Eur Radiol (2015) 25:1303–1309
DOI 10.1007/s00330-014-3504-3

VASCULAR-INTERVENTIONAL

Can measurement of apparent diffusion coefficient before treatment predict the response to uterine artery embolization for adenomyosis?

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Received: 12 June 2014 / Revised: 26 October 2014 / Accepted: 13 November 2014 / Published online: 7 December 2014

Abstract
Objectives To determine the usefulness of the apparent diffusion coefficient (ADC) in predicting response to uterine artery embolization (UAE) for symptomatic adenomyosis.
Methods A prospective study was performed on 25 patients who underwent diffusion-weighted (DW) magnetic resonance imaging (MRI) before UAE between June 2011 and December 2012. All patients underwent 3-month follow-up MRI after UAE using non-spherical polyvinyl alcohol (PVA) particles ranging from 150 to 500 μm. Quantitative measurement of the ADC was performed for each adenomyosis. Complete response and incomplete response were defined as ≥90 % or <90 %, respectively, of the non-perfusion area with adenomyosis at the follow-up MRI. The ADC values were compared between patients who achieved complete or incomplete response which was assessed according to the MRI findings after UAE.
Results Nineteen patients showed complete response, and six showed incomplete response. The ADC value ranged from 0.842 to 1.346×10^{-3} mm^2/s (mean 1.075±0.117). The mean ADC was 1.043±0.237 in the complete response group and 1.176±0.429 in the incomplete response group (0.012). Using a threshold of $<1.147\times10^{-3}$ mm^2/s, the sensitivity and specificity of the ADC to predict success after UAE were 83.3 % and 84.2 %.
Conclusion The ADC of adenomyosis may potentially predict a successful response to UAE for adenomyosis.

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Key Points
- *Pre-procedural MRI might help clinicians predict response of UAE in adenomyosis*
- *ADC might help predict UAE outcomes in adenomyosis*
- *MR predictors might be used to counsel patients with symptomatic adenomyosis*

Keywords Uterine arterial embolization · Adenomyosis · Magnetic resonance · Apparent diffusion coefficient · Prediction of improvement

Abbreviations and acronyms

ADC	Apparent diffusion coefficient
UAE	Uterine artery embolisation
AUC	Area under the ROC curve
DW	Diffusion-weighted
ROI	Region of Interest
ROC	Receiver operating characteristic

Introduction

Adenomyosis is a common gynaecological condition characterized by benign invasion of ectopic endometrium into the myometrium with adjacent smooth muscle hyperplasia. Approximately one-third of women with adenomyosis show symptoms, including dysmenorrhoea, menorrhagia, and abnormal uterine bleeding as reported by Benson et al., Ascher et al., and Tamai et al. [1–3]. The definite treatment for adenomyosis is hysterectomy [4–6]. Uterine artery embolization (UAE) is emerging as an alternative for patients with leiomyomas and may also be useful as an alternative treatment for patients with symptomatic adenomyosis. UAE has a

positive short-term outcome and preserves fertility [7–12]. Mid-term or long-term durability of UAE for adenomyosis is still controversial. According to studies by Pelage and Bratby, approximately 50 % of patients experienced recurrent symptoms at the 2-year follow-up [11, 12], but Kim et al. [8] reported that 57 % of patients had sustained improvement of symptoms at the 5-year follow-up, which is superior to that in other studies.

