Predicting the results of uterine artery embolization: correlation between initial intramural fibroid volume and percentage volume decrease

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Abstract

Introduction and objective: Uterine artery embolization (UAE) is a minimally invasive treatment option for symptomatic fibroids. Long-term follow-up studies have shown that at five-year follow-up after UAE, up to 30% of patients required a hysterectomy. Therefore, it seems of utmost importance to identify patients, who are unlikely to benefit from UAE. It has been postulated that the percentage volume reduction of fibroids may predict long-term UAE outcome. The results of available studies are equivocal, therefore it seemed of interest to investigate the correlation between the preinterventional intramural fibroid volume and imaging outcome of UAE in premenopausal patients.

Material and methods: Uterine artery embolization was performed in 65 premenopausal patients with symptomatic, intramural fibroids. Dominant fibroid volume was assessed using an integrated VOCAL (Virtual Organ Computer-aided AnaLysis) imaging program at baseline and 3 months after UAE. The percentage reduction of fibroid volume was calculated. The association between preinterventional fibroid volumes and percentage volume reductions was determined with the Spearman rank correlation test.

Results: Before UAE, the median dominant fibroid volume was 101 cm^3 (range 23.6-610). At three-month follow-up the median dominant leiomyoma volume decreased to 50.4 cm^3 (range 6.9-193.9). Median percentage reduction of fibroid volume three months after UAE was calculated at 50.1% (range 2.7-93.5). The Spearman correlation test between the preinterventional dominant fibroid volume and percentage volume reduction showed a statistically significant, positive correlation ($R = 0.33$; $p = 0.006$).

Conclusions: The percentage volume reduction of intramural leiomyomas after UAE seems to be more pronounced in the case of larger tumors.

Key words: uterine artery embolization, fibroid, ultrasound.

Introduction

Uterine fibroids are benign, smooth muscle cells tumor of the uterus. Fibroids occur in 20-40% of women of reproductive age, being the most common female benign tumors. Their incidence increases with age and may be as high as 70% by the age of 50, and then declines after the menopause. Risk factors include family history, nulliparity, early menarche, obesity and hypertension. On the other hand, menopause, increasing parity and smoking reduce the risk. Ethnicity also seems to play a role in the pathogenesis of fibroids – the incidence is the highest among African-American women. Biochemical and epidemiological evidence points to the involvement of a genetic element [1].

The majority of fibroids are asymptomatic and require no treatment. Such fibroids are an incidental finding during gynecological or ultrasound examination and routine monitoring is sufficient. However, the presence of uterine fibroids may lead to significant clinical symptoms. The symptoms may be associated with menstruation (heavy menstrual bleeding and painful menstruation) or with local pressure effects (pelvic pain, urinary frequency or urgency, constipation). Fibroids may also be responsible for subfertility and early pregnancy loss [2].

The cost of uterine fibroid tumor treatment is a major economical problem. Uterine fibroids were estimated to cost the United States up to a total of 34.4 billion USD annually. Interestingly, the estimated direct costs (medications, surgery, hospital admissions, medications) are much lower than estimated lost work-hour costs (9.4 vs. 17.2 billion USD annually) [3]. This justifies the use of minimally invasive treatment options, which besides clinical benefits for the patients, may decrease the amount of work time lost.

The mainstay of treatment of symptomatic uterine fibroids is myomectomy or hysterectomy performed by

laparotomy. However, alternative less-invasive techniques are also available. Since fibroids are estrogen- and progesterone-dependent tumors, pharmacological treatment can be considered. GnRH-agonists reduce the volume and symptoms of fibroids, but due to significant side effects are unsuitable for long-term use. Other pharmacological treatment options include mifepristone (a progesterone receptor antagonist) and selective progesterone receptor modulators, such as ulipristal acetate [4]. Minimally invasive management includes uterine artery embolization, percutaneous laser ablation, cryoablation, transvaginal uterine artery occlusion and magnetic resonance imaging-guided focused ultrasound. Of the above, undoubtedly the most significant innovation in the treatment of uterine fibroids is uterine artery embolization (UAE) [5].

Uterine artery embolization for the treatment of fibroid-related menorrhagia was first introduced in 1995 [6]. During UAE an angiographic catheter is positioned by an interventional radiologist through the common femoral artery into bilateral uterine arteries. The procedure is X-ray guided. Finally, embolic material (polyvinyl alcohol particles or tris-acryl gelatin microspheres) is administered into both uterine arteries to occlude them. The block or significant reduction in blood flow at the arteriolar level leads to irreversible ischemic injury of fibroid cells. As a result, necrosis occurs in the tumor, while normal myometrium is able to recover [7].

In comparison to surgical management, UