

# Evaluation of Junctional Zone Differential and Ratio as Possible Markers of Clinical Efficacy in Uterine Artery Embolization of Adenomyosis

Kolos Turtóczki

turtoczki.kolos@semmelweis.hu

Semmelweis University: Semmelweis Egyetem <https://orcid.org/0009-0007-3296-3230>

Hyunsoo Cho

Semmelweis University: Semmelweis Egyetem

Sorour Dastaran

Semmelweis University: Semmelweis Egyetem

Pál N. Kaposi

Semmelweis University: Semmelweis Egyetem

Zoltán Tömösváry

Semmelweis University: Semmelweis Egyetem

Szabolcs Várbíró

Semmelweis University: Semmelweis Egyetem

Nándor Ács

Semmelweis University: Semmelweis Egyetem

Ildikó Kalina

Semmelweis University: Semmelweis Egyetem

Viktor Bérczi

Semmelweis University: Semmelweis Egyetem

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## Research Article

**Keywords:** adenomyosis, embolization, MRI, clinical efficacy, safety

**Posted Date:** April 10th, 2024

**DOI:** <https://doi.org/10.21203/rs.3.rs-4164108/v1>

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# Abstract

## Introduction

Uterine artery embolization is a well-established method of adenomyosis treatment. Changes in uterine volume and maximal junctional zone thickness (JZmax) after embolization are thoroughly analyzed in the literature. Changes in other suggested morphological diagnostic markers of adenomyosis (junctional zone differential – JZdiff - and junctional zone ratio - JZratio) on the other hand are rarely evaluated. This single-center retrospective study aimed to analyze the changes in morphological parameters used for the MR imaging diagnosis of adenomyosis (including JZdiff and JZratio) after UAE. Clinical effectiveness and safety were also analyzed.

## Materials and methods

Patients who underwent UAE for adenomyosis from 2008-2021 were evaluated. Adenomyosis was diagnosed based on JZmax, JZdiff, and JZratio measured on MR imaging. To assess clinical efficacy numerical-analog-quality-of-life (QoL) score was routinely obtained from patients at our centre. MRI morphological data were analyzed. Wilcoxon signed-rank test, uni- and multivariate regression models, Pearson product-moment correlation, and Kruskal-Wallis tests were used for statistical analysis.

## Results

From our database of 801 patients who underwent UAE in 14 years, preprocedural MR images were available in 577 cases, 15 patients had pure adenomyosis (15/577, 2.6%). Uterine volume, JZmax, and JZdiff decreased significantly after UAE; QoL score increased significantly. A significant correlation was found between QoL change vs. JZmax and JZdiff change. Permanent amenorrhoea and elective hysterectomy 5 years after UAE were both 7.1%.

## Conclusion

Change of JZdiff after UAE in adenomyosis is a potential marker of clinical success. UAE is clinically safe and effective treatment in adenomyosis.

**Level of Evidence:** Level 4, Case Series.

## INTRODUCTION

Adenomyosis is characterised by the presence of heterotopic endometrial glands and stroma deep within the myometrium with adjacent myometrial hyperplasia [1]. Heavy menstrual bleeding, pain, and fertility issues are the most common symptoms affecting 2/3 of premenopausal women with adenomyosis [2]. Magnetic Resonance (MR) imaging is currently used as a second-line investigation technique for adenomyosis after transvaginal ultrasound with a higher sensitivity, specificity, and lower operator dependence than the latter [3]. Diagnosis of adenomyosis on MRI is based on identifying direct and

indirect signs. T1 or T2 hyperintense submucosal microcysts are considered the only direct sign of the disease representing ectopic endometrial glandular and stromal components displaced in the inner myometrium [4]. Maximalis junctional zone thickness (JZmax) > 12 mm was the main indirect diagnostic criteria of the disease for a long time. Due to the conflicting values for the sensitivity and specificity of this threshold, other indirect signs were introduced [5]. Junctional zone differential (JZdiff) is the difference between the maximal and the minimal thickness of the junctional zone. The junctional zone ratio (JZratio) is the ratio of the junctional zone thickness and the myometrial thickness at the location of maximal JZ thickness [6].

Uterine artery embolization (UAE) has been proposed as a minimally invasive alternative to hysterectomy in the treatment of patients with symptomatic adenomyosis [7–10]. A decrease in uterine volume and JZmax after embolization is a well-documented finding in the literature [9]. However, only scarce data is available regarding the change and possible predictive role of JZdiff and JZratio [11].

This single-centre retrospective study aimed to assess the change in MR morphological parameters after UAE in adenomyosis and to analyse the relation of morphological and clinical parameters. Long-term follow-up information is also provided.

## MATERIALS AND METHODS

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in this study. Ethical approval was given by the Research Ethical Committee of XXXXXXXXXXX (172/2022).

Reports and MR images of all patients from our UAE database containing 801 patients who had UAE in the period between April 1, 2008, and September 30, 2021, were reviewed by a senior radiology resident (XX) and validated by a certified radiologist (YY) with experience in female pelvic MR imaging for more than 20 years to identify patients with adenomyosis. All patients who had preprocedural MRI examination where the images were still available were enrolled. PostUAE MR imaging for the pure adenomyosis patients was performed at  $7.6 \pm 3.8$  months.

MR imaging was performed with 1.5 T and 3.0 T systems (Philips Ingenia 1.5 T, Philips Achieva 1.5 and 3.0 T, and Siemens Magnetom Harmony 1.0 T). MRI protocol contained T1, T2, and T1 contrast-enhanced sequences.

Adenomyosis was diagnosed if T1 or T2 hyperintense submucosal microcysts were detected as the principal direct sign of the disease [4]. Adenomyosis was also diagnosed if the maximal junctional zone thickness (JZmax) was greater than 12 mm. In the case of a JZmax measurement between 8 and 12 mm, the diagnosis was given if the JZdiff was higher than 5 mm and the JZratio was higher than 0.4 [12, 13]. Junctional zone differential (JZdiff), and junctional zone ratio (JZratio) were also obtained in each

case [6]. The minimal thickness was measured on the anterior and posterior uterine walls, for the calculation of the JZ differential, the smaller value was used regardless of which wall the maximal JZ thickness was measured (Fig. 1).

Differences between pre- and postprocedural values of uterine volume (Uvol), JZmax, JZdiff, and JZratio were obtained. Non-perfused volume on contrast-enhanced T1 sequences following embolization were categorized as total, partial or none. Preprocedural MRI morphological parameters (JZmax, JZdiff, JZratio, Uvol) were correlated with preUAE QoL score. Correlation between UAE-induced change in MRI morphological parameters and change in QoL score was also analysed. PreUAE MRI morphological parameters and change in QoL score were correlated.

All embolization procedures were performed using standard procedures by the same interventional radiologist (XX) with more than 20 years of experience. A catheter was inserted using the unilateral right common femoral artery access, and super-selective angiography of both uterine arteries was obtained with a 4F catheter. Embolization was achieved by injecting non-spherical polyvinyl alcohol (PVA) particles into each uterine artery (500–710 µm, COOK PVA-500, Bloomington, IN, USA; 500–700 and 355–500 µm Contour, Boston Scientific-Target Therapeutic, Fremont, CA, USA) until it reached a near-stasis flow state. The volume of injected PVA was noted. The puncture site was manually compressed after the procedure. Patients routinely received antibiotic prophylaxis (amoxicillin-clavulanic acid or clindamycin). Tramadol, meloxicam, metamizole-Na, nalbuphine, and drotaverine were additionally given for postoperative pain control.

At our centre clinical success was routinely assessed by interviews where patients were asked whether their symptoms have improved, have improved partially, or have not improved; also if they would recommend UAE to other patients with symptomatic adenomyosis. A numerical analogue quality-of-life (QoL) score (0: intolerable symptoms, 100: perfect QoL) was obtained before and after the embolization in all patients to assess the clinical efficacy of the procedure [14, 15]. A difference between pre- and postUAE values of QoL was obtained. Long-term clinical follow-up for QoL score was also analyzed. Complications were documented. Follow-up time ended by the last office meeting/telephone interview, or at the time of menopause or elective hysterectomy.