Magnetic resonance imaging (MRI) is useful in patients with adenomyosis for treatment planning and monitoring after treatment. Few reports have described the MRI characteristics of adenomyosis as a predictive factor for UAE outcome. Kim et al. [13] reported that a dark signal intensity of adenomyosis was a favourable MRI predictive factor for UAE, whereas a heterogeneous signal intensity or signal intensity equal to that of the myometrium were unfavourable factors. Jung et al. [14] suggested that the T2 signal ratio of adenomyosis on preprocedural MRI can be used as a predictor of an early therapeutic response of UAE. On the other hand, Lee et al. [15] reported that in uterine leiomyomas, the ADC value was significantly related to the volume reduction after UAE. However, no study has reported the procedural apparent diffusion coefficient (ADC) value of adenomyosis as a predictor factor for the outcome of UAE. Thus, in the current study, we aimed to evaluate objectively the usefulness of the ADC for the prediction of the potential response to uterine artery embolization (UAE) for symptomatic adenomyosis

Materials and methods

The institutional review board approved the study protocol, and all patients provided written informed consent after receiving explanations concerning the possibility of treatment failure, recurrence, and need for hysterectomy after UAE, and to undergo follow-up MRI examinations after 3 months.

Our prospective study included 25 patients who underwent diffusion-weighted (DW) MRI before UAE for symptomatic adenomyosis, including adenomyosis with intramural or subserosal myomas less than 1 cm, between June 2011 and December 2012.

The inclusion criteria were patients who visited the study site for symptomatic adenomyosis. Symptoms included menorrhagia, dysmenorrhoea, or bulk-related symptoms. There was no limitation in patient age, but patients desiring a future pregnancy were excluded.

MRI

All patients underwent preprocedural MRI using a scanner (3-T Signa HD/HDx; GE Healthcare, Waukesha, WI, USA) equipped with a high-performance gradient system with a maximum amplitude of 50 mT/m, a slew rate of 150 mT/m/ms, and a body array coil. MR imaging included fast spin-echo T2-weighted imaging (TR/effective TE, 3780/85; matrix size, 384×269; field of view, 300×300 mm; section thickness, 4 mm), pre- and post-contrast enhanced T1-weighted gradient-echo imaging sequences with fat suppression (TR/effective TE, 675/11; flip angle 90°; matrix size, 320×224; field of view, 300×300 mm; section thickness, 4 mm). Contrast-enhanced MR imaging was carried out 2 min after an intravenous infusion of 10 ml of gadolinium (Dotarem; Laboratorie Andre Guerbet, Anulnaysous – Bois, France). DW imaging was performed using single-shot spin-echo echo planar imaging during one or more breath-holds, and the exact sequence parameters were as follows: TR/TE, 6300/85 m/s; slice thickness/gap, 4/4 mm; band width, 1.628 kHz; pixel/partial Fourier factor, 6/8; non-selective fat saturation; b values, 0 and 1000 s/mm^2 (Figs. 1, 2).

Image analysis

All MR images were assessed independently by two radiologists (M.D.K. and Y.W.P with 14 and 3 years of clinical experience, respectively, in gynaecological MRI) who were unaware of the MRI outcomes for UAE.

Adenomyosis was categorized morphologically as either diffuse or focal. The MRI diagnostic criteria for adenomyosis include diffuse or focal thickening in the junctional zone (>12 mm in thickness), an ill-defined, low-signal-intensity area of the myometrium, or punctate high-signal-intensity myometrial foci on T2 weighted images [16, 17].

The ADC of each adenomyosis before UAE was calculated by measuring the signal intensity, placing ROIs on three consecutive DW imaging slices in the central portion of the lesion, avoiding areas of the artefact [18]. The ROI was intended to be as large as possible, without containing non-adenomyosis lesions. The ADC was derived automatically on a pixel-by-pixel basis from the DW images according to the following equation:

$$D = -[\ln(S1) - \ln(S0)]/(b1 - b0),$$

where b0 and b1 represent b-values of lower and higher values, respectively, and S0 and S1 are the signal intensities for these b values, respectively [19].

