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Evaluation of high-intensity focused ultrasound ablation for uterine fibroids: an IDEAL prospective exploration study

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Objective To evaluate the clinical outcomes of high-intensity focused ultrasound (HIFU) and surgery in treating uterine fibroids, and prepare for a definitive randomised trial.

Design Prospective multicentre patient choice cohort study (IDEAL Exploratory study) of HIFU, myomectomy or hysterectomy for treating symptomatic uterine fibroids.

Setting 20 Chinese hospitals.

Population or sample 2411 Chinese women with symptomatic fibroids.

Methods Prospective non-randomised cohort study with learning curve analysis (IDEAL Stage 2b Prospective Exploration Study).

Main outcome measures Complications, hospital stay, return to normal activities, and quality of life (measured with UFS-Qol and SF-36 at baseline, 6 and 12 months), and need for further treatment. Quality-of-life outcomes were adjusted using regression modelling. HIFU treatment quality was evaluated using LC-CUSUM to identify operator learning curves. A health economic analysis of costs was performed.

Results 1353 women received HIFU, 472 hysterectomy and 586 myomectomy. HIFU patients were significantly younger ($P < 0.001$), slimmer ($P < 0.001$), better educated ($P < 0.001$), and wealthier ($P = 0.002$) than surgery patients. Both UFS and QoL improved more rapidly after HIFU than after surgery ($P = 0.002$ and $P = 0.001$, respectively at 6 months), but absolute differences were small. Major adverse events occurred in 3 (0.2%) of HIFU and in 133 (12.6%) of surgical cases ($P < 0.001$). Median time for hospital stay was 4 days (interquartile range, 0–5 days), 10 days (interquartile range, 8–12.5 days) and 8 days (interquartile range, 7–10 days).

Conclusions HIFU caused substantially less morbidity than surgery, with similar longer-term QoL. Despite group baseline differences and lack of blinding, these findings support the need for a randomised controlled trial (RCT) of HIFU treatment for fibroids. The IDEAL Exploratory design facilitated RCT protocol development.

Keywords Fibroid, learning curve, trial methodology, ultrasound.

Tweetable abstract HIFU had much better short-term outcomes than surgery for fibroids in 2411-patient Chinese IDEAL format study.

Linked article This article is commented on by N Tempest and D Hapangama. To view this mini commentary visit https://doi.org/10.1111/1471-0528.14691.

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Introduction

Uterine fibroids are the most common benign gynaecological tumours in women of childbearing age, with a

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prevalence of 20–25%.[1] Conventional therapy comprises hysterectomy, myomectomy, or hormonal manipulation. Hysterectomy has a 10% risk of significant complications,[2] and while myomectomy preserves the uterus, it has recognised risks of local recurrence, growth of new fibroids, or failure of symptom relief.[3] Since 1994, uterine artery embolisation (UAE) has become extensively used. It has a better safety profile than surgery,[4] but potential complications include pelvic pain, nausea, vomiting, fever, and embolisation of other organs. High-intensity focused ultrasound ablation (HIFU) is a non-invasive technique that causes instant coagulative necrosis (1–3 seconds) in a well circumscribed area a few mm in diameter, and can be performed under either magnetic resonance imaging (MRI) guidance or ultrasound guidance.

In 2002 Wang Wei et al. found ultrasound-guided HIFU to be safe and effective in managing uterine fibroids.[5] In 2004, a large case-matching study that focused on technical details and feasibility as recommended for Development studies in the IDEAL Framework was published.[6,7] HIFU has been increasingly performed in China, with over 10 000 patients treated in 2014, and has now become the preferred therapy in some Chinese centres.[8] However, scientifically valid comparisons with other treatments have not been reported.

Randomised controlled trials (RCTs) are accepted as the most appropriate study design for comparing treatments, but are more difficult to perform in complex interventional therapies than in drug treatments.[9] Expert consensus groups have described the natural history of innovation in complex treatments, and shown how this results in barriers to a successful RCT until certain preliminary studies have been completed.[10,11] The IDEAL Framework describes at least two intermediate stages through which a complex therapy has to pass after proof-of-concept in humans before an RCT is appropriate.[7] In the Development stage (2a), the treatment is still undergoing regular modification, and so cannot be compared with other therapies. In the Exploration stage (2b), the treatment is stable, but there is uncertainty about the best choice of patient population and precise details of technique, and information is needed about outcomes to allow estimation of a trial sample size. At this time operators are often going through a learning curve, which may bias outcomes against the new treatment in comparisons. The IDEAL Recommendations propose a large prospective collaborative cohort study (Prospective Exploration Study or PES) at this stage, to deal with these issues and allow development of an RCT.[7] We carried out a PES of HIFU treatment, to facilitate development of a successful RCT of this therapy versus current standard treatment options.

Methods

We conducted a 20-centre non-randomised controlled prospective cohort study of treatments for uterine fibroids, in which patients were fully informed about the treatment options and then chose whether to receive hysterectomy, myomectomy or HIFU therapy.

Setting and data collection

The centres of clinical investigation were selected from respondents to a nationwide call for participation in the trial. Twenty centres were selected based on having the required ultrasound therapeutic devices in place and conforming to a uniform treatment protocol. Recruitment opened in March 2011 and closed in December 2013. Data entry clerks and data managers from each centre of investigation were trained at the Chinese Evidence-based Medicine Centre (Chengdu) before entering data (clerks) and validating it (managers). Stored data were locked and analysed by qualified personnel from the Chinese Evidence-based Medicine Centre after quality inspection and further validation.

Eligibility criteria for patients

(1) Premenopausal women who had completed their planned family (and had no recent plan for a further pregnancy). (2) Imaging-confirmed diagnosis of symptomatic fibroids with any of the following indications for hysterectomy: (a) enlarged uterus (uterine volume equal to or greater than that at 10 week' gestation); (b) menorrhagia and/or secondary anaemia; (c) pelvic pain, urinary frequency, or constipation. (3) For patients with multiple fibroids, no more than three fibroids with minimal diameters of 2 cm based on abdominal ultrasound present. (4) Fibroids clearly imaged by abdominal ultrasound. For patients with abdominal surgical scars, the width of image blurring due to acoustic attenuation had to be <10 mm.

Exclusion criteria

(1) Patients with uterine adenomyosis. (2) Previous myomectomy. (3) Concurrent pregnancy. (4) Pedunculated subserous or submucosal fibroids. (5) Any single fibroid >10 cm maximum diameter. (6) Acute pelvic inflammation or uncontrolled systemic disease. (7) Patients unable to communicate adequately with physicians, or unwilling to sign informed consent. Patients were provided with 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 three options. All centres were able to perform both HIFU treatment and surgery. The study was approved by a multicentre study ethics committee (IRB approval number: CHiECRCT-2011034).

Eligibility criteria for doctors

Prior training and quality control. (1) Surgeons were required to be board-certified for more than 3 years, with a specialisation in gynaecology. (2) Specialists in HIFU treatment underwent a programme of training and certification authorised by the Ministry of Health of China. All operators were required to complete ablation treatment for 40–60 patients under guidance and supervision before entering the trial, with no major complications among treated patients, and a mean non-perfused volume (NPV) ratio of treated fibroids >70% (see outcome measures below).

MRI evaluation of HIFU group. All patients enrolled for HIFU therapy underwent MRI scanning before the procedure, including T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), and enhanced T1 weighted gradient-echo imaging (CE-T1WI). Patients were rescanned by enhanced MRI within 4 weeks after treatment, allowing measurement of the volumes of the dominant fibroids and uterus based on T2WI and NPV on CE-T1WI. Patients enrolled in the surgery arms were not routinely scanned by MRI either before or after their operation.

HIFU ablation procedure

A single session of HIFU ablation was performed using the JC (JC200) Focused Ultrasound Therapeutic Unit for Tumour (Chongqing Haifu Medical Technology Co., Ltd, Chongqing, China) with a therapy transducer focal region of 1.5 × 1.5 × 10 mm, under intravenous conscious sedation with fentanyl (0.8–1 μg/kg) and midazolam hydrochloride (0.02–0.03 mg/kg), administered every 30–40 minutes. Treatment was monitored by real-time ultrasonography, using massive grey-scale changes in the treated area as a measure of treatment effect. After the procedure, patients lay prone for 2 hours under observation. Outpatients were then discharged home with a companion if their vital signs were stable and they appeared fully orientated. Patients with medical insurance cover who required hospital stay remained on a normal hospital ward for 1 night and were discharged the next morning. Follow-up visits were scheduled at 6 months and 12 months post-procedure.