Data are expressed as median and range. Wilcoxon signed-rank test, uni- and multivariate regression models, Pearson product-moment correlation, and Kruskal-Wallis tests were used for statistical analysis (R Statistical Software, v4.1.2; R Core Team 2021). P values < 0.05 were considered statistically significant.

## RESULTS

From our database of all UAE patients (801 patients between April 2008 and September 2021), 577 patients had available MR reports and images before UAE. Pre- and postUAE MR images and reports were available in 420 cases. Pure adenomyosis without uterine fibroids was identified in 15 cases; 12 of 15

patients had pre- and post-procedural MRI. The mean age of patients at the time of UAE was  $44.4 \pm 5.4$  years. The mean value of the total amount of injected PVA during UAE was  $3.0 \pm 1.5$  ml.

No significant correlation could be observed between preprocedural MRI morphological factors and preprocedural QoL score, or QoL score change.

Pre- and post-procedural MR parameters are presented in **Table 1**: Uvol, JZmax, and JZdiff decreased significantly after UAE ( $p = 0.003$ ,  $0.013$ , and  $0.023$ , respectively); there was no significant change in JZratio ( $p = 0.5529$ ). A representative case is shown in Fig. 2.

A significant correlation was found between QoL change and JZmax change ( $p = 0.005$ ,  $r = 0,776$ ), and between QoL change and JZdiff change ( $p = 0.016$ ,  $r = 0,704$ ), while no significant correlation could be found between QoL change and uterine volume change and between QoL change and JZratio change.

Non-perfused volume was total in 1 case (1/12, 8.3%), partial in 5 cases (5/12, 41.7%), and none in 6 cases (6/12, 50%). QoL score significantly improved both in the partial (QoL score change  $81 \pm 19$ ,  $p = 0.029$ ) and none (QoL score change  $61 \pm 27$ ,  $p = 0.031$ ) groups; there were no significant differences between the “partial” and “none” groups neither in the preUAE QoL score nor in the postUAE QoL score, nor in the QoL score changes.

Clinical follow-up data are presented in **Table 2**. Clinical data, changes in QoL score and any complications were available from 14 patients (14/15, 93.3%). All patients reported clinical success, and at least partial improvement in their symptoms (14/14, 100%;  $n = 12$  “Yes”,  $n = 2$  “partially”), and all of them would recommend UAE to other patients (14/14, 100%). The mean follow-up time was  $64.6 \pm 46.5$  months (range: 9-147 months). QoL score increased significantly 1 year after UAE ( $p = 0.001$ ), the increase was permanent up to 11 years (**Table 2**; Fig. 3). Permanent amenorrhoea was observed in one 47-year-old patient within 1 year (1/14, 7.1%), this patient considered menopause at this age as an advantage and not as a complication. For a 44-year-old patient, elective hysterectomy was performed 5 years after UAE (1/14, 7.1%).

## DISCUSSION

### Morphological data

Multiple papers showed a uterus volume decreased 8–54% within a year following UAE assessed by MRI [9]. Our data ( $25 \pm 14\%$ ) on pure adenomyosis falls within the range reported in the literature.

The decrease of JZmax following UAE was 12.0–33% in the studies of 1999–2010 [10]. In the other systematic review of studies between 2001–2016, 4 papers reported a decrease in JZ of 13.7–38%, however, most papers (26/30, 86.7%) cited in this systematic review did not report on JZ [9]. JZ thickness was shown to be thicker in patients who underwent hysterectomy for persistent symptoms [14], however,

the insufficient response was not correlated with significantly thicker JZ in another paper [15]. Our finding of a 15% mean reduction in JZ thickness is in line with previous reports.

Besides the widely used junctional zone thickness, JZ differential and JZ to myometrial ratio have also been suggested as objective measures to improve the diagnostic accuracy of MRI in adenomyosis [6, 13, 16]. Kitamura et al. found no significant decrease in JZratio after embolization of 19 patients with pure or dominant adenomyosis [11] – our findings regarding JZratio change align.

