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INTERVENTIONAL

MRI predictors of clinical success in MR-guided focused ultrasound (MRgFUS) treatments of uterine fibroids: results from a single centre

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Abstract
Objectives To assess the technical and clinical results of MRgFUS treatment and factors affecting clinical treatment success.
Materials and methods A total of 252 women (mean age, 42.1±6.9 years) with uterine fibroids underwent MRgFUS. All patients underwent MRI before treatment. Results were evaluated with respect to post-treatment nonperfused volume (NPV), symptom severity score (SSS), reintervention rate, pregnancy and safety data.
Results NPV ratio was significantly higher in fibroids characterized by low signal intensity in contrast-enhanced T1-weighted fat saturated MR images and in fibroids distant from the spine (>3 cm). NPV ratio was lower in fibroids with septations, with subserosal component and in skin-distant fibroids ($p<0.001$). NPV ratio was highly correlated with clinical success: NPV of more than 80 % resulted in clinical success in more than 80 % of patients. Reintervention rate was 12.7 % (mean follow-up time, 19.4±8 months; range, 3–38). Expulsion of fibroids (21 %) was significantly correlated with a high clinical success rate. No severe adverse events were reported.
Conclusions Adequate patient selection and correct treatment techniques, based on the learning curve of this technology, combined with technical advances of the system, lead to higher clinical success rates with low complications rate, comparable to other uterine-sparing treatment options.
Key Points
- *MRgFUS appears to be a valid alternative to other uterus-preserving therapies*
- *Patient selection is a significant factor in achieving high NPV ratios*
- *MRI screening parameters correlate with the amount of fibroid ablation in MRgFUS*
- *NPV results of more than 80 % correlate with higher clinical success rates*

Keywords High-intensity focused ultrasound ablation · Leiomyoma · Ablation · MRI · MR guided interventional procedures

Abbreviations

NPV	Nonperfused volume
UAE	Uterine artery embolization
SSS	Symptom severity score

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Introduction

Uterine leiomyomas (fibroids) are the most common benign, solid tumours of the female genital tract arising from myometrium and have a cumulative lifetime incidence of up to 70–80 % [1, 2]. Fibroids become symptomatic in about

25 % of the affected women. Common symptoms are dysmenorrhoea, menorrhagia, pressure, urinary frequency, pelvic pain and infertility [1].

There are various approaches established for the treatments of uterine fibroids: drug treatment (gonadotropin-releasing hormone analogues, selective progesterone receptor modulators), surgery (myomectomy and hysterectomy) and minimally invasive techniques such as uterine artery embolization (UAE) and MR-guided focused ultrasound (MRgFUS) [3].

The advantages of minimally invasive treatment modalities include a lower morbidity, a lower probability of bleeding and infection, no need for general anaesthesia and shorter recovery times compared to surgical approach [4–7]. However, postprocedural pain and an average recovery time of a few weeks are frequently described as drawbacks to UAE [8].

MRgFUS treatment is a non-invasive treatment method combining the heat-generating ability of ultrasound with magnetic resonance imaging (MRI) allowing a real-time thermal and anatomical monitoring during treatment for safe and effective ablation [9]. MRgFUS is typically an outpatient procedure (using conscious sedation), which enables most patients to return to their usual routine within 24 h.

Immediate post-treatment contrast-enhanced T1-weighted fat saturated (CE-T1w-fs) imaging allows for calculation of the nonperfused volume (NPV) ratio. The NPV correlates with mid-term clinical success rate in terms of reduction of fibroid-related symptoms and reintervention rate [10]. There is a large variety of published NPV results based on clinical studies carried out using different protocols, mostly deriving from restrictive US Food and Drug Administration (FDA) treatment guidelines that were imposed at the beginning of clinical use [10, 11]. Clinical results have been continuously improved since, through less restrictive treatment protocols in terms of NPV and based on the growing MRgFUS clinical experience [12–15]. Moreover, patient selection has been demonstrated to be a significant factor affecting technical and clinical outcome [16, 17]. In this study we analysed technical and clinical outcomes of MRgFUS treatment of uterine fibroids, in a single centre, assessing the impact of patient and fibroid-related characteristics.

Materials and methods

This retrospective study includes patients with uterine fibroids that were consecutively treated using MRgFUS during an 18-month period, from 2010 to 2012, at an academic affiliated centre, Helios Amper-Klinikum Dachau, Germany. In this study we extended the patient cohort of the previously published investigation [18] with longer follow-up period and enhanced clinical outcomes, while further assessing the technical and clinical treatment success parameters with regards to specific patient and fibroid characteristics. We have performed more than 1,000 MRgFUS procedures for uterine fibroids at our institution to date. This retrospective study was approved by the local ethics committee. Data were collected according to GCP guidelines.

All patients were clinically assessed regarding their symptoms and underwent MRI screening to evaluate their overall pelvic anatomy and fibroid characteristics. Pelvic MRI with intravenous administration of gadolinium-based contrast agent was performed in the prone position prior to treatment to determine patient suitability. The fibroid most likely to be associated with patient symptoms was determined and defined as the "dominant fibroid". Patient eligibility criteria were technical accessibility of the clinically symptomatic fibroid(s); absence of severe abdominal scaring (>3 mm in thickness) in the beam pathway; absence of bowel loops that can not be displaced from the beam pathway using mitigation techniques [19]; hypo- to isointense fibroid signal intensity (SI) on T2-weighted (T2w) images, as per Funaki et al. [16, 20]; hypo- to isointense fibroid contrast uptake on CE-T1w-fs images, as compared to myometrium [21]. All patients were advised about the potential risks of MRgFUS with respect to future pregnancies [22].

Treatment

All patients underwent MRgFUS treatment on an ExAblate 2100 UF2 (version 1) system (Insightec Ltd, Haifa, Israel) integrated into a 1.5-T MRI system (General Electric Healthcare, WI, USA). The treatment procedure in our institution was previously reported [18]. In short, after positioning the patient on the treatment table, a localizer scan was performed to identify the uterus location and presence of intestine in the beam pathway. If needed, mitigation techniques were used to move the intestine away from the potential beam pathway. These techniques include temporary bladder filling using sterile saline through a Foley catheter, rectal filling using ultrasound gel or placement of a bowl-shaped gel skin–device interface. The operator delineated the volume of the fibroids to be treated and the sensitive organs on the basis of acquired T2w MR planning images. A three-dimensional treatment plan was automatically created by the system with adjusted shapes, sizes and angles of the sonication spots and transducer apertures to avoid transmission of the beam pathway through sensitive organs, like sacral nerves, intestine and pubic bone. During the treatment, we followed the plan, adjusting energy levels to achieve temperatures of 85 °C and spot locations to achieve maximum coverage of fibroids. During the treatment session all technically device-accessible fibroids were treated. In case of proximity of fibroid(s) to the spine, small sonications were used with low energy to avoid damage of sacral nerves and pain. Sonications passing through a scar were performed with reduced energy level following the nominal cooling time, with special attention to skin heating and patient

sensation. After the treatment, CE-T1w-fs MR images were acquired to quantify the NPV ratio of all treated fibroids. As part of the standard of care in our hospital all patients were invited for a 6-month MRI follow-up scan.

Evaluation of "dominant fibroid" MRI characteristics

We retrospectively analysed the signal intensity on T2w and CE-T1w-fs images. Using multiplanar acquisition, we categorised the signal intensity of the dominant fibroid as follows: (I) T2w SI into 1–3 types, as per Funaki classification [20] (type 1, low intensity, with intensity equal to skeletal muscle; type 2, intermediate intensity, lower than myometrium but higher than skeletal muscle; type 3, high intensity, equal to or higher than myometrium) [20]; (II) CE-T1w-fs images, relative to myometrium (CE-type 1, hypointense; CE-type 2, hypo- to isointense; CE-type 3, isointense; CE-type 4, hyperintense). Patients with hyperintense Funaki type 3 and/or CE-type 4 were originally excluded from the treatment, as in both our experience and according to prior studies these fibroids are not amenable to adequate ablation [16, 23]. However, isointense Funaki type 3 fibroids were included in the study (Funaki's original classification of type 3 includes both iso- and hyperintense fibroids, regarding T2w-SI). Special note was made of internal T2 hyperintense septations (typically seen in multilobular fibroids) [21] and of the T1w-fs homogeneity of the fibroids' contrast enhancement.

Evaluation of fibroids' characteristics

We used the MR images acquired immediately before treatment to collect the following data: total number of fibroids; total fibroids volume; largest fibroid diameter; proximity to sacral nerves (classified as distance between closest posterior fibroid margin and spine (more or less than 3 cm)); location of each fibroid in the uterus (anterior wall, posterior wall, side wall or fundus); location of each fibroid in the uterine wall in eight categories, as described in Table 1; distance from skin (defined by the distance between anterior margin of the most anterior fibroid and posterior margin of the most posterior fibroid to skin); presence of scars in the beam pathway and thickness of the subcutaneous fat layer.

Technical data

We analysed the following treatment parameters: total procedure duration (patient time inside the MRI system); total sonication duration (total procedure duration excluding patient positioning, imaging and planning); total number of sonications and maximum energy used.

To evaluate the technical treatment results we used the post-treatment CE-T1w-fs images to measure the NPV and calculated the NPV ratio by dividing the post-treatment NPV by the pretreatment fibroid volume. We also used the post-treatment T2-weighted fat-saturated (T2w-fs) images to determine if there is hyperintensity (indicating oedema) in the subcutaneous fat or the abdominal muscles.

Univariate and multivariate analyses were used to identify which parameters correlate with the post-treatment NPV ratio. All baseline patient and fibroid characteristics, as well as technical factors, were checked.

Clinical results evaluation

We contacted all patients enrolled in this study in order to collect their clinical information. The retrospective assessment was done by mail, using a predefined questionnaire; in case of a missing reply, patients were contacted by phone.

The follow-up questionnaire included the eight questions of the symptom severity score (SSS) questionnaire, an assessment regarding additional fibroid interventions (hysterectomy, myomectomy, uterine artery embolization, second MRgFUS), pregnancies and delivery data and treatment-related complications. A sensitivity analysis was used to check for differences of baseline characteristics or treatment results between responders and non-responders to the questionnaire.

The SSS before and after treatment were compared. A 10 points reduction in the SSS used to be regarded as a common

Table 1 Classification of the fibroid location in the uterus wall

Intracavitary*	Submucosal fibroid located completely in the uterine cavity, pedunculated, type 0 [40]
Intracavitary/submucosal	Submucosal fibroid, distorting the uterine cavity by more than or equal to 50 %
Submucosal*	Located in the myometrium beneath the endometrium, less than 50 % of the intramural extension, type I [40]
Submucosal/intramural*	Submucosal fibroid with more than or equal to 50 % of the intramural extension, type II [40]
Intramural	Located within the uterine wall
Intramural/subserosal	Subserosal fibroid with more than or equal to 50 % of myometrium
Subserosal	Fibroid located just beneath the serosa, less than 50 % of the intramural extension
Transmural	Fibroid extending from the submucosa to less than or equal to 3 mm from the serosa

*According to European Society of Hysteroscopy guidelines for submucosal fibroids

criterion for significant symptom improvement [11, 24]. However, we took into consideration that a patient with a reduction in symptoms from 70 to 60 points differs from a patient with a reduction in symptoms from 30 to 20 points. Therefore, we divided the patients into three groups based on their baseline SSS: "mild" (22–30 points), "moderate" (30–50 points) and "severe" (>50 points). Patients who had less than 22 points at baseline were excluded from this analysis, because of the limited ability to evaluate improvement in symptoms using the SSS questionnaire [25]. Each group was expected to present a different amount of symptom reduction.

We also defined a clinical success criterion, adjusted per the baseline SSS: "mild" baseline symptoms required follow-up SSS of less than 20 points; "moderate" baseline symptoms required follow-up SSS of less than 25 points and "severe" baseline symptoms required follow-up SSS of less than 30 points in order to be considered as success. Any patients with less than 10 points improvement or any patients undergoing additional treatment were considered as treatment failures (see Table 2).

Logistic regression models were used to identify parameters correlating with the treatment success (based on our defined criteria) and with additional treatments (similar to the model of Stewart et al. [10]). The odds ratio (OR) and 95 % confidence intervals (CI) of the significant parameters are presented.

In order to find out the NPV threshold for clinical success higher than 80 % of patients, we segmented the data multiple times, each time with different NPV thresholds. We measured the success rate for each of the resulting NPV groups.

Statistical analysis

For statistical analysis, IBM SPSS 18.0 for Windows (IBM Corp, NY, USA) was used. The level of statistical significance was $p<0.05$.

In the univariate analysis Pearson correlation was used for continuous variables, Student's *t* test or Mann–Whitney *U* test for dichotomous variables and ANOVA or Kruskal–Wallis *H* for categorical variables. The significance of results was adjusted for multiple comparisons using the false discovery rate (FDR) method. In the multivariate analysis we used linear regression for continuous variables and logistic regression for success or failure (binomial) variables. Variables included in the models were all variables found significant in the univariate analysis, using the forward stepwise method.

Table 2 Clinical success criteria

Baseline SSS	Clinical success	
	Follow-up SSS	Improvement in SSS
Severe (>50 points)	<30 points	≥10 points
Moderate (30–50 points)	<25 points	≥10 points
Mild (22–30 points)	<20 points	≥10 points

Results

Patients

During the study period, 277 consecutive patients considered suitable for MRgFUS were scheduled to undergo MRgFUS treatment. Nine patients (3.2 %) were not treated because of inability to position the uterus anteriorly (7 patients), malfunction of the system (1 patient) or constant patient movement not enabling the treatment (1 patient). We excluded 16 patients who were treated because of the presence of a concomitant adenomyosis or other pathologies. In total, 252 patients (mean age, 42.1±6.9 years; range, 23–68) who successfully completed the treatment for uterine fibroids were included in this analysis. The characteristics of the patients and fibroids are summarized in Tables 3 and 4.

Treatment

Technical treatment and outcome parameters

Treatment parameters The average number of sonications per patient was 71.1±25.7 (range, 13 – 146). The total procedure duration was 03:59±1:03 h (range, 01:39–06:36). Of this, the mean preparation time was 00:59±00:27 h (00:06–02:21). In mean, the maximum energy level was 5,530±1,160 joules (range, 2,400–7,400 J).

Bowel mitigation Ninety-five patients (37.7 %) did not need bowel mitigation. In the other patients, the following combinations of mitigation techniques were used in order to move the intestine from the ultrasound beam pathway: rectal filling (with ultrasound gel) was applied in 47 patients (18.7 %); rectal filling combined with temporary bladder filling (with saline) was applied in 76 patients (30.2 %); rectal filling with temporary bladder filling combined with a use of a bowl-shaped gel was applied in 28 patients (11.1 %). Six patients (2.4 %) were treated through a full bladder, because of the inability to remove their intestine from the beam pathway using the methods described above. Although being a small number of patients, treatments with full bladder showed lower NPV ratios (77 % vs. 89 %, $p=0.047$). Patients requiring bowel mitigation had significantly smaller fibroid volumes (68 cm^3 vs. 132 cm^3, $p<0.0005$), but had no difference in their resulting NPV ratio. Preparation time for the patients with no bowel mitigation was 0:41 (±0:16) h, while patients

Table 3 Baseline characteristics of the patients (n=252 patients)

Category		
Age (years)		42.1±6.9 (23–68)
BMI (kg/m^2)		23.1±3.1 (15–38)
Subcutaneous fat layer thickness (cm)		1.5±0.7 (0.2–4.3)
Race	White	242 (96 %)
	Black	5 (2 %)
	Asian	5 (2 %)
Menopausal status	Premenopausal	248 (98 %)
	Postmenopausal	4 (2 %)
Family complete	Yes	130 (52 %)
	No	122 (48 %)
Patient symptoms	Heavy menstrual bleeding	157 (62.3)
	Bladder/intestine pressure	112 (44.4 %)
	Iron deficiency	63 (25 %)
	Pain during menstruation	145 (57.5 %)
	Pain during intercourse	29 (11.5 %)
	Non-specific pain	60 (23.8 %)
Baseline symptoms severity score (SSS)		45.1±18 (3–84)
Baseline SSS level	Mild (≤30)	46 (18.3 %)
	Moderate (30–50)	113 (44.8 %)
	Severe (≥50)	93 (36.9 %)
Presence of abdominal scar	29 (11.5 %)	

Table 4 Characteristics of the fibroids

Number of fibroids	1	97 (38.5 %)
	2–4	106 (42.1 %)
	5–10	45 (17.9 %)
	>10	4 (1.6 %)
Largest fibroid diameter (cm)		5.3±2.1 (1–12)
Targeted fibroid volume (cm^3)		91.8±99.2 (3–530)
Dominant fibroid T2w intensity [20]	Type 1	159 (63.1 %)
	Type 2	69 (27.4 %)
	Type 3 (only isointense)	24 (9.5 %)
Dominant fibroid T1w-fs contrast enhancement	CE-type 1 (hypointense)	174 (69 %)
	CE-type 2 (hypo- to isointense)	26 (10.3 %)
	CE-type 3 (isointense)	52 (20.7 %)
Dominant fibroid T1w-fs contrast enhancement homogeneity	Homogenous	180 (71.4 %)
	Heterogeneous	72 (28.6 %)
Fibroid septation in T2w		88 (34.9 %)
Fibroid components	Intracavitary	21 (8.3 %)
	Intracavitary/submucosal	36 (14.3 %)
	Submucosal	18 (7.1 %)
	Submucosal/intramural	78 (31 %)
	Intramural	32 (12.7 %)
	Intramural/subserosal	31 (12.3 %)
	Subserosal	11 (4.4 %)
	Transmural	100 (39.7 %)
Fibroids location in the uterus	Anterior wall	181 (71.8 %)
	Posterior wall	86 (34.1 %)
	Side wall	111 (44 %)
	Fundus	60 (23.8 %)
	Proximity to spine <3 cm	75 (29.8 %)

with rectal filling required 0:54 (±0:21) h, patients with rectal filling and temporary bladder filling required 1:10 (±0:26) h and with use of an additional gel bowl required 1:24 (±0:23) h in mean for preparation (p<0.0005). However, the overall procedure duration was similar in all groups.

Nonperfused volume (NPV) ratio The total mean NPV ratio was 88.7±14.4 % (range, 20–100 %). A total of 202 patients (80.2 %) had an NPV ratio larger than 80 %. In the univariate analysis, the following fibroid characteristics showed significant correlation with the NPV ratio: fibroids with septations had lower NPV ratios (80.7 % versus 92.9 %, respectively) (Fig. 1); fibroids without subserosal component had higher NPV ratios (92.9 % versus 85.1 %, respectively); fibroids located near the spine (less than 3 cm) had lower NPV ratios (81.4 % versus 91.7 %, respectively); dominant fibroid intensity and contrast enhancement also affected NPV, while comparing type 1–3 fibroids in T2w (91.3 %, 85 % and 81.9 %, respectively) and CE-type 1–3 in CE-T1w-fs (91.9 %, 84.7 % and 79.6 %, respectively) (Figs. 2 and 3). Treated fibroid volume and distance from skin had a negative correlation with the NPV ratio (−0.268 and −0.256, respectively). Table 5 shows the univariate analysis results.

In the multivariate analysis, five factors were found to significantly affect NPV ratio: presence of septation (reduced 8.0 % in the NPV) (Fig. 1), dominant fibroid enhancement in CE-T1w-fs (reduced 6.2 % for type 2 and 11.3 % for type 3) (Fig. 3), distance from skin (reduced 1.5 % per cm distance), proximity to spine less than 3 cm (reduced 3.9 %) and presence of subserosal component (reduced 3.6 %).

Additional fibroid treatments During the data collection period, 28 (12.7 %) of the patients underwent an additional treatment as a result of symptom persistence or recurrence: 11 (5 %) patients had a second MRgFUS treatment, 11 (5 %) patients underwent embolization (UAE) and 6 (2.7 %) had surgery (hysterectomy or myomectomy). Although not symptomatic, an additional 5 (2.3 %) patients underwent a second MRgFUS treatment as a preventive measure after detecting vital fibroid tissue in the follow-up MRI scan, as was suggested by Pelage et al. [26]. Two (0.8 %) patients had an additional intervention because of newly emerged uterine pathology (endometrial hyperplasia and adenomyosis).

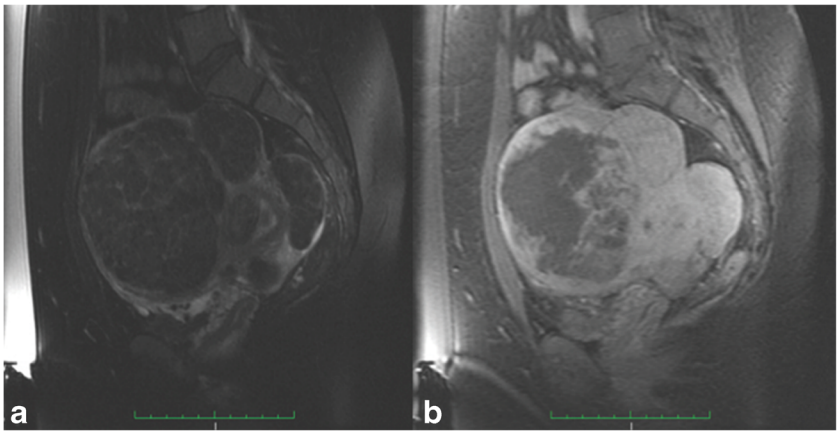

Fig. 1 A 33-year-old woman with one treatable 345-cm^3 fibroid experiencing hypermenorrhoea, pressure on bladder and unfulfilled desire for pregnancy. **a** Sagittal T2-weighted fat-saturated MR image before treatment shows a hypointense, transmural fibroid in the anterior uterine wall with hyperintense intramyomal septations. **b** Sagittal contrast-enhanced fat-saturated MR image after treatment shows contrast enhancement of residual vital tissue (NPV ratio of 66 %) probably due to energy absorption of septa

A multivariate logistic regression showed that the NPV ratio is the only statistically significant variable for predicting the risk of retreatment. A higher NPV ratio results in lower chances for additional treatments (OR 0.67 per 10 % increase of NPV, 95 % CI 0.53–0.83). Figure 4 shows the probability of additional fibroid treatment as a function of NPV ratio, based on the logistic model.

Fibroid expulsion rate Of the 165 patients (65 %) with MRI follow-up, in 35 patients (21 %) formerly treated fibroids were no longer detectable in the MRI follow-up, indicating fibroid expulsion. The mean MRI follow-up time for these patients was 7.5±3.5 months (range, 4–20). Depending on the fibroid type (see Table 1), 57 % of the patients with treated intracavitary fibroid component and 29 % of the patients with treated submucosal fibroid component had a fibroid expulsion. No expulsion was observed in patients without intracavitary or submucosal components. The average diameter of expelled fibroids was based on pretreatment MRI scan 2.5±1.3 cm (range, 0.7–6.4). These patients had slightly lower total fibroid volumes (64 cm^3 vs. 97 cm^3, p=0.004) and were more symptomatic at baseline (SSS of 52 points vs. 44 points, p=0.007). The treatment of patients with expelled fibroids resulted in higher NPV ratios (94 % vs. 88 %, p=0.002) and their mean SSS at follow-up was reduced down to 10 or less points, significantly lower than other patients (p=0.001).

Clinical outcome

Symptom relief Of the 252 treated patients, 31 patients (12 %) could not be reached through mail or phone. Sensitivity analysis showed that baseline characteristics of non-responders did not significantly differ from characteristics of responders. These non-responders, as well as patients who underwent an

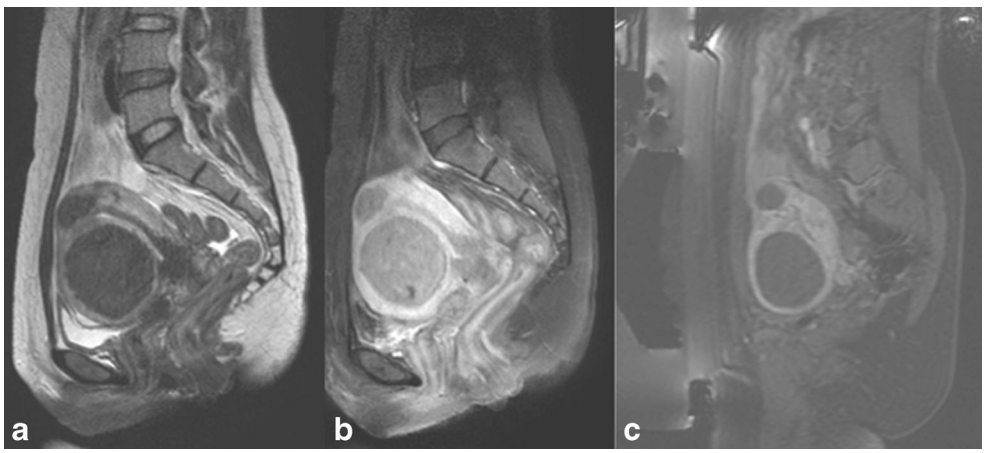

Fig. 2 A 47-year-old woman with 98 cm^3 of fibroid experiencing hypermenorrhoea. **a** Sagittal T2-weighted MR image before treatment shows a hypointense, non-septated submucosal/intramural fibroid and an intramural/subserosal fibroid in the anterior uterine wall and fundus. **b** Sagittal contrast-enhanced fat-saturated MR image before treatment shows a homogeneous low enhancement, as compared to myometrium. **c** Sagittal contrast-enhanced fat-saturated MR image after treatment shows a complete ablation of both fibroids with NPV ratio of 100 %

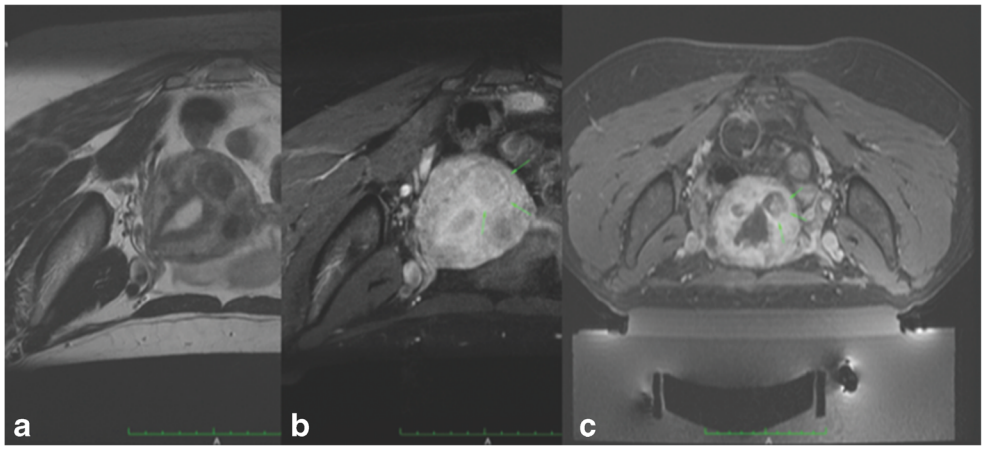

Fig. 3 A 48-year-old woman with 25 cm^3 of multiple fibroids experiencing hypermenorrhoea and pressure on bladder. **a** Axial T2-weighted MR image before treatment shows a hypointense submucosal/intramural fibroid with signal intensity lower than myometrium but higher than skeletal muscle (type 2, as per Funaki et al. [19]). **b** Axial contrast-enhanced fat-saturated MR image before treatment shows an isointense contrast enhancement (*green arrows*), compared to myometrium (CE-type 3). **c** Axial contrast-enhanced fat-saturated MR image after treatment shows contrast enhancement of residual vital tissue (*green arrows*), an NPV ratio of only 40 % was achieved

Table 5 Univariate analysis of factors influencing the NPV ratio

Binary factor		Yes	No	*p* value
Dominant fibroid homogenous contrast enhancement		89.2±13.1 % (*n*=180)	87.4±17.1 % (*n*=72)	0.366
Dominant fibroid septated		80.7±16.4 % (*n*=88)	92.9±11.0 % (*n*=164)	<0.0005*
Rectal filling		89.2±14 % (*n*=157)	87.8±15 % (*n*=95)	0.46
Bladder filling		89.2±12.9 % (*n*=109)	88.2±15.4 % (*n*=143)	0.606
Treating through full bladder		77.2±17 % (*n*=6)	88.9±14.2 % (*n*=246)	0.047
Use of gel bowl		90.7±12.8 % (*n*=35)	88.3±14.6 % (*n*=217)	0.374
Subserosal component		85.1±15.7 % (*n*=138)	92.9±11.2 % (*n*=114)	<0.0005*
Fibroid location near spine		81.4±15.1 % (*n*=75)	91.7±12.9 % (*n*=177)	<0.0005*
Fibroid in the anterior wall		88.7±13.9 % (*n*=181)	88.5±15.6 % (*n*=71)	0.932
Fibroid in the posterior wall		86.5±14 % (*n*=86)	89.7±14.5 % (*n*=166)	0.093
Fibroid in the side wall		86.7±14.8 % (*n*=111)	90.2±13.9 % (*n*=141)	0.06
Fibroid in the fundus		89.4±13.5 % (*n*=60)	88.4±14.6 % (*n*=192)	0.654
Presence of scar		89.3±10.4 % (*n*=29)	88.6±14.8 % (*n*=223)	0.804
Categorical factor		*N*	NPV	*p* value
Number of fibroids	1	95	88.1±15.1 %	0.241
	2–4	108	90.2±13.8 %	
	≥5	49	86.3±13.9 %	
Dominant fibroid intensity in T2w [20]	Type 1	159	91.3±12.2 %	<0.0005*
	Type 2	69	85±16.4 %	
	Type 3 (only isointense)	24	81.9±17.2 %	
Dominant fibroid enhancement in CE-T1w-fs	CE-type 1 (hypointense)	174	91.9±10.7 %	<0.0005*
	CE-type 2 (hypo- to isointense)	26	84.7±14.8 %	
	CE-type 3 (isointense)	52	79.6±19.8 %	
Continuous factor		Pearson correlation with NPV ratio		*p* value
Fibroids volume		−0.268		<0.0005*
Fat layer		−0.103		0.102
Distance from skin		−0.256		<0.0005*
Age		−0.019		0.767
BMI		−0.135		0.032

*Significant

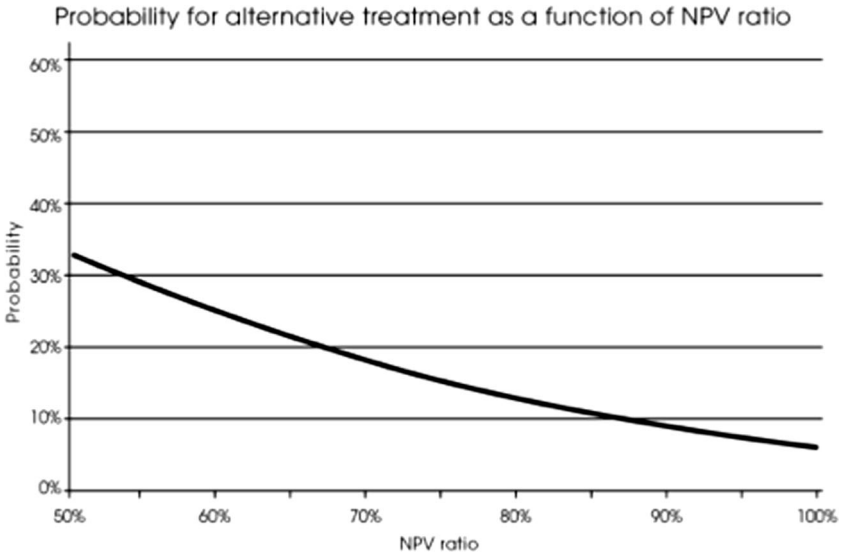

Fig. 4 The probability of undergoing an additional fibroid treatment as a function of NPV, during mean follow-up time of 19.4 months after MRgFUS. The *line* in the graph represents the logistic regression model results. The chance of additional treatment is significantly reduced as NPV is increased

additional treatment, were not included in the symptoms relief analysis.

The baseline SSS was 45.1±18 points (range, 3–84) that decreased post-treatment to 14.5±12.2 points (range, 0–69). The mean follow-up time was 19.4±8 months (range, 3–36).

Of patients with follow-up data available, 93 % had an improvement of more than 10 points.

There was significant symptom relief in all patient groups of "mild", "moderate" and "severe" symptoms score (Fig. 5). Fourteen patients had less than 22 points SSS at baseline: 8 patients had only desire to conceive, 5 patients had only pain symptoms and 1 patient had only bleeding symptoms.

Clinical success analysis For the clinical success analysis we excluded 31 patients who had no follow-up and 14 patients who had less than 22 points SSS at baseline, resulting in a total of 207 patients. Of them, 153 patients (74 %) were considered as a clinical success, according to the predefined success criteria. Logistic regression model analysis shows that the only parameter correlating with treatment success was NPV (OR 1.8 per 10 % increase of NPV, 95 % CI 1.4–2.4).

We found that NPV ratios of more than 80 % resulted in an 81 % clinical success rate (n=162 patients; mean NPV, 95.2 %) as compared to the group with NPV less that or equal to 80 % (n=45 patients; mean NPV, 67.8 %; clinical success rate, 51 %). The full results are presented in Fig. 6.

Pregnancy Out of 99 patients who reported at baseline that they had not completed family planning and who answered the questionnaire, 15 patients (15 %) got pregnant during this study. During this period 12 patients delivered without reported complications (mean of 19.7 months after treatment), two others are still pregnant and one had a spontaneous abortion. The mean age of these patients was 35.3±3.4 years (range, 30–42). To date, all reported pregnancies proceeded without pregnancy-related complications.

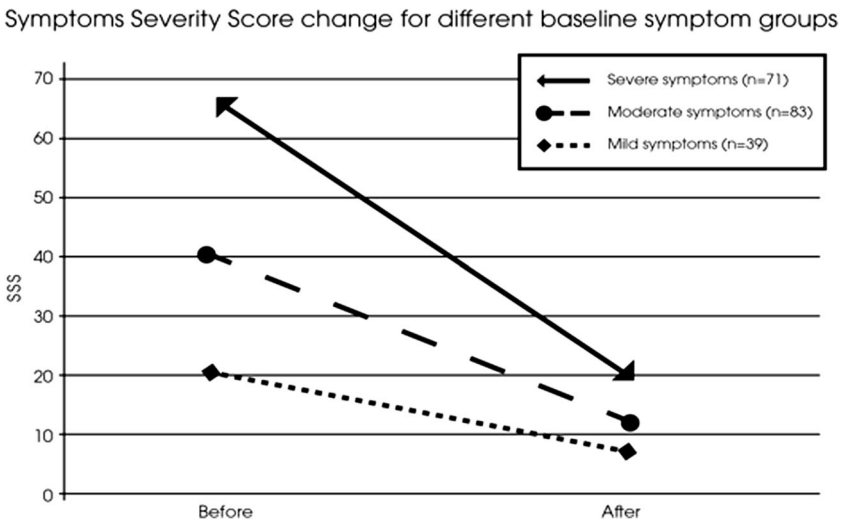

Fig. 5 Measured mean symptoms severity scores (SSS) of the Uterine Fibroid Symptoms Quality of Life scale stratified by 3 baseline symptoms ("mild": 22–30 points, "moderate": 30–50 points, and "severe": > 50 points) before treatment and during follow-up. In this graph we included only patients with available follow-up SSS. There is a significant difference between the SSS before and after treatment for each of the 3 baseline symptom groups

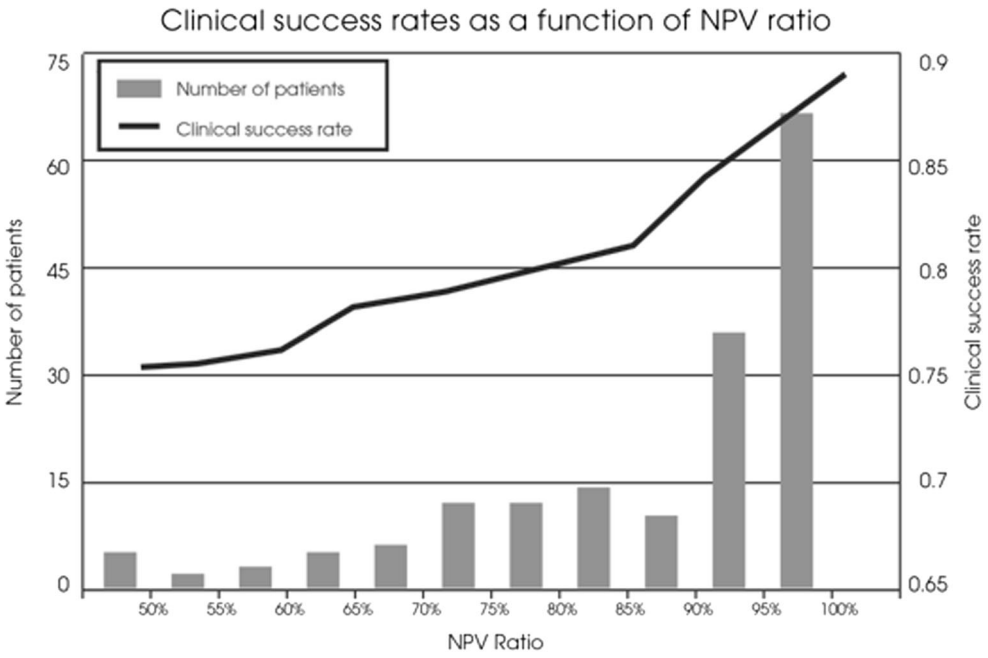

Fig. 6 This graph illustrates how clinical success rate increases as NPV ratio increases. Data is segmented at each NPV ratio level and the line graph showing the clinical success rate for each segmented group. Clinical success of 81 % is achieved when the NPV ratio threshold is 80 %. Superimposed is also this study's NPV ratio distribution showing that most patients achieved NPV ratios≥90 %

Adverse events No serious adverse events [27] were documented during treatment or reported during follow-up. One patient treated for a 6.2-cm submucosal fibroid experienced strong menstrual bleeding for 4 months and underwent hysteroscopic surgery for the necrotic fibroid tissue remnant removal.

Three patients had a first-degree skin burn after treatment and two of them had a scar from previous surgeries. These patients were given topical anti-inflammatory medications and all events resolved within 1 week without any sequelae.

Although patients, on the basis of post-treatment T2w-fs images, did not directly report complaints we found that 26 patients (10.4 %) had oedema in the subcutaneous fat layer and or the abdominal muscle. The only parameter correlating with edema was the fat layer size; the average fat layer of patients without oedema was 1.5±0.6 cm, while the average fat layer of patients with oedema was 2.1±0.9 cm (p=0.002).

Discussion

To the best of our knowledge this is the first study conducted in a single centre, evaluating both NPV results and its clinical success in the largest consecutive patient series for MRgFUS treatments of uterine fibroids. This is also the first study reporting fibroid expulsion rates and pregnancy rates following MRgFUS treatment.

The analysis shows that patient age does not affect the clinical success or the probability of additional treatment and therefore the NPV ratio is the dominant factor for clinical success, independent of age. The targeted fibroid volume in this study is lower compared to previous studies [10, 28], which can be explained by the selection process in our institution.

Bowel mitigation techniques mainly included rectal filling and temporary bladder filling, which were implemented as a standardized process and can explain the low treatment cancellation rate (2.7 %) owing to interposition of the bowel anterior to the uterus. Treatments with full bladder were pursued after other mitigation possibilities to remove the bowel had failed and showed lower NPV ratios, probably as a result of close proximity to the sacral nerves not allowing one to use high energy for adequate ablation and progressive bladder filling resulting in uterus movement. The use of bowel mitigation technique was required more frequently in patients with smaller fibroids, as large fibroids naturally avoid bowel interposition in the beam pathway.

Technological development of the second generation system (such as transducer aperture and elevation, elongated spot types, automatic optimal planner) and the learning curve in our hospital (such as patient selection and bowel mitigation techniques) resulted in a significant improvement of the NPV ratios as published in our previous studies [29, 18] and is presented in the current study on a larger patient series.

Our results suggest that some fibroid characteristics significantly correlate with NPV ratio. Specifically, in the univariate analysis, the characteristics include the fibroid's subserosal component, fibroid septation, targeted fibroid volume, fibroid T2w and CE-T1w-fs intensity and distance from spine and skin. In the multivariate analysis the fibroid volume and T2w intensity were not found to be significant factors. This may be explained by the fact that large fibroids have components close to the spine, to the serosa and often show multilobular

structures with septations. The T2w intensity is correlated with the CE-T1w-fs data. The influence of fibroid septations and the CE-T1w-fs intensity on MRgFUS treatment results should be further investigated.

Previous studies showed the correlation of NPV results with fibroid intensity as shown in T2w images. Although we also observed this correlation, the multivariate analysis in this study shows that the NPV ratio can be effectively predicted on the basis of the fibroid enhancement shown in CE-T1w-fs images, similar to [23]. This finding suggests that physicians should in addition consider incorporating CE-T1w-fs screening images in the patient selection process.

All uterine-preserving treatments have a potential risk of reintervention, caused by fibroid regrowth and symptom recurrence. The reintervention rate in our patient series was 12.7 % in this study's follow-up time, which is comparable with UAE [5, 30, 31] and with surgical procedures [32, 33]: in a large meta-analysis of 54 UAE studies, Toor et al. [30] found a reintervention rate of 5.3 % (4.2–6.4 %) calculated per patient year, with follow-up range from 0.25 to 5 years. Cumulative risk of recurrence for laparoscopic myomectomy in a study based on 114 patients was 10.6 %, 31.7 % and 51.4 % after 1, 3 and 5 years respectively, 12 % of them had additional treatments [32]. A recently published study [34] comparing UAE (n=41 patients) and MRgFUS (n=36 patients) at a median follow-up time of 62 months showed a 12.2 % reintervention rate after UAE and 66.7 % after MRgFUS. In this MRgFUS study, patients were treated using the first generation system (with limited technical capabilities compared to the system used in our current study) and under FDA limitations that significantly confined the maximum allowed fibroid treatment volume. Furthermore fibroid perfusion was not taken as an exclusion criterion for MRgFUS treatment. Overall, some patients in this study may be considered as undertreated. The variation of MRgFUS reintervention rates in published studies can be explained by patient selection criteria and consecutive NPV ratio achieved. For fibroids of type 1 and 2, Funaki et al. reported a reintervention rate of 14 % at 24-month follow-up, which is similar to our study [35].

In a prior study by Stewart et al. a logistic model showed that the probability of reintervention decreases as the NPV ratio increases. Our findings support these results in higher NPV ratio range [10].

On the basis of the SSS results, this study shows significant symptom relief with an average SSS reduction of 31 points in the mean follow-up time of 19.4 month, similar to 28.1 points and 29.4 points reduction at 12-month follow-up reported in prior studies [12, 24].

The significant symptom improvement was defined in previous studies by a decrease in the SSS questionnaire results of 10 points or greater. Early results of MRgFUS measured such significant symptom improvement in 51–91 % of the patients at 12-month follow-up [11, 12, 24], to be compared with 93 % in our patient series. However in our study we defined clinical success differently, combining two criteria to define clinical success: reintervention and SSS improvement based on baseline SSS. According to these criteria, we had a success rate of 74 %. All three SSS groups improved, reaching an average score below 22 points. This can be considered as the average score of premenopausal women with no fibroids [25].

Our results show that in order to achieve a clinical success rate of 80 % or higher an NPV ratio of more than 80 % should be aimed at. We suggest this NPV ratio level as a treatment success threshold. The patient selection criteria used in this study could be used as a recommendation to achieve a higher NPV ratio and the clinical success of the treatment.

Technical data in this study has shown a high clinical success rate and relatively low complication rate in patients having expelled fibroids (21 %). Expulsion of fibroids has been reported after UAE as a frequent phenomenon [36] and may be considered as the natural progress of a curing process rather than a complication [37, 38]. Only one patient reported a prolonged tissue sloughing requiring a hysteroscopic intervention. The symptom improvement in patients who had fibroid expulsion was significantly higher, probably owing to complete natural removal of the symptomatic fibroid. Nevertheless we recommend to inform patients with submucosal and intracavitary fibroid components in the pretreatment consultation about potential expulsion of the fibroids and about associated abdominal pain, bleeding or secondary infection [39].

Promising results about the pregnancy and delivery rate in this study group should be further investigated to provide extended evidence for MRgFUS treatment.

The rate of adverse events (1.8 %) in this study was low, three minor skin burns occurred and one patient required surgery due to prolongated post-treatment symptoms. We encountered asymptomatic patients with subcutaneous fat or abdominal muscle oedema post-treatment, which correlates with larger subcutaneous fat layer. On the basis of these results we suggest increasing the cooling time between sonications or frequent T2w-fs imaging in order to control the presence of oedema or its progress in patients with thicker fat layers.

As shown in this study MRgFUS treatment is a valid alternative to other uterus-preserving therapies in terms of safety and symptom control. It requires a close cooperation between gynaecologists and radiologists. It is important to evaluate further long-term follow-up results of patients treated with a high NPV ratio and support scientific and technical development of MRgFUS treatments.

Adequate patient selection and correct treatment techniques combined with technical advances of the system lead to higher clinical success rates with low complications rate, comparable to other uterine-sparing treatment options.

Limitations

This is a single centre retrospective study with a homogenous patient cohort including mainly Caucasian women. In this study we did not evaluate patients that were excluded from the treatment. The treatments followed specific inclusion criteria established under consideration of scientific data published until the study period and of the previous treatment experience in our institution. These are mid-term follow-up results; long-term follow-up results should be further investigated for better assessment of the post-treatment MRgFUS outcome. Although we evaluated treatment success based on combining SSS criteria and additional treatment, it should be mentioned that the SSS score does not capture pain or desire to conceive in fibroid patients.

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