7	9.3
Anterior wall and Posterior wall (%)	20.9	2.4
Treatment details		
Sonication power (W)	366.2 ± 56.4	373.1 ± 47.8
Total duration (min)	120.2 ± 63.0	104.0 ± 63.6
Sonication time (s)	908.0 ± 519.9	726.7 ± 433.8
Sonication time/hour (s/h)	453.4 ± 135.4	434.4 ± 206.8
Exposure energy (J)	346,331.9 ± 281,401.9	284,044.6 ± 194,732.2
Before treatment		
Size of uterus (cm ³)	599.6 ± 546.4	473.7 ± 346.5
Size of lesion (cm ³)	193.9 ± 458.0	162.4 ± 191.7
After treatment (3 months follow up)		
Size of uterus (cm ³)	440.5 ± 401.7	345.5 ± 249.2
Size of lesion (cm ³)	118.7 ± 240.0	87.3 ± 140.9
Size reduction (%)		
Uterus	25.5 ± 16.1 (p < 0.05)	26.3 ± 15.8 (p < 0.05)
Lesion	40.2 ± 21.6 (p < 0.05)	46.3 ± 25.4 (p < 0.05)

Table 2
Pre-HIFU and post-HIFU comparisons. Numbers are given in percentage, count, or mean ± standard deviations.

	Fibroids N = 404			Fibroid + Adenomyosis N = 53			Adenomyosis N = 149		
	Baseline	3 months	P value	Baseline	3 months	P value	Baseline	3 months	P value
Questionnaire Scores									
UFS-QOL	63.9 ± 29.9	45.3 ± 26.9	0.000 ^a	74.5 ± 26.7	61.6 ± 41.4	0.202	84.1 ± 23.7	55.4 ± 27.2	0.000 ^a
VAS	3.4 ± 3.2	2.1 ± 2.4	0.000 ^a	7.6 ± 2.5	5.7 ± 3.4	0.029 ^a	8.0 ± 2.1	3.7 ± 3.1	0.000 ^a
ICIQ-SF	15.5 ± 23.7	9.5 ± 16.5	0.001 ^a	19.3 ± 23.6	16.9 ± 21.8	0.759	17.6 ± 23.4	14.0 ± 20.3	0.147
POPDI-6	58.4 ± 50.9	34.7 ± 42.3	0.000 ^a	66.0 ± 54.5	37.2 ± 49.9	0.084	49.0 ± 47.0	46.3 ± 42.3	0.744
UDI-6	14.3 ± 14.4	9.2 ± 10.8	0.000 ^a	20.2 ± 14.8	13.6 ± 19.1	0.173	12.8 ± 14.4	13.3 ± 16.4	0.768
IIQ-7	10.7 ± 17.0	5.9 ± 13.5	0.000 ^a	7.9 ± 9.2	6.6 ± 12.3	0.722	6.1 ± 13.5	9.8 ± 20.7	0.193
OABSS	27.2 ± 24.0	19.8 ± 17.4	0.000 ^a	17.7 ± 12.5	20.0 ± 15.1	0.629	20.4 ± 21.3	21.4 ± 20.6	0.704
FSFI	32.5 ± 31.3	39.9 ± 34.3	0.003 ^a	44.2 ± 31.9	44.2 ± 34.4	0.080	45.3 ± 35.2	39.8 ± 33.9	0.113
Serum markers									
LDH	147.2 ± 31.9	129.8 ± 67.5	<0.05 ^a	146.8 ± 24.3	159.7 ± 63.9	NS	141.7 ± 24.5	154.6 ± 91.1	NS
CA125	60.5 ± 80.6	39.0 ± 40.2	<0.05 ^a	155.9 ± 106.9	174.2 ± 231.9	<0.05 ^a	223.7 ± 253	140.6 ± 147.1	<0.05 ^a
Pregnancy outcomes									
NSD	3			0			0		
CS	1			1			0		
Ongoing	4			0			2		
Abortion	0			0			1		

UFS-QOL: uterine fibroid symptom health-related quality of life [4]; VAS: visual analogue score [5]; ICIQ-SF: international consultation on incontinence modular questionnaire, short form Ref. [6]; POPDI-6: pelvic organ prolapse distress inventory 6 [7]; UDI-6: urogenital distress inventory-6 [8]; IIQ-7: incontinence impact questionnaire-7 [8]; OABSS: overactive bladder symptom scores [9]; FSFI: female sexual function index [10]; NSD: normal spontaneous delivery; CS: cesarean section.

^a Denotes statistical significance.

Treatment success was evaluated by the patient's degree of symptom relief, vascularity and size reduction in the fibroids or adenomyosis, and the patient's self-reported most troublesome concerns. Adverse events were assessed using the Society of Intervention of Radiology (SIR) classification [11], where class A to F signifying the severity of adverse events from being none, mild requiring only observation to the worse of death. Adverse events were documented and analyzed in Table 3. Statistical data analysis

conducted using SPSS 20.0 software and average tallied as mean + SD. Comparison with baseline done with paired t test, with P < 0.05 as statistically significant.

Results

Of the 500 patients included for analysis, 404 have pure uterine fibroids and 149 pure adenomyosis (Table 1). Fifty-three cases were

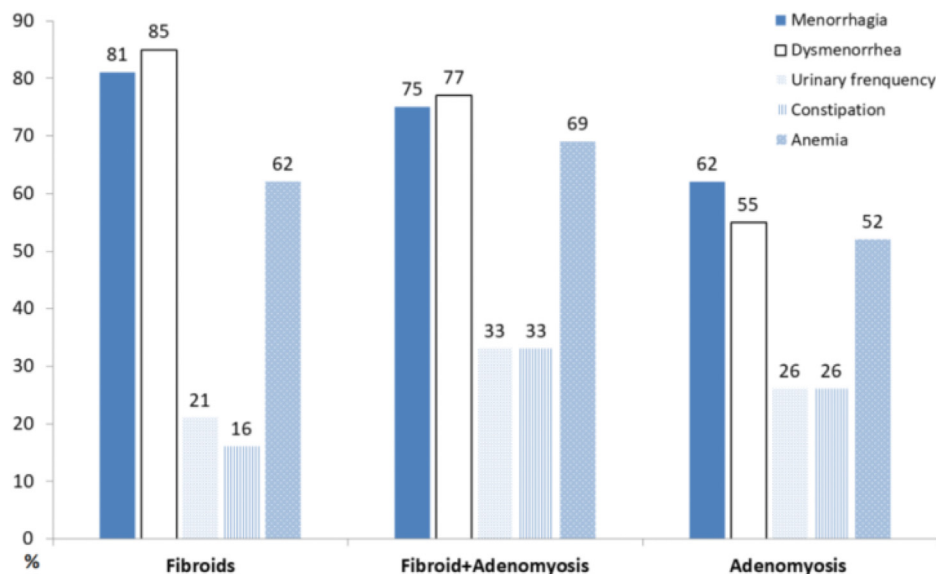


Fig. 2. Symptoms before HIFU.

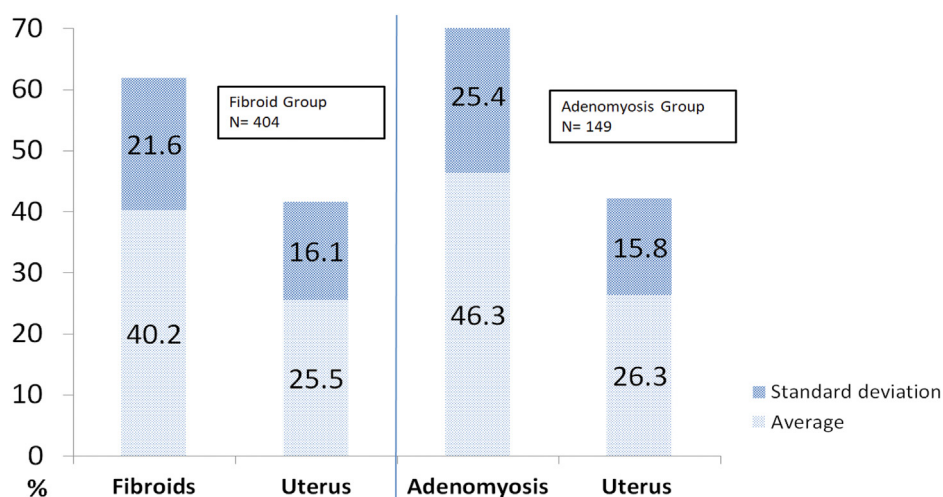


Fig. 3. Uterus and lesion reduction after HIFU.