This is the first study to our knowledge to report on the correlation between QoL change and junctional zone characteristics. A significant correlation between QoL change vs. JZmax change, and QoL change vs. JZdiff change underlines the importance of these measurements and their relation to the imaging appearance of adenomyosis. JZmax is the classic and long-debated MR morphological factor still in use in everyday practice that forms the base of the imaging diagnosis of adenomyosis and is a main pillar in some aspects of disease classification [13, 16, 17]. JZdiff on the other hand is considered as a second-line measurement in imaging diagnosis. Based on our findings JZdiff could have a more significant role in the imaging diagnosis than it is presently used and the ever-evolving classification of adenomyosis as a marker of junctional zone inhomogeneity. Moreover, the change of JZdiff after UAE in adenomyosis may be a potential marker of clinical success.

The infarction rate of adenomyosis following UAE seems to be smaller than that of fibroids, its reported range is 44.2%-82.5%, however, most studies (26/33, 78.8%) have not reported the infarction rate [9]. Bae et al concluded that an infarction cut-off rate of < 34.4% has 7 times higher risk of symptom recurrence [18]. One other study, however, showed that correlation between improvement of symptoms and imaging at 3 months follow-up was statistically not significant [19]. Our results resonate with this latter paper: there was a significant improvement in QoL score in both the „none” and „partial” group, in addition, symptom improvement (increase in QoL score) was not significantly different between the „none” and „partial” group, thus total infarction of the adenomyotic region seems not to be a prerequisite for clinical success.

The exact mechanism of heavy menstrual bleeding and dysmenorrhoea in adenomyosis, and the mechanism of how UAE improves symptoms in adenomyosis is not fully understood. Microvessel density, endometrial surface and overall uterine size may be contributing factors [11, 20]. Following embolisation, as opposed to normal myometrium, adenomyotic tissue presumably is not capable of opening up vessels, thus, it may be less tolerant to ischaemia [20, 21].

## **Clinical data (patient satisfaction, short-term and long-term clinical success, complications)**

The overall satisfaction in the systematic review by Popovic et al. was 75.7% [10]. The more recent systematic review reported patient satisfaction rates for < 12 months follow-up pure adenomyosis and combined adenomyosis 89.6% and 94.3%, respectively; long-term data (> 12 months) for pure adenomyosis and combined adenomyosis was 74.0% and 85.4%, respectively. A recent study showed

90% clinical success [20]. The longest follow-up ( $95 \pm 9$  months) was reported by de Bruijn et al [22]. Our data with the second longest follow-up data (mean follow-up time was  $65 \pm 47$  months [median 55, range: 9-147 months]) on patients with pure adenomyosis showed 100% patient satisfaction (symptom improvement „yes” in 85.7%, „partial” in 14.3%), all our patients would recommend UAE to another patient with adenomyosis.

Clinical follow-up in the literature is mostly provided as symptom improvement; UFS-QoL scores ( $n = 5$ ) or HRQOL ( $n = 1$ ) were analysed only in 20.0% (6/30) of the studies, showing significant improvements in UFS-QOL [9]. Uterine fibroid questionnaires have been used since adenomyosis-specific QoL questionnaires are not available. We used numerical analogue QoL score to assess clinical efficacy, which was used in previous publications [23, 24] to assess clinical effectiveness of UAE in symptomatic uterine fibroids, however, this score is not specific for fibroid symptoms, it gives a score for the clinical improvement of preUAE symptoms.

Popovic showed that not all studies reported on complications; among the reported cases, 13.2% (1.5 to 29.3%) had a hysterectomy, the majority occurring approximately 12 months (range 2–27 months) after UAE (10). In the review by de Bruijn from 2017, only 20/30 (66.6%) studies reported on complications; hysterectomy in the short-term (< 12 months) follow-up group for pure adenomyosis and combined adenomyosis was 2.6% and 1.4%, respectively [9]. The same numbers for long-term (> 12 months) follow-up were 7.2 and 7.0%, respectively. Hysterectomy was 18% with 7-year follow-up (22). In our cohort, the hysterectomy rate was 7.1% with the second longest follow-up period of  $65 \pm 47$  months.