The same two radiologists who analyzed the preprocedural MRI also reviewed the postprocedural MRI to determine complete or incomplete response. The radiologists were blinded of the outcome information at the postprocedural MRI evaluation. A complete response was defined as ≥90 % of the non-perfusion area of adenomyosis and was observed as well-defined necrosis almost completely replacing the adenomyosis. An incomplete response was defined as less than 90 % of the non-perfusion area of adenomyosis at

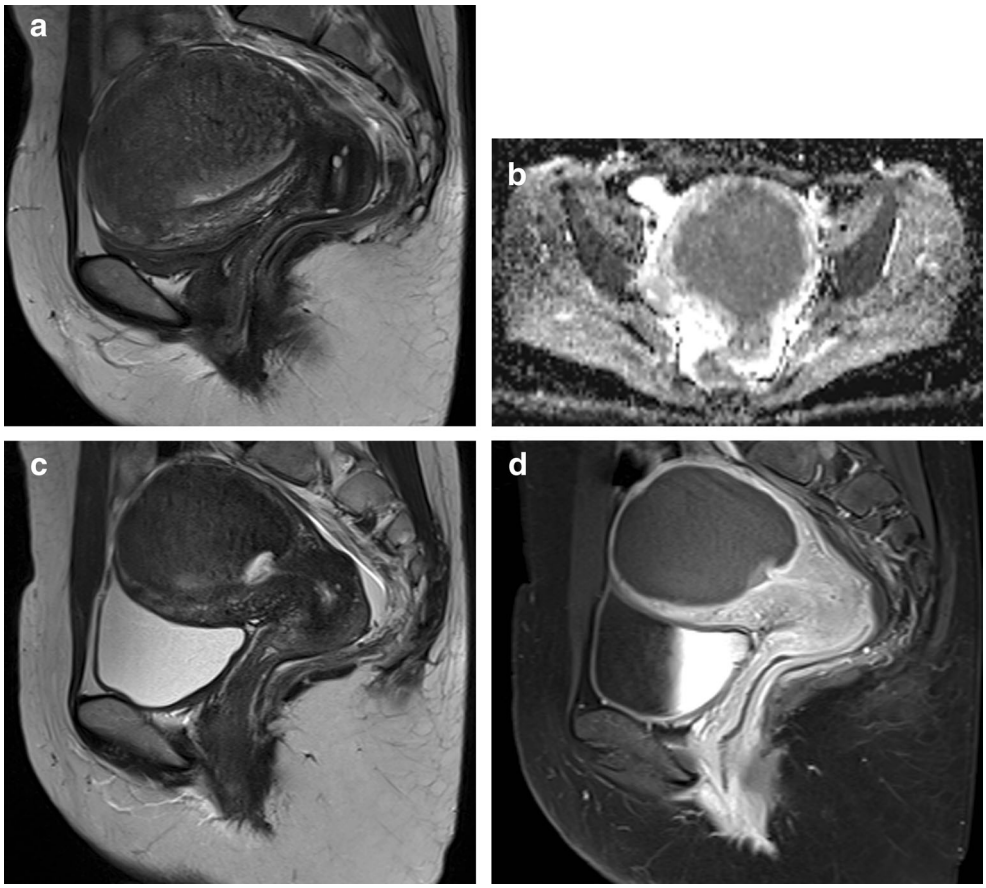

Fig. 1 (*a*) A preprocedural sagittal T2-weighted MR image in a 39-year-old woman shows focal adenomyosis. (*b*) The ADC of adenomyosis on the axial DW image is 0.908×10^{-3} mm^2/s. (*c-d*) Sagittal T2-weighted MR and gadolinium-enhanced T1 sagittal image after embolization. The uterine adenomyosis shows a complete response

follow-up MRI. Disagreements in interpretation were resolved by consensus.