diagnosed with combined conditions and were analyzed in a subgroup. Before HIFU, 81%, 85%, 21%, 16% and 62% in the fibroids group; 75%, 77%, 33%, 33%, and 69% in the combined fibroid plus adenomyosis; and 62%, 55%, 26%, 26% and 52% in the adenomyosis group suffered from menorrhagia, dysmenorrhea, urinary frequency, constipation and anemia, respectively (Fig. 2).

For fibroids group, patients' average age was 40.7 ± 5.9 years old with averaged body mass index of 22.7 ± 3.8 kg/m². The position of uterus was 71.1%, 18.0% and 10.4% for anteverted, retroverted and neutral, respectively. The location of fibroids was 34.7%, 35.7%, 8.7% and 20.9% at posterior wall, anterior wall, fundal and both anterior plus posterior wall, respectively. During HIFU, the averaged sonication power was 366.2 ± 56.4 W with averaged total duration of 120.2 ± 63.0 min, averaged sonication time 908.0 ± 519.9 s, or 453.3 ± 135.4 s/h and averaged exposure energy of $346,331.9 \pm 281,401.9$ J. Before HIFU, the averaged uterine size was 599.6 ± 546.4 cm³ and that of the fibroids 193.9 ± 458.0 cm³. Three months post-HIFU, the size of the uterus was reduced 25.5 ± 16.1 cm³ by average and the fibroids were also

reduced 40.2 ± 21.6 cm³ by average, both with statistical significance (Fig. 3).

For the adenomyosis group (Table 1), the patients' average age was 41.7 ± 5.3 years old with averaged body mass index of 23.2 ± 4.5 kg/m². The position of uterus was 72.5%, 21.5% and 6.0% for anteverted, retroverted and neutral, respectively. The location of adenomyoma was 53.1%, 35.2%, 9.3% and 2.4% at posterior wall, anterior wall, fundal and both anterior plus posterior wall, respectively. During HIFU, the averaged sonication power was 373.1 ± 47.8 W with averaged total duration of 104.0 ± 63.6 min, averaged sonication time 726.7 ± 433.8 s, or 434.4 ± 206.8 s/h and averaged exposure energy of $284,044.6 \pm 194,732.2$ J. Before HIFU, the averaged uterine size was 473.7 ± 346.5 cm³ and that of the adenomyosis 162.4 ± 191.7 cm³. Three months post-HIFU, the size of the uterus was reduced 26.3 ± 15.8 cm³ by average and the adenomyosis was also reduced 46.3 ± 25.4 cm³ by average, both with statistical significance (Fig. 3).

In self-reported questionnaires, scores were all significantly improved in the fibroids group, so as reflected by their serum LDH

Table 3
Adverse reaction sorted by Society of Interventional Radiology (SIR) Classification.

Classification	Total	A	B	C	D	E	F
Definition		No sequelae	Observation	Hospitalization <48 h	Hospitalization >48 h	Permanent sequelae	Death
KMUH data (total n=500)							
Total	51 (10.2)	45 (9.00)	3 (0.60)	1 (0.20)	2 (0.40)	0 (0.00)	0 (0.00)
Vaginal secretion	30 (6.00)	30 (6.00)	0	0	0	0	0
Low abdominal pain	11 (2.20)	11 (2.20)	0	0	0	0	0
Leg or buttock pain	2 (0.42)	0	2 (0.42)	0	0	0	0
Hematuria	4 (0.83)	4 (0.83)	0	0	0	0	0
Uterine bleeding	0 (0.00)	0	0	0	0	0	0
Blurred vision	0 (0.00)	0	0	0	0	0	0
Skin burns	1 (0.20)	0	1 (0.20)	0	0	0	0
Urinary retention	1 (0.20)	0	0	1 (0.20)	0	0	0
Fever	0 (0.00)	0	0	0	0	0	0
Acute renal failure	1 (0.20)	0	0	0	1 (0.20)	0	0
Bowel perforation	0 (0.00)	0	0	0	0	0	0
Abdominal hernia	0 (0.00)	0	0	0	0	0	0
Thrombocytopenia	1 (0.20)	0	0	0	1 (0.20)	0	0
Major complication	4 (0.80)						
Chongqing data (total n=9988)							
Total	1305 (10.7)	1228 (12.29)	45 (0.45)	26 (0.26)	6 (0.06)	0 (0.00)	0 (0.00)
Vaginal secretion	874 (8.75)	874 (8.75)	0	0	0	0	0
Low abdominal pain	225 (2.25)	225 (2.25)	0	0	0	0	0
Leg or buttock pain	76 (0.76)	55 (0.55)	19 (0.19)	2 (0.02)	0	0	0
Hematuria	52 (0.52)	52 (0.52)	0	0	0	0	0
Uterine bleeding	24 (0.24)	20 (0.20)	4 (0.04)	0	0	0	0
Blurred vision	2 (0.02)	2 (0.02)	0	0	0	0	0
Skin burns	26 (0.26)	0	22 (0.22)	2 (0.02)	2 (0.02)	0	0
Urinary retention	16 (0.16)	0	0	16 (0.16)	0	0	0
Fever	4 (0.04)	0	0	4 (0.04)	0	0	0
Acute renal failure	3 (0.03)	0	0	0	3 (0.03)	0	0
Bowel perforation	2 (0.02)	0	0	0	2 (0.02)	0	0
Abdominal hernia	1 (0.01)	0	0	0	1 (0.01)	0	0
Thrombocytopenia	0 (0.00)	0	0	0	0	0	0
Major complication	108 (1.08)						

Numbers are given in n (%).

and CA125 levels (Table 2). On the contrary, only VAS and CA125 for fibroid + adenomyosis group; VAS, UFS-QOL and CA125 for the adenomyosis group showed significant improvement at 3 months post-HIFU. Four livebirths and 4 ongoing pregnancies were reported the fibroids group; 1 livebirth for the fibroid + adenomyosis group; and 2 ongoing pregnancies and 1 spontaneous abortion case in the adenomyosis group.

Fifty-one adverse events or 10.2% were reported in total for this cohort (Table 3). All were able to resolve with observation of treatment without leaving permanent sequelae (SIR class E) or death (SIR class F). Documented adverse events included vaginal secretion (6.0%), low abdominal pain (2.20%), leg or buttock pain (0.42%), hematuria (0.83%), skin burn (0.20%), urinary retention (0.20%), acute renal failure (0.20%) and thrombocytopenia (0.20%). The rates of adverse events are comparable to the Chongqing data [1]. Major complications account for 0.80% of all adverse events in this cohort, compared to 1.08% of that from the Chongqing cohort.

Discussion

Our cohort represents a diverse geographical area, as only half our cases were locals. Others were from Northern or Central Taiwan, and yet others from broad. Many foreigners receive treatment at our International Medical Center, as HIFU availability is still limited to specific parts of the world. Our clientele includes patients from China, USA, Switzerland, UK, Vietnam, Australia, New Zealand, Japan, Korea, Hong Kong, Singapore, Canada, Guan and Malaysia. Although there are many HIFU ablation machines on the market, the Chongqing Haifu tumor therapeutic system has gained significant bounds and leaps in terms of domestic and local development, training and support. The body of literature concerning the use of

this machine is growing rapidly, as is the need for global access, recognition and installation to meet the current needs of women taunted by the socio-economic effects of fibroids and adenomyosis on reproductive health and well-being.

The preliminary results or this current study are reassuring and further confirm the safety and feasibility of HIFU ablation for fibroids and adenomyosis in non-surgical candidates. Our study demonstrated comparable treatment efficacy to that of Chongqing study even without the aid of contrast-enhanced ultrasonography (CEUS) [1,3]. CEUS utilizes a contrast media, Sonovue (Bracco International B.V, Amsterdam, Netherlands) for enhanced imaging resolution to add treatment efficiency. Currently, the contrast medium is only approved for liver diseases in Taiwan, thus not used in our study. Regardless, the post-HIFU 3 month follow up still showed good treatment response as revealed by MRI studies, patient-reported questionnaires and serum biomarker levels. Specifically, patients with HIFU-treated uterine fibroids reported significantly improved quality of life scores, pain scores, sexual satisfactions and compression related symptoms at 3 months post treatment (Table 2). Those with adenomyosis or combined lesions also reported significantly improved quality of life and pain scores (Table 2). The results of the current study are consistent with reports elsewhere, mostly using QOL-UFS questionnaires [12,13]. Our study is unique for employing sexual performance assessment (e.g. FSFI) and compression related symptoms evaluations (e.g. ICIQ-SF, POPDI-6, UDI-6, IIQ-7 and OABSS). Both are also considered important aspects of patient's quality of life affected by uterine lesions. Collectively, HIFU ablation of fibroids and adenomyosis at our tertiary institution has yielded consistent success rates of 97% over 3 years since the service has been offered. The literature substantiating the safety and efficacy of

HIFU ablation in fibroids and adenomyosis is extensively accumulating [14–20].

Twenty-two out of the 500 cases underwent reoperation after HIFU with a reoperation rate of 4.4% in this study. Seventeen cases had uterine fibroids, 3 had adenomyosis and 2 had combined lesions. Length of the time between HIFU and reoperation was 13 months in average with a range of 1 month–30 months. Eight underwent total hysterectomy, 14 myomectomy, among which 3 had laparotomy, 4 laparoscopy and 7 hysteroscopy. The reasons to re-operate include persistent menorrhagia, dysmenorrhea and lesions volume at follow ups. It is reasonable that more than half of these patients received hysteroscopic myomectomy, for HIFU performs best with intramural lesions. Operators attempt to spare endometrium of HIFU ablation for fertility concerns, thus submucosal lesions often require hysteroscopy treatment as a complement. All patients were satisfied after these reoperations with regular surveillance without further intervention at the time of manuscript preparation.

Uterine fibroids and adenomyosis are common benign conditions faced by women at childbearing ages. They can be detrimental to the affected women's quality of life by causing menorrhagia, dysmenorrhea, infertility and compression symptoms. To the extreme of disease manifestation, repetitive blood production transfusion, emergency department visits and hospitalization are deemed necessary. The diseases are often refractory to conservative managements, such as symptom-relieving medications, transarterial embolization (TAE) or radiofrequency ablation (RFA). These methods are either of limited efficacies or pose complications such as vessel injury, hematoma, reduced fertility, injuries to surrounding organs and wound infection at site of instrument entry. Myomectomy is more curative, yet its invasiveness brings more blood loss, longer recovery time, and increased risk of uterine rupture during subsequent pregnancies. Recurrence after myomectomy is very common as well. Conventionally hysterectomy is the definitive option, but at the expense of childbearing ability. HIFU emerged as a competent alternative for the above-mentioned dilemma for women desiring organ preservation, for being truly non-invasive with good efficacy.

A major concern for such non-invasive treatment modality is the lack of pathology evidence that confirms the benign nature of the uterine lesions. The current study relies on patients' medical history, lesion progression and most importantly MRI studies to differentiate benign and malignant lesions. Sun et al. has conducted a comprehensive review with a detailed algorithm that utilizes ill-defined margins, high diffusion-weighted images (DWI) and low apparent diffused coefficient (ADC) with lack of central contrast enhancement as warning signs for leiomyosarcoma [21]. Thomassin-Naggara reported a diagnostic accuracy of leiomyosarcomas using these MRI features as high as 92.4% [22]. The employment of serum markers, CA 125 and LDH, serves two purposes. Some studies advocate for their potential role in indicating malignant lesions [23,24], although no robust or consistent findings have proved their efficacies. Moreover, CA125 elevates upon peritoneal irritation caused by pelvic tumors [25] and LDH is associated with tumor necrosis [26]. Both markers serve as surrogate indicators to obnoxious symptoms caused by uterine fibroids and adenomyosis, thereby evaluated pre- and post-procedure as part of evaluation parameters in the current study.

Unfortunately so far we are unable to provide a full time-scale of shrinkage rates beyond 3 months. Due to economic constraints, certain target parameters such as the non-perfusion volume (NPV) ratios are not possible under our current government regulation. The HIFU package at our institution includes an MRI before and at 3 months after treatment. Further scans would be elective and expensive. However, the improvement of symptoms on patient follow-up is clear indication of improvement of life quality and

function. HIFU ablation functions by 2 mechanisms, thermal destruction with temperatures of 65–80°C and mechanical cavitation and necrosis. Although residual adenomyosis tissue remains, at least 70% of the lesion is ablated within safety and technical margins. Many other results also confirm a 70% ablation rate to achieve optimal outcome. Another advantage is that HIFU ablation may be repeated until desirable effect is achieved. Usually this is necessary in huge (larger than 10 cm) fibroids and multiple fibroids.

There are several limitations in our analysis. Firstly, only the first 3 months post-operation data and information is available. Many patients do not live in the vicinity, and choose to receive further care at their nearby gynecologist or in their respective countries. Secondly, NPV ratio is not able to be calculated as patients do not receive a contrast-enhanced MRI immediately after the HIFU ablation procedure. We use instead the 3 month post-operative MRI contrast-enhanced reduction in volume. Lastly, more and longer-term data are warranted to evaluate HIFU ablation clinical outcome and efficacy.

Conclusion

HIFU is safe and effective in treating uterine fibroids and adenomyosis. It is a reasonable treatment alternative with the advantages of symptom-relieving, non-invasiveness, minimal adverse reactions, rapid recovery and readiness for pregnancy.

Author contributions

Professor CJ Jeng has recruited most patients for treatment, directed the study design and revised the manuscript. Professors CJ Jeng, Dr. KY Ou and Professor CY Long performed HIFU treatment and assisted in data collection. Professor L Chuang advised for data analysis and interpretation. Dr. CR Ker analyzed the data and prepared the manuscript.

Declaration of competing interest

The authors declared no conflict of interest.

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None.

References

- [1] Chen J, Chen W, Zhang L, Li K, Peng S, He M, et al. Safety of ultrasound-guided ultrasound ablation for uterine fibroids and adenomyosis: a review of 9988 cases. *Ultrason Sonochem* 2015;27:671–6.
- [2] Zhang L, Zhang W, Orsi F, Chen W, Wang Z. Ultrasound-guided high intensity focused ultrasound for the treatment of gynaecological diseases: a review of safety and efficacy. *Int J Hyperther* 2015;31:280–4.
- [3] Shui L, Mao S, Wu Q, Huang G, Wang J, Zhang R, et al. High-intensity focused ultrasound (HIFU) for adenomyosis: two-year follow-up results. *Ultrason Sonochem* 2015;27:677–81.
- [4] Yeung SY, Kwok JWK, Law SM, Chung JPW, Chan SSC. Uterine fibroid symptom and health-related quality of life questionnaire: a Chinese translation and validation study. *Hong Kong Med J* 2019;25(6):453–9.
- [5] Karcioğlu O, Topacoglu H, Dikme O, Dikme A. A systematic review of the pain scales in adults: which to use? *Am J Emerg Med* 2018;36(4):7707–14.
- [6] Tubaro A, Zaitoni F, Prezioso D, Scarpa RM, Pesce F, Rizzi CA, et al. Italian validation of the international consultation on incontinence questionnaires. *BJU Int* 2006;97(1):101–8.
- [7] Lo TS, Tan YL, Khanungkitkong S, Dass AK, Cortes EF, Wu PY. Assessment of collagen-coated anterior mesh through morphology and clinical outcomes in pelvic reconstructive surgery for pelvic organ prolapse. *J Minim Invasive Gynecol* 2014;21(5):753–61.
- [8] Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fanti JA. Short forms to assess life quality and symptom distress for urinary incontinence in women: the incontinence impact questionnaire and the urogenital distress inventory. *Continence program for women research group. NeuroUrol Urodyn* 1995;14(2):131–9.

- [9] Homma Y, Yoshida M, Seki N, Yokoyama O, Kakizaki H, Gotoh M, et al. Symptom assessment tool for overactive bladder syndrome—overactive bladder symptom score. *Urology* 2006;68(2):318–23.
- [10] Chang SR, Chang TC, Chen KH, Lin HH. Developing and validating a Taiwan version of the female sexual function index for pregnant women. *J Sex Med* 2009;6(6):1609–16.
- [11] Kim HK, Kim D, Lee MK, Lee CR, Kang SY, Chung YJ, et al. Three cases of complications after high-intensity focused ultrasound treatment in unmarried women. *Obstet Gynecol Sci* 2015;58:542–6.
- [12] He M, Jacobson H, Zhang C, Setzen R, Zhang L. A retrospective study of ultrasound-guided high intensity focused ultrasound ablation for multiple uterine fibroids in South Africa. *Int J Hyperther* 2018 Dec;34(8):1304–10.
- [13] Lee JS, Hong GY, Lee KH, Kim TE. Changes in anti-mullerian hormone levels as a biomarker for ovarian reserve after ultrasound-guided high-intensity focused ultrasound treatment of adenomyosis and uterine fibroid. *BJOG* 2017 Aug;124(Suppl 3):18–22.
- [14] Peng S, Zhang L, Hu L, Chen J, Ju J, Wang X, et al. Factors influencing the dosimetry for high-intensity focused ultrasound ablation of uterine fibroids: a retrospective study. *Medicine (Baltim)* 2015;94:e650.
- [15] He H, Lu L, Zhou Y, Nie Y. Clinical of study on curing uterine leiomyoma/a with high intensity focused ultrasound. *China J Mod Med* 2004, Oct;14:19.
- [16] Fan TY, Zhang L, Chen W, Liu Y, He M, Huang X, et al. Feasibility of MRI-guided high intensity focused ultrasound treatment for adenomyosis. *Eur J Radiol* 2012 Nov;81(11):3624–30. <https://doi.org/10.1016/j.ejrad.2011.05.036>.
- [17] Gong C, Setzen R, Liu Z, Liu Y, Xie B, Aili A, et al. High intensity focused ultrasound treatment of adenomyosis: the relationship between the features of magnetic resonance imaging on T2 weighted images and the therapeutic efficacy. *Eur J Radiol* 2017 Apr;89:117–22.
- [18] Zhang X, Zou M, Zhang C, He J, Mao S, Wu Q, et al. Effects of oxytocin on high intensity focused ultrasound (HIFU) ablation of adenomyosis: a prospective study. *Eur J Radiol* 2014 Sep;83(9):1607–11. <https://doi.org/10.1016/j.ejrad.2014.05.008>.
- [19] Cheung VY. Sonographically guided high-intensity focused ultrasound for the management of uterine fibroids. *J Ultrasound Med* 2013 Aug;32(8):1353–8.
- [20] Lee JS, Hong GY, Park BJ, Kim TE. Ultrasound-guided high-intensity focused ultrasound treatment for uterine fibroid and adenomyosis: a single center experience from the Republic of Korea. *Ultrason Sonochem* 2015 Nov;27:682–7.
- [21] Sun S, Bonaffini PA, Nougaret S, Fournier L, Dohan A, Chong J, et al. How to differentiate uterine leiomyosarcoma from leiomyoma with imaging. *Diagn Interv Imaging* 2019 Oct;100(10):619–34.
- [22] Thomassin-Naggara I, Dechoux S, Bonneau C, Morel A, Rouzier R, Carrette MF, et al. How to differentiate benign from malignant myometrial tumours using MR imaging. *Eur Radiol* 2013 Aug;23(8):2306–14.
- [23] Juang CM, Yen MS, Horng HC, Twu NF, Yu HC, Hsu WL. Potential role of preoperative serum CA 125 for the differential diagnosis between uterine leiomyoma and uterine leiomyosarcoma. *Eur J Gynaecol Oncol* 2006;27(4):370–4.
- [24] Song KJ, Yu XN, Lv T, Chen YL, Diao YC, Liu SL, et al. Expression and prognostic value of lactate dehydrogenase-A and -D subunits in human uterine myoma and uterine sarcoma. *Medicine (Baltim)* 2018 Apr;97(14):e0268.
- [25] Menczer J, Schreiber L, Berger E, Ben-Shem E, Golan A, Levy T. CA 125 expression in the tissue of uterine leiomyosarcoma. *Isr Med Assoc J* 2014 Nov;16(11):697–9.
- [26] Chan FK, Moriwaki K, De Rosa MJ. Detection of necrosis by release of lactate dehydrogenase activity. *Methods Mol Biol* 2013;979:65–70.