In the systematic reviews, permanent amenorrhea occurred in 20.9%, all > 45 years old (10); it was 6.3%, all > 40 years old (3), our data showed similar results (7.1%) at the age of 47 years.

Other published complications included spontaneous fibroid expulsion in 10 patients, four suspected endometritis, all responded well to broad-spectrum antibiotics, and deep venous thrombosis in the calf in 1 case (9). In the study of the longest (7-year) follow-up, 36% of the patients experienced the absence of menstrual periods for at least 12 months [22]. No death or serious adverse event (including emergency hysterectomy) occurred [9, 10].

## **Strengths and limitations**

This is the first study to our knowledge to report on the correlation between QoL change and junctional zone characteristics in adenomyosis after UAE with the second longest clinical follow-up.

Limitations include a low number of patients in this single centre, retrospective study. Procedures performed within a long period.

## **CONCLUSION**

UAE is safe and clinically effective for up to 11 years in pure adenomyosis. A randomized controlled trial confirmation would be essential, thus, such data from the QUESTA trial are much awaited [25]. The level

of non-perfused areas seems not to be a prerequisite to clinical improvement. JZdiff as a marker of junctional zone inhomogeneity may have a more significant role in the MR imaging diagnosis of adenomyosis. Changes of JZmax and JZdiff after UAE in adenomyosis are potential markers of clinical success. Further research is needed with a larger number of patients to establish the potential role of the marker to test its relationship with other junctional zone characteristics.

## List of abbreviations

JZ Junctional zone

JZdiff Junctional zone differential

JZmax Maximal junctional zone thickness

JZratio Junctional zone ratio

HRQOL Health-related quality of life

MRI Magnetic Resonance Imaging

PVA Polyvinyl alcohol

QoL Quality of life

UAE Uterine artery embolization

UFS-QOL Uterine Fibroid Symptom and Health-related Quality of Life

Uvol Uterine volume

## Declarations

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

### Consent for publication

Consent for publication was obtained for every individual person's data included in the study.

### Availability of data and materials



The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

### **Competing interests**

The authors declare that they have no competing interests.

### **Funding**

This study was not supported by any funding.

### **Author contribution**

- Conceptualization: Kolos Turtóczki, Hyunsoo Cho, Sorour Dastaran, Ildikó Kalina, Viktor Bérczi
- Data curation: Kolos Turtóczki, Hyunsoo Cho, Sorour Dastaran, Viktor Bérczi
- Formal analysis: Pál N. Kaposi
- Funding acquisition: Nándor Ács, Viktor Bérczi
- Investigation: Kolos Turtóczki, Hyunsoo Cho, Sorour Dastaran, Ildikó Kalina, Viktor Bérczi
- Methodology: Kolos Turtóczki, Pál N. Kaposi, Zoltán Tömösváry, Ildikó Kalina, Viktor Bérczi
- Project administration: Kolos Turtóczki, Ildikó Kalina, Viktor Bérczi
- Resources: Zoltán Tömösváry, Szabolcs Várbíró, Nándor Ács, Viktor Bérczi
- Software: Pál N. Kaposi
- Supervision: Ildikó Kalina, Viktor Bérczi
- Validation: Pál N. Kaposi, Ildikó Kalina, Viktor Bérczi
- Visualization: Kolos Turtóczki, Viktor Bérczi
- Writing-original draft: Kolos Turtóczki, Viktor Bérczi
- Writing-review & editing: Kolos Turtóczki, Pál N. Kaposi, Nándor Ács, Szabolcs Várbíró, Ildikó Kalina, Viktor Bérczi

### **Acknowledgments**

Not applicable.

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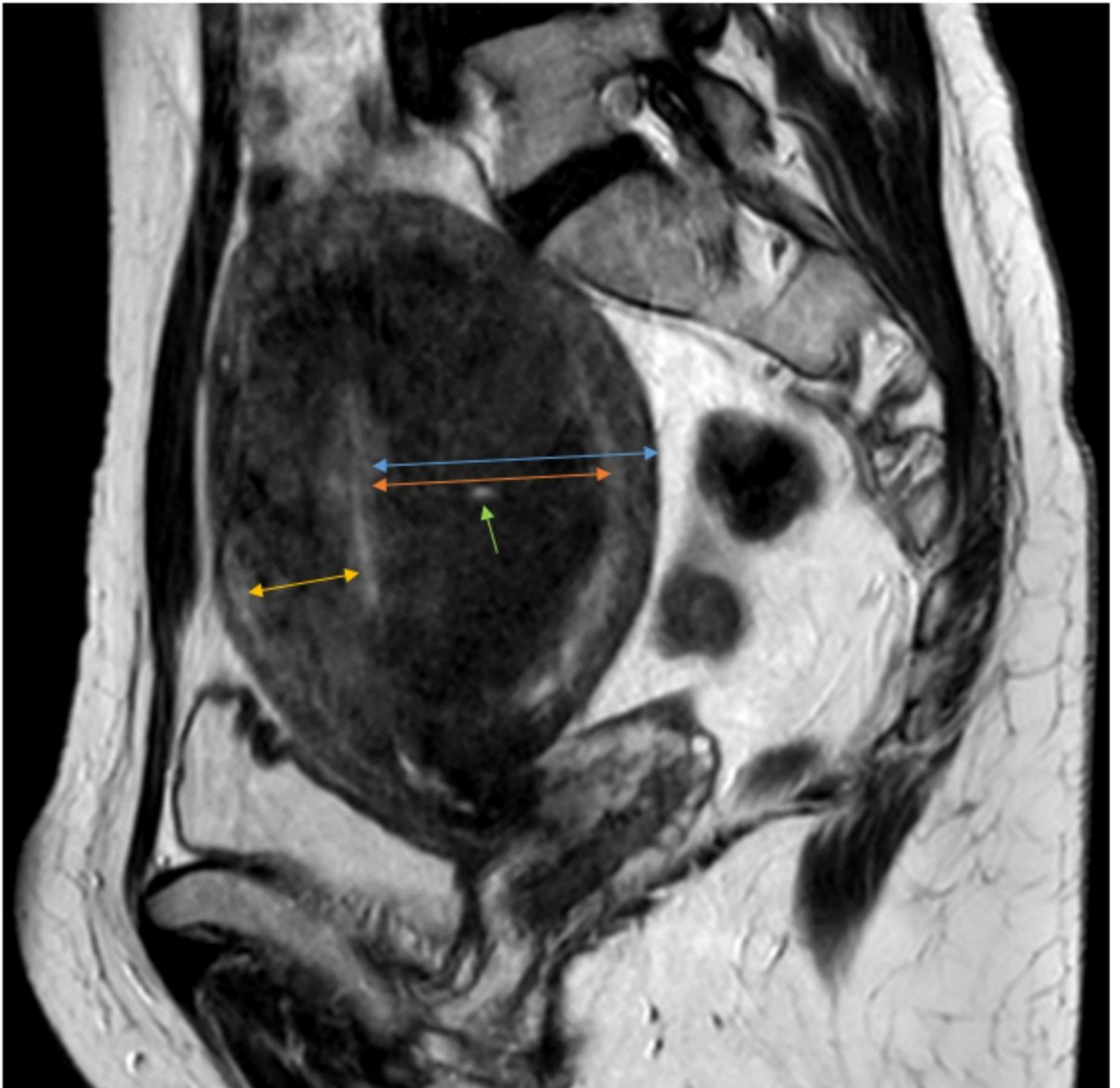
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**Table 2.** Short- and long-term clinical data. Wilcoxon signed-rank test was used for statistical analysis in case of short-term data. Kruskal-Wallis rank sum test was used for statistical analysis in case of long-term data.