Surgical procedures

Among patients who chose surgery, the surgical route of hysterectomy or myomectomy (open surgery, laparoscopic or transvaginal) was left to the discretion of the attending gynaecologist. Postoperative inpatient stay was determined according to The Clinical Pathway of Abdominal Hysterectomy for Uterine Fibroids issued by China's Ministry of Health (2009 version). This pathway allows for an expected (routine) hospitalisation of no more than 11 days, no more than 7 days of which should be postoperative, but with prolongation for any abnormal condition (e.g. pyrexia, bleeding, infection, etc.). Follow-up visits were scheduled at 6 months and 12 months after surgery.

Outcome measures

Complications

Complications were recorded and graded using the guidelines of the Society of Interventional Radiology, which classifies the severity of complications as: no therapy required or no consequence (grade A); minimal therapy required or no consequence, including overnight admission for observation only (grade B); therapy required, including minor hospitalisation of <48 hours (grade C); major therapy required, including unplanned increases in the level of care, or prolonged hospitalisation for at least 48 hours (grade D); permanent adverse sequelae (grade E); and death (grade F). Grades A and B were considered to be minor; grades C to F were considered to be major.[12,13]

HR-QoL measures

The 36-Item Short-Form General Health Survey (SF-36) was used to evaluate the changes in quality of life, comparing before and 6 and 12 months after HIFU or surgery. The uterine fibroid symptom quality-of-life (UFS-QoL) questionnaire is a secondary instrument that specifically measures the severity of fibroid-related symptoms and health-related quality of life for fibroid patients using separate scales. Both scales range from 0 to 100, but high scores indicate better QoL but more serious symptoms on the UFS scale.[14]

Re-intervention

Any need for recurrent treatment of fibroid-related symptoms was considered a re-intervention, but the re-intervention rate was assessed for the HIFU and myomectomy groups only. Any re-intervention or re-hospitalisation was monitored during the course of the study.

Evaluation of learning curves

Procedure time and percent NPV on enhanced MRI at 4 weeks were measured, to assess the quality of treatment delivery and assess learning curves. For each centre, %NPV was analysed sequentially using the LC-CUSUM method to identify the point at which a stable satisfactory performance could be demonstrated.[15,16] The target for %NPV was set at 70%, and acceptable and unacceptable failure rates were set at 0.1 and 0.2, i.e. 10% and 20% failure to achieve the 70% target.

Economic analysis

Both direct and indirect medical costs were ascertained. Direct costs include, but are not limited to, the costs of

preoperative diagnosis and investigation, operation or procedure, and hospitalisation. Indirect costs arising from loss of working ability were calculated using the product of the time required for treatment and return to work and per capita disposable income (National Bureau of Statistics of the People's Republic of China: 2013 China Statistical Yearbook. http://www.stats.gov.cn/tjsj/ndsj/2013/indexch.htm).

Statistical analysis

Group comparisons were carried out using the chi-square test for comparison of proportions, two-sided Student's *t*-test for continuous parametric variables and the Kruskal–Wallis (3 group) and Wilcoxon (2 group) tests for categorical non-parametric data comparison. To adjust for the effects of inequalities between treatment groups, multiple regression modelling was performed to identify the influence of preselected covariates on the dependent variable. This process was carried out for each of the dimensions of SF-36, and for the total UFS and QoL scores. Covariates were selected using a combination of preselection for known mechanistic relevance and significance in univariate regression analysis. For the latter, variables showing a significant association with the outcome at $P < 0.05$ were included in the model. The final list of covariates included centres of investigation, age, and body mass index (BMI). The regression model equation was applied to produce adjusted comparisons between groups.

Results

A total of 2411 patients were enrolled in the study, 1353 in the HIFU group and 1058 in the surgery group, of whom 586 had myomectomy and 472 hysterectomy (Figure 1). Of 586 myomectomies, 284 (48%) were performed laparoscopically, 233 (40%) by open surgery, and 69 (12%) either transvaginally, by hysteroscopy, or by laparoscopic transvaginal surgery. Of 472 hysterectomies, 251 (53%) were by laparotomy, 93 (20%) by laparoscopy, and 128 (27%) transvaginally. A comparison of baseline data of the two groups is shown in Table 1. The mean age of the HIFU group was lower than that of the surgery group, and other group differences included BMI, uterine volume and UFS score.

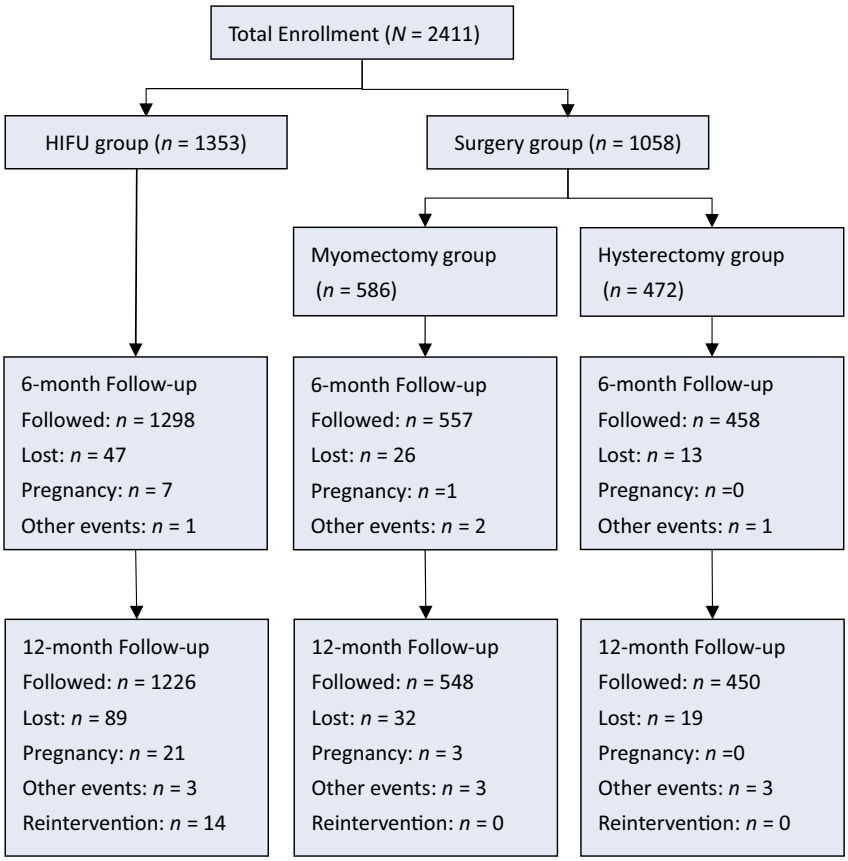

Figure 1. CONSORT diagram showing patient allocation and follow-up.

Table 1. Baseline characteristics of 2411 women with uterine fibroids allocated to treatment by high-intensity focused ultrasound (HIFU) or surgery (myomectomy or hysterectomy)

Characteristic	HIFU group (*n* = 1353)	Total surgery group (*n* = 1058)	Myomectomy subgroup (*n* = 586)	Hysterectomy subgroup (*n* = 472)	*P* / HIFU vs surgery	*P* / HIFU vs myomectomy vs hysterectomy
Age (years)	41.31 ± 5.08	43.43 ± 5.21	40.93 ± 5.02	46.54 ± 3.48	0.000	0.000
BMI (kg/m^2)	22.68 ± 2.99	23.41 ± 3.02	22.90 ± 2.91	24.05 ± 3.03	0.000	0.000
UFS score*	19.89 ± 14.29	17.04 ± 14.01	15.34 ± 13.34	19.15 ± 14.54	0.000	0.000
QoL score*	72.75 ± 16.33	72.22 ± 14.91	72.85 ± 14.46	71.45 ± 15.44	0.119	0.133
Parity						
1	1225	908	518	290	0.000	0.000
2	111	125	60	65		
≥3	17	25	8	17		
Educational level						
Basic	171	181	78	103	0.000	0.000
High school	640	647	333	314		
Non-smoker	1325	1045	577	468	0.093	0.252
Smoker	28	13	9	4		
Non-drinker	1194	968	530	438	0.078	0.114
Regular/occasional drinker	159	90	56	34		
Family income [1000 RMB/year; median (IQR)]	70.00 (50.00–100.00)	60.00 (40.00–100.00)	70.00 (40.20–100.00)	60.00 (40.00–100.00)	0.002	0.001
Volume of dominant fibroid (cm^3)	104.84 ± 81.73	115.23 ± 96.35	112.56 ± 90.72	118.54 ± 102.91	0.093	0.235
Uterine volume (cm^3)	292.30 ± 148.26	241.54 ± 151.78	220.37 ± 133.77	267.81 ± 168.00	0.000	0.000

Data given as *n* or mean ± SD except where indicated.
BMI, body mass index; IQR, interquartile range; QoL, Quality of life; UFS, Uterine fibroid symptoms score; vs, versus.
*The UFS-QoL cannot be used appropriately after hysterectomy.

Table 2. Comparison of adverse reactions in 2411 women with uterine fibroids allocated to treatment by high-intensity focused ultrasound (HIFU) or surgery (myomectomy or hysterectomy)

Adverse event	HIFU group (*n* = 1353)	Surgery group (*n* = 1058)	Myomectomy group (*n* = 586)
Minor adverse event	335 (24.8)	719 (68.0)	397 (67.7)
Abdominal distension	0 (0.0)	4 (0.4)	3 (0.5)
Lumbar and back (sacrum) pain	150 (11.1)	134 (12.7)	64 (10.9)
Shoulder and back pain	0 (0.0)	11 (1.0)	11 (1.9)
Numbness and pain in lower limb	34 (2.5)	18 (1.7)	11 (1.9)
Weakness in lower limb	9 (0.7)	62 (5.9)	30 (5.1)
Pain and distension of anus	11 (0.8)	38 (3.6)	18 (3.1)
Subcutaneous emphysema	0 (0.0)	5 (0.5)	5 (0.9)
Uterine bleeding	88 (6.5)	222 (21.0)	150 (25.6)
Urinary retention	2 (0.15)	25 (2.4)	7 (1.2)
Haematuria	3 (0.2)	18 (1.7)	7 (1.2)
Fever (no therapy)	2 (0.15)	6 (0.6)	3 (0.5)
Respiratory tract infection	1 (0.1)	9 (0.9)	4 (0.7)
Fat liquefaction of incision	0 (0.0)	4 (0.4)	3 (0.5)
Incision infection	0 (0.0)	1 (0.1)	0 (0.0)
Skin burn (1st to 2nd degree)	2 (0.15)	0 (0.0)	0 (0.0)
Nausea and vomiting	21 (1.6)	158 (14.9)	80 (13.7)
Dizziness and headache	2 (0.15)	1 (0.1)	0 (0.0)
Blood pressure unsteadiness		1 (0.1)	
Blurred vision	10 (0.7)	0 (0.0)	0 (0.0)
Choking sensation in chest	0 (0.0)	1 (0.1)	1 (0.2)
Stomach pain	0 (0.0)	1 (0.1)	
Major adverse events	3 (0.2)	133 (12.6)	60 (10.2)
Intraoperative massive hemorrhage*	0 (0.0)	11 (1.0)	7 (1.2)
Intraoperative blood transfusion	0 (0.0)	96 (9.1)	41 (7.0)
Fever (>38°C)	0 (0.0)	3 (0.3)	2 (0.3)
Pelvic abdominal infection	0 (0.0)	5 (0.5)	3 (0.5)
Incision infection	0 (0.0)	3 (0.3)	1 (0.2)
Second-degree skin burn	3 (0.2)	0 (0.0)	0 (0.0)
Respiratory tract infection	0 (0.0)	2 (0.2)	1 (0.2)
Readmission	0 (0.0)	3 (0.3)	0 (0.0)
Deep venous thrombosis (lower limbs)	0 (0.0)	2 (0.2)	1 (0.2)
Vaginal cuff bleeding	0 (0.0)	1 (0.1)	0 (0.0)
Vaginal cuff infection	0 (0.0)	1 (0.1)	0 (0.0)
Drainage-site infection	0 (0.0)	1 (0.1)	1 (0.2)
Pelvic haematoma (drainage)	0 (0.0)	1 (0.1)	1 (0.2)
Pelvic abscess (drainage)	0 (0.0)	1 (0.1)	1 (0.2)
Bladder injury	0 (0.0)	1 (0.1)	0 (0.0)
Abdominal distension and vomiting (indwelling gastric tube)	0 (0.0)	1 (0.1)	0 (0.0)
Arrhythmia (emergency)	0 (0.0)	1 (0.1)	1 (0.2)

Data are given as *n* (%).
*Intraoperative haemorrhage of ≥400 ml.

Adverse events

Minor adverse events occurred in 335 (25%) patients in the HIFU group and in 719 patients (68%) in the surgery group ($P < 0.001$). The events recorded included pain, weakness, or numbness in the lower limbs, back or perineum, haematuria, and general symptoms such as nausea and dizziness. The only categories where HIFU treatment had a higher percentage of minor complications than did surgery were superficial skin burns (2 versus 0), blurred vision and transient pain, and weakness or numbness in the back, shoulder, or lower limb (Table 2).

Major adverse events attributable to the intervention occurred in three (0.22%) HIFU cases and in 133 (12.6%) surgical cases within 30 days after treatment. All three HIFU events were second-degree skin burns. Events in the surgery group included haemorrhage, infection, thromboembolic events, and injury to the bladder. There were three major events requiring readmission (vaginal cuff bleeding and abdominal distension) in the hysterectomy group. Major events were slightly less frequent in the myomectomy group (10.2%) than in the hysterectomy group (15.5%).

Other adverse events

One patient with rectal cancer and one with cervical cancer were diagnosed within 12 months after HIFU treatment and one patient with cervical cancer was diagnosed within 12 months after myomectomy. Pathology reports identified three histologically sarcomatous uterine tumours, of which two were considered potentially malignant. One of these underwent hysterectomy as the initial surgery, and the other underwent re-exploration removal of the uterus, at which no dissemination was found. There was no uterine sarcoma in the HIFU group, but one case with intravenous leiomyomatosis was found 6 months after the HIFU procedure. There were two unrelated deaths during follow-up (one from a road accident and one from myocardial infarction, both after hysterectomy). Within 1 year after treatment 14 (1%) HIFU patients but no myomectomy patients had received re-intervention for recurrence (one second HIFU treatment, 12 myomectomies and one hysterectomy).

QoL measures

The mean UFS scores improved successively from pre-treatment to 6 and then 12 months post-treatment for the HIFU and myomectomy groups (Table 3). The baseline symptom score was higher for HIFU patients, and the degree of improvement experienced was somewhat greater than for surgery patients at both 6 and 12 months. After correction for the factors identified in the regression model, these differences remained significant. The QoL scores for both groups also improved successively, with the improvement in HIFU patients slightly but significantly greater after adjustment at both 6 and 12 months ($P = 0.001$, $P = 0.002$, respectively; Table 3). Changes in the elements of the SF-36 scale showed a similar general trend towards progressive improvement over the 12 months after treatment in all groups. The HIFU group showed obvious improvements in physiological function, which were significantly greater than the changes in the two surgical groups (Table S1). In the other seven components of the SF-36 measure, there were small but significant advantages for HIFU treatment in the absolute improvement in bodily pain at 6 months, in vitality at 12 months and in emotional role at 12 months, but no other significant differences between the treatment groups at either 6 or 12 months.

Health economic analysis

Duration of hospital stay and period before returning to work were both considerably shorter for the HIFU patients than for those in the two surgical groups (Table S2). Mean duration of hospital stay was 3.6 days for HIFU, 9 days for myomectomy and 10.5 days for hysterectomy. The figures for return to work (or normal household activities) were 4.1, 24.0 and 29.5 days, respectively, for the three groups. The differences between HIFU and surgery were highly significant for both measures ($P < 0.001$).

Table 3. Effects of high-intensity focused ultrasound (HIFU) and myomectomy on measures of uterine fibroid symptoms quality of life (UFS-QoL) score in women with uterine fibroids

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	
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 average costs of treatment were calculated at 11 910 RMB (£1184 or $1953 at an exchange rate [December 2013] of ¥1 = £0.0994 or ¥1 = $0.1640) for HIFU therapy, 14 111 RMB (£1403 or $2314) for surgical therapy [15 389 RMB (£1530/$2524) for hysterectomy and 13 082 RMB (£1301/$ 2146) for myomectomy]. HIFU was significantly cheaper than either form of surgery ($P = 0.000$), largely owing to the considerably shorter hospital stay, with an average cost of 427 RMB (£42/$70) versus 2239 RMB (£223/$367) for myomectomy and 2816 RMB (£280/$462) for hysterectomy.

Learning curve

The mean NPV score within the study was 87.2%, with a range for individual centre means from 69.8 to 96.6%. Nineteen of the 20 centres achieved a median NPV higher than the target of 70% set *a priori*. Three centres recorded a mean NPV below the 95% centile, with a 95% CI of 82.5–88.1% (Figure S1). Learning-curve effects were evaluated using the LC-CUSUM method, which tests for the presence of a stable 'in control' level of performance.[15,16] Cases were judged failures if their NPV was <70% or the patient suffered any significant adverse event. Four centres did not demonstrate stable satisfactory performance by the end of the study. Among the 16 centres that did achieve this, the median number of cases at which stable satisfactory performance was reached was 11 procedures.

Discussion

Main findings

This is by far the largest study of HIFU treatment for fibroids completed to date, and the encouraging outcomes show that HIFU is safe and effective, and affords speedy recovery. The study also demonstrates that rapid recruitment of large numbers of patients for studies of HIFU treatment of fibroids is feasible in this population; the selection criteria for both patients and operators appear to function well; and quality-of-life measures at 6 months and beyond are not appropriate primary outcomes for comparing fibroid treatments, since the effects of surgery and HIFU on these measures are very similar.

Quality of life showed considerable improvement at both 6 and 12 months, in both the HIFU and myomectomy groups. Although there were statistically significant differences between the groups, the size of the differences was small and clinically insignificant, and regression modelling did not change this picture. There was a small re-intervention rate in HIFU patients – 14 patients (1.0%) at 1 year and 33 patients (2-year re-intervention was 2.4%) at 2 years, but no recorded re-intervention was required after surgery.

Both hospital-stay and return-to-work periods were shorter after HIFU than after surgery, by a considerable margin; the more rapid recovery after HIFU was partly responsible for its significantly lower cost of treatment, although the cost of the procedure was also less than the cost of surgery.

This study also illustrates the successful use of NPV as a quality-control measure for HIFU treatment of fibroids. The mean NPV achieved (87.2%) was higher than those of two contemporary studies, while adverse effects remained very infrequent.[17,18] These data demonstrate the ability to deliver high-quality treatment safely across a large and diverse group of hospital settings, which can be attributed to the strict criteria for training, mentoring, and surveillance.

Strengths and limitations of the study

In this study HIFU treatment performed very well in terms of both frequency of complications and postoperative recovery period. The comparator surgical treatment groups were not randomised and the surgical treatments were not standardised, exposing comparisons to major risks of bias, but it seems unlikely that the very large differences in some short-term outcomes could be attributed to selection bias.

In China, as in many countries, medical insurance coverage for hospital inpatient stay is determined by the primary diagnosis and treatment. Most Chinese enjoy partial medical insurance coverage with a specific subvention for in-hospital recovery time, and this may help to explain the relatively long hospital stay in all groups, but there was no difference in cover for hospitalisation expenses between the groups, so the intergroup differences cannot be explained in this manner.

The NPV ratio is recognised as a predictor of clinical outcome for HIFU ablation of fibroids, with short–medium-term re-intervention rates closely correlated to the mean NPV achieved.[19,20] Based on regression analysis, the probability of additional treatment at 12 months after HIFU ablation would be around 5%, when NPV reached 80%, a prediction consistent with our data.[21] The use of NPV also clearly showed the potential benefits of evaluating operator learning curves with LC-CUSUM, a key IDEAL Recommendation for Exploration studies. Sixteen centres demonstrated a completed learning curve, while one centre scored persistently below the acceptable NPV range. This clear objective data on learning-curve effects identifies centres that would be able to enter an RCT without any concerns about bias against HIFU due to inadequate operator performance. The literature reports an accumulated re-intervention rate of around 5% 2 years after myomectomy,[3,22] but no recurrences were reported in the myomectomy group. Baseline differences between the HIFU and myomectomy groups may have contributed to this difference, or it may be that myomectomy is associated with a longer time to recurrence than is HIFU. For international

relevance, UAE may be a better control group in any trial designed for the assessment of the therapeutic efficacy of HIFU, and for this treatment also, recurrence would be an important outcome measure. To date there are no published outcome data from direct RCT comparisons of UAE and HIFU, although a report on a small RCT was recently published.[23]

Interpretation

The research leading to ultrasound-guided HIFU treatment of uterine fibroids began with experiments *in vitro*, followed by animal studies inducing tissue destruction within the uteri of monkeys and confirming correspondence between tissue damage and grey-scale ultrasonography changes.[24] In 2002, HIFU was first used to treat patients with uterine fibroids. This 'first-in-man' study showed that ultrasound-guided HIFU ablation resulted in markedly increased echogenicity in the treated area, and achieved remission of symptoms and tumour volume regression.[5] Wu et al. then demonstrated the feasibility and effectiveness of the treatment in a prospective study of 85 patients.[6] This series of studies recapitulates the transition from preclinical studies to the Idea (Stage 1) and Development (Stage 2a) stages of the IDEAL framework, moving from *in-vivo* studies to clinical studies focused on technical details, feasibility, safety, and effectiveness.[7]

HIFU is now recognised as a fully-developed state-of-the-art technology, supported by a growing literature, however definitive comparison of the effectiveness and safety of HIFU versus conventional therapies is required before it can be accepted as the standard of care for uterine fibroids. RCTs are widely accepted as the most valid study design for comparing treatments, but have proved more difficult to perform in complex interventional therapies than in drug treatments.[9] The IDEAL Recommendations propose a pre-RCT stage (Stage 2b, Exploration) at which potential RCT primary outcomes, operator learning curves, quality control and definitions of the patient group and comparator for an RCT should be worked out, usually in a non-randomised prospective trial. This IDEAL prospective exploration study has fulfilled all of these objectives, and has demonstrated that HIFU is safe, effective, and deliverable in a large group of unconnected health facilities at high patient volumes. Because they do not compare randomly selected equivalent patient groups (and may not involve any comparison groups), IDEAL Exploratory studies cannot provide definitive evidence of relative advantage between treatments, but they can be very helpful in forming hypotheses, and preparing the way for an RCT. Our findings make it clear that RCT proposals comparing complications or short-term recovery in this context might not attract support or funding, as the very large differences we found are likely to affect equipoise. Conversely, QoL measures at 6 months or later would not be a useful primary outcome, as we can predict very similar outcomes and therefore a very large trial population requirement.

Conclusions

The short-term outcomes for HIFU in this study appeared better than those for surgery. Quality-of-life measures appeared to be equal to or better than those for surgery 1 year after the procedure. Since similar data for these outcomes can be anticipated for UAE, any future RCT involving HIFU, UAE, and surgery may need to focus on comparing re-intervention rates, since lack of equipoise or statistical power may preclude using the outcomes we measured.

The study greatly enhanced experiential understanding of the treatment and confidence in its use among a large group of clinical staff, and demonstrated completion of learning curves. Performance bias problems were therefore eliminated, and staff ability to deliver a future RCT enhanced. These benefits are among those expected of an IDEAL Exploratory study, making this study an excellent practical example of how IDEAL studies may assist in the development of RCTs for complex interventions. An RCT of HIFU therapy versus best current practice is now both feasible and necessary.

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Disclosure of interest

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

Jinghe Lang is chief investigator for the study; Wenzhi Chen contributed to the design of the trial and was in charge of the overall execution of the study; Jinyun Chen is the trial coordinator and wrote the first draft of paper; Youping Li contributed to the design of the study; Zhibiao Wang signed the research contract; Peter McCulloch contributed to the IDEAL framework, statistical methods for data analysis, writing and editing of the manuscript; Liang Hu carried out the health economic analyses. Guanjian Liu conducted the statistical analysis and was responsible for data management; Jing Li contributed to the design of the study. The above-named authors were all involved in analysis and interpretation of data. The others provided advice on all the clinical aspects of the study and completed patients' enrolment and follow-up. All authors approved the final version. The Committee of the Clinical Trial of

HIFU versus Surgical Treatment for Fibroids contributed to the design and management of the study. The members of the committee provided advice on all the clinical aspects of the study and input to the study design, and supervised and completed patients' enrolment and follow-up. All authors commented on drafts of the manuscript and approved the final version.

Details of ethics approval

Ethics approval (ref ChiECRCT-2011034) was obtained from China Ethics Committee of Registering Clinical Trials on 26 March 2011. The document confirming this is in Chinese, but a translation and copy will be made available on request to Professor Rosie Xing.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Mean NPV values for HIFU procedures at 20 centres.

Table S1. Effects of HIFU and Surgery on Measures of Quality of Life (SF-36).

Table S2. Duration of hospital stay and period before returning to work. ■

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Appendix

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