UAE procedure

All procedures were performed by an interventional radiologist (M.D.K.) with 13 years of angiographic experience in UAE who has performed more than 900 embolization procedures for the treatment of uterine fibroid tumours or adenomyosis. Unilateral right femoral artery access was used for all the cases. A 5.0-F RHR catheter (Cook Medical Inc. Bloomington, IN, USA) was placed in the internal iliac artery, and a coaxial microcatheter (Renegade; Boston Scientific, Natick, MA, USA) was advanced distally into the uterine artery. Embolization was performed with the catheter tip beyond the origin of the cervicovaginal branch, using nonspherical polyvinyl alcohol (PVA) particles (Contour; Boston Scientific, Natick, MA, USA) were the embolic agent. One-third (20 mL) of a 60-mL mixture comprising 150- to 250-μm PVA particles was injected at the beginning of embolization into each uterine artery, followed by injection of two-thirds (40 mL) to all (60 mL) of a mixture comprising 250- to 355-μm PVA particles, and finally completion with 355- to 500-μm PVA particles. This method was previously termed the "1-2-3 protocol" [13]. Embolization was carried out until complete cessation of blood flow was achieved in the ascending and transverse segment of the UA for 10 cardiac beats.

Statistical analysis

After consensus interpretation of MR by two readers, the intraclass correlation coefficient [ICC (2,1)] was measured. The two-sample t-test was used to compare the mean ADC value of the adenomyosis area between the complete necrosis and incomplete response groups. The mean values were given as mean±standard deviation. The sensitivity, specificity, and positive and negative predictive values for predicting the complete response were calculated by dichotomizing the results. Receiver operating characteristic (ROC) analysis was performed to determine the diagnostic performance of the ADC. Areas under the ROC curves (AUCs) and cut-off values for the ADC were calculated. Comparisons of the adenomyosis type between the patient groups were performed using Fisher's exact test. All analyses were performed using IBM SPSS software version 20 for Windows. A p value less than 0.05 was considered to be statistically significant.

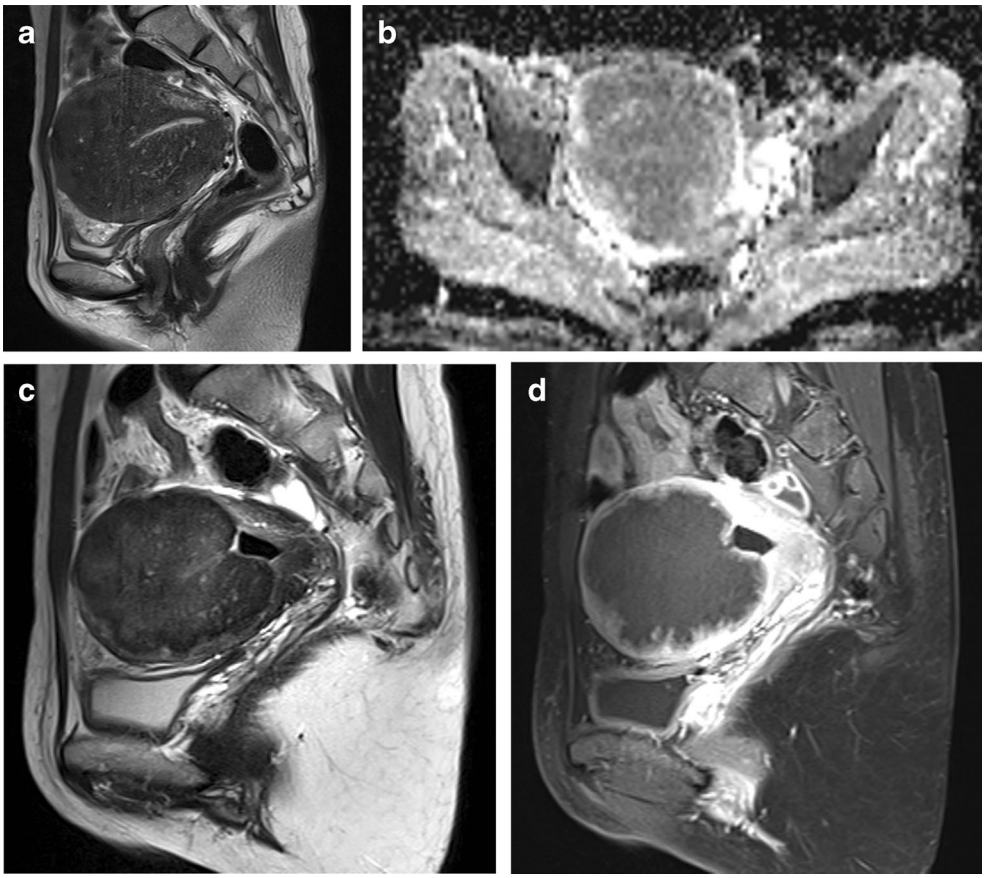

Fig. 2 (*a*) A preprocedural sagittal T2-weighted MR image in a 41-year-old woman shows diffuse adenomyosis. (*b*) The ADC of adenomyosis on the axial DW image is 0.957×10^{-3} mm^2/s. (*c-d*) Sagittal T2-weighted MR and gadolinium-enhanced T1 sagittal image after embolization. The uterine adenomyosis shows a complete response

Results

The MRI characteristics of 25 patients enrolled in the study, including UAE outcomes, are summarized in Table 1. The technical success rate was 100 %, and all of the uterine arteries were embolized. Of the 25 patients who had received UAE for adenomyosis, 19 (76 %) showed a complete response, and six (24 %) showed an incomplete response on MRI-based findings. The intraclass correlation coefficient [ICC (2,1)] for measuring the ADC of adenomyosis between the two radiologists was 0.95 [95 % confidence interval (CI): 0.88 to 0.98], which represented good reliability.

The ADC of adenomyosis ranged from 0.842×10^{-3} to 1.346×10^{-3} mm^2/s (1.075 ± 0.117). The mean ADC of the complete response group was $1.043\pm0.2367\times10^{-3}$ mm^2/s, and the mean ADC of the incomplete response group was $1.176\pm0.4291\times10^{-3}$ mm^2/s. A statistically significant difference in mean ADC value was noted between the two groups by the two-sample t-test (0.012). No significant difference was found regarding age and adenomyosis type (focal vs. diffuse) between the patient groups.

The AUC for distinguishing the complete response from the incomplete response was 0.794 (95 % CI: 0.669–0.915) for the ADC value in prediction model (Fig. 3). From the ROC analysis, we calculated an ADC 1.147×10^{-3} mm^2/s as the optimal cut-off value for differentiating the complete from the incomplete response. The ADC cut-off value of 1.147×10^{-3} mm^2/s had a sensitivity, specificity, positive predictive value, and negative predictive value of 83 %, 84 %, 84 %, and 84 %, respectively. The latter result indicated that when adenomyosis with an ADC value less than 1.147×10^{-3} mm^2/s was subjected to UAE, a high probability of complete response is expected.

Table 1 Outcomes of Uterine Artery Embolization for Adenomyosis and the ADC value (n=25)

	Incomplete Response (n=6)	Complete Response (n=19)	*p*-value
Age (years)	40.0 (±1.21)	43.1 (±1.12)	0.167*
Type			0.630*
Diffuse	3	13	
Focal	3	6	
Mean ADC# (mm^2/s)	1.176 (±0.4291)	1.043(±0.2367)	0.012*

ADC: apparent diffusion coefficient

Values were given as mean±standard deviation

* independent two sample t-test

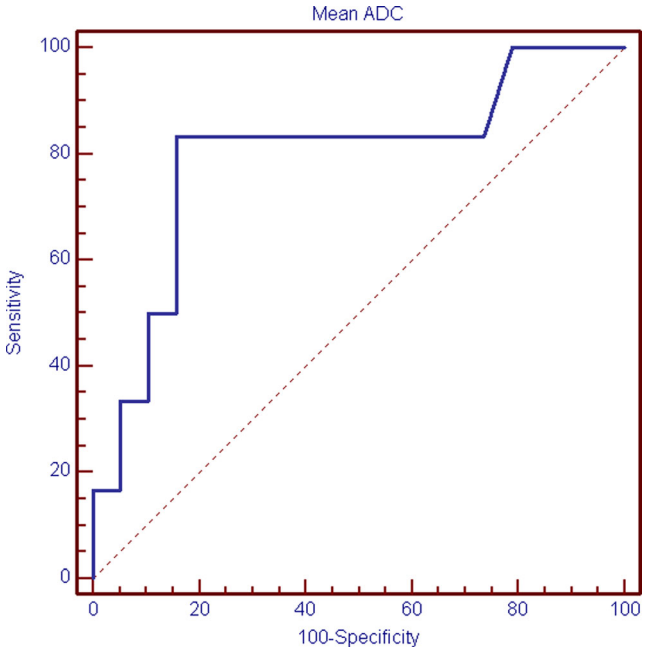

Fig. 3 ROC curves for predicting complete necrosis for uterine artery embolization. With a cut-off value of 1.147×10^{-3} mm^2/s, the AUC of the pre-procedural ADC value of adenomyosis was 0.794×10^{-3} mm^2/s. Mean ADC was calculated by averaging the ADC of each adenomyosis

There was no significant difference in the complete response rate and ADC value between focal and diffuse adenomyosis (Table 2).

Discussion

In our study, the ADC of uterine adenomyosis could be used to predict the successful response to UAE in adenomyosis.

Since Ravina et al. [20] introduced UAE as an alternative to hysterectomy, UAE has been accepted as an alternative treatment to reduce symptoms of uterine leiomyomas. Based on the positive results from its use [7, 9, 10, 21–24] in uterine leiomyomas, many studies have investigated using UAE as a possible therapeutic tool for adenomyosis by Siskin et al., Kim et al., Bratby and Walker, and Pelage et al. [7, 8, 11, 12]. However, as stated in a recent review article by Popovic M et al. [9], because previous studies used different embolization techniques, the outcomes after UAE were difficult to assess.

In addition to methodological standardization of UAE, proper patient selection is required to validate this procedure. In uterine leiomyomas, UAE can only be used if the fibroids fit clinical imaging criteria. However, for UAE in adenomyosis, few reports have assessed the recommended indications for patient selection or any predictive factors for the outcomes of UAE.

Additionally, adenomyosis necrosis following UAE is thought to be essential for long-term durability [13]. Kim et al. [13] reported that a dark signal intensity of adenomyosis was a favourable MRI predictive factor for UAE, whereas a heterogeneous signal intensity or signal intensity equal to that of the myometrium were unfavourable factors. None of the patients with complete necrosis reported recurrent menorrhagic symptoms at 18 months. However, this study used subjective criteria to evaluate the signal intensity of adenomyosis. To remedy these shortcomings, Jung et al. [14] suggested that the T2 signal ratio of adenomyosis on preprocedural MRI can be used to predict early therapeutic response of UAE in adenomyosis. They suggested adenomyosis with a T2 signal intensity equal to 0.475 above that of the rectus muscle was associated with complete necrosis after UAE. However, T2 parameters are frequently varied, and more objective values are required to predict the result of UAE for adenomyosis. In our study, we aimed to evaluate the usefulness of the ADC to predict the response to UAE for symptomatic adenomyosis.

Since DW imaging has emerged, interest in the application of DW imaging for various diseases has increased, particularly for monitoring and predicting treatment response [25]. DW imaging explores the random motion of water molecules in the body. DW imaging signals in biologic tissue are derived from the motion of water molecules in the extracellular space, intracellular space, and intravascular space. By performing DW imaging using different b values (e.g., b=0 mm^2/s and other b values from 0 to 1000 mm^2/s), quantitative analysis of the ADC is possible [25]. Some reports have investigated the usefulness of the ADC for predicting the response to UAE. Recently, Hecht et al. [18] used DW imaging to predict the volumetric response of leiomyomas following UAE. They suggested that the ADC of leiomyomas may reflect the degree of fibrosis in hyaline-degenerated leiomyomas; a lower ADC was associated with more fibrotic leiomyomas, which shrank

Table 2 Baseline characteristics and Outcomes after UAE according to the type of adenomyosis

	Focal (n=9)	Diffuse (n=16)	*p*-value
Mean ADC (mm^2/s)	1.046 (±0.134)	1.091±(0.107)	0.369[a]
Complete response	6 (66.7 %)	13 (81.2 %)	0.630[b]
Baseline uterine volume (cm^3)	346.5 (±435.8)	342.1 (±264.8)	0.975[a]
Uterine volume after UAE	174.0 (±435.8)	158.3 (±133.9)	0.818[a]
Mean volume reduction rate (%)	45.4 (±22.9)	55.3 (±15.7)	0.214[a]

[a] independent two sample t-test

[b] Fisher's exact test

less following UAE and showed a significant positive correlation between the volume reduction and ADC value of the pretreatment leiomyomas.

Lee et al. [15] reported that the ADC of uterine leiomyomas was significantly related to the volume reduction after UAE. They found that a higher ADC value was closely related to a larger volume reduction of the leiomyoma after UAE; however, a lower ADC value was related to less volume reduction of the fibroid even if the fibroid was completely infarcted.

We believe that the mechanism of the embolization effect in leiomyomas and adenomyosis may differ; therefore, the ADC value of leiomyomas and adenomyosis should be interpreted differently when predicting the response to UAE. Leiomyomas with a high ADC value suggest oedema, increased vascularity, and cellularity, and those leiomyomas may respond well to UAE, while adenomyosis with a low ADC value was a favourable factor, indicating that smooth muscle hyperplasia with a lesser component of endometrial tissue may contribute to the UAE response. However, a pathologic correlation for this mechanism was not observed, and further study is needed.

Factors related to necrosis of adenomyosis after UAE have are not well understood. Many factors are involved, including the T2 signal intensity of adenomyosis, presence of collaterals, types of embolic materials and their sizes. Because of the relatively higher treatment failure rate of UAE for adenomyosis than for fibroids, the importance of good patient selection cannot be emphasized enough. Our data revealed that the ADC value can be useful to select patients more objectively.

The present study has a few limitations. First, there were a limited number of cases. Second, we did not correlate necrosis with patients' symptoms. However, we assumed that necrosis is important in the symptom response and long-term durability based on data from previous studies [8, 13]. Kim et al. [13] reported that in patients with complete necrosis followed up to 18 months, none reported recurrent menorrhagia. Third, we used a fixed protocol of UAE method, and results using different embolic materials and embolic particle sizes may provide different results. Fourth, the cut-off value in our study needs validation.

It must be acknowledged that in the present study, complete response was defined as a ≥90 % non-perfusion area of the adenomyosis after UAE, but the associated percent necrosis of adenomyosis has not been determined previously. Kroencke et al. [26] reported that patients with leiomyoma infarction greater than 90 % experienced improved symptom control and fewer reinterventions than did patients with a low infarction rate. Although adenomyosis is different from leiomyomas, this definition was employed.

Despite these limitations, we conclude that the ADC of uterine adenomyosis could be used to predict the successful response to UAE in adenomyosis, but further studies are necessary to confirm these results. We found that a low ADC value was associated with better results for UAE than a high ADC value. This may be helpful for interventional radiologists in counselling and selecting the patients.

Acknowledgments The scientific guarantor of this publication is Dr. Do Yun Lee. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. The authors state that this work has not received any funding. No complex statistical methods were necessary for this paper. Institutional review board approval was obtained. Written informed consent was obtained from all subjects (patients) in this study. Methodology: observational, performed at one institution.

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