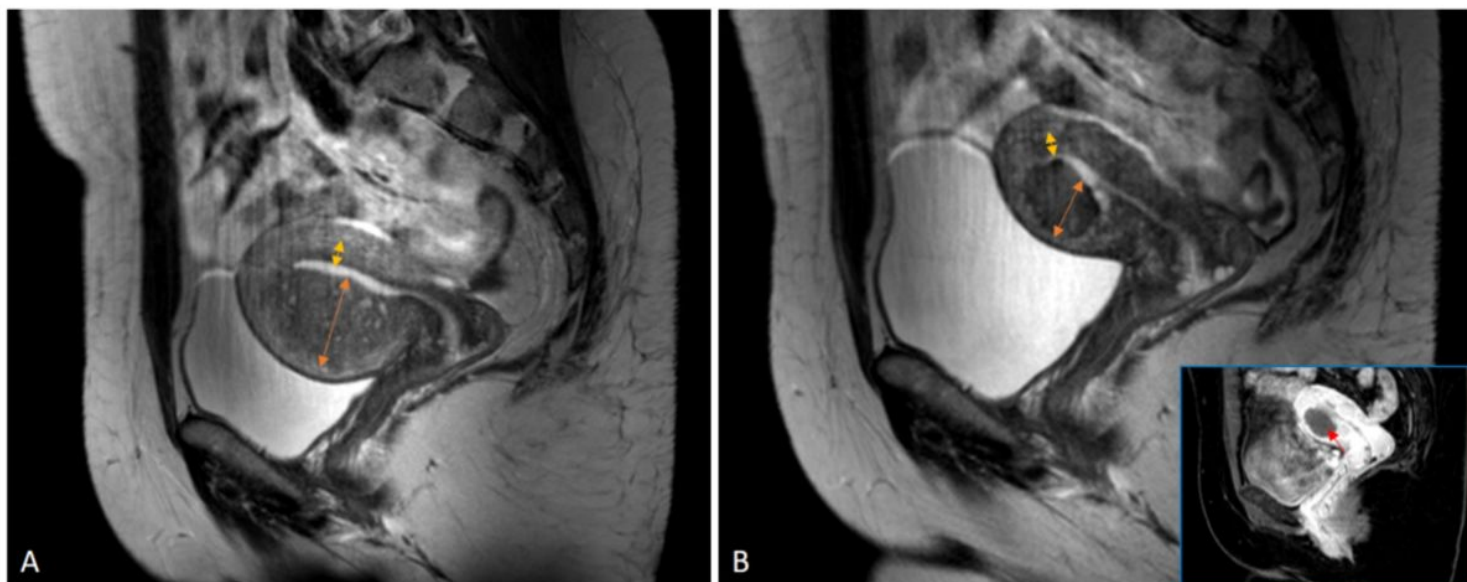
Short-term				
	Median	Range	p values	Number of patients
QoL score before UAE	5	30	0.0011	14
QoL score 1 year after UAE	95	70		14
Difference in QoL score before and after UAE	75	70		
Long-term				
QoL score 3 years after UAE	97.5	70	1	8
QoL score 5 years after UAE	77.5	70	0,2012	6
QoL score 7 years after UAE	95	40	0,4227	5
QoL score 9 years after UAE	95	20	1	3
QoL score 11 years after UAE	87.5	15	1	2

## Figures



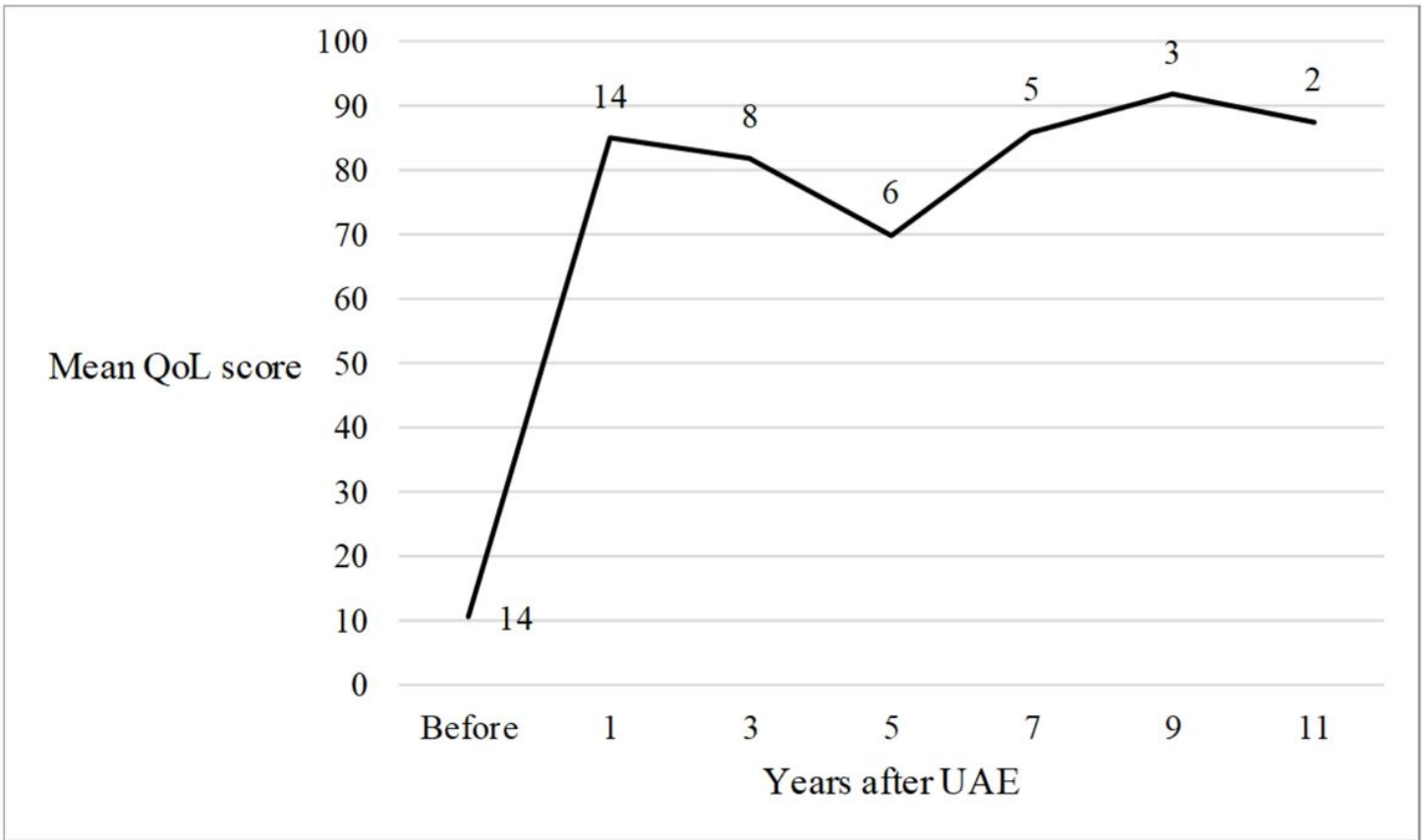
**Figure 1**

Sagittal T2W image of a 50-year-old patient. JZmax (orange arrow) is 42 mm. JZmin (yellow arrow) is 20 mm. JZdiff is 22 mm in this case (JZmax-JZmin). Myometrial thickness at the point of JZmax (blue arrow) is 55 mm. JZratio is 0.76 (JZmax/ myometrial thickness at the point of JZmax). The green arrow marks a T2 hyperintense focus within the thickened junctional zone. The radiological diagnosis of uterine adenomyosis is evident.



**Figure 2**

Preprocedural (A) and postprocedural (B) sagittal T2W images of a 49-year-old patient. The postprocedural examination was obtained 6 months after the UAE. Inserted sagittal contrast-enhanced T1-weighted image shows a necrotic area without contrast enhancement (red arrow on inserted image). Jzmax (marked by an orange arrow on both images) was 35 mm before, and 21 mm after UAE. The minimal junctional zone thickness (JZmin) is marked by a yellow arrow on both images. JZdiff (JZmax-JZmin) was 33 mm before, and 16 mm after UAE. JZratio (not marked on images) was 0.88 and 0.84 before and after UAE, respectively. Uterus volume (not marked on the images) was 182 cm<sup>3</sup> and 90 cm<sup>3</sup> before and after UAE, respectively.



**Figure 3**

Long-term follow-up data on QoL score. Numbers on the curve indicate the number of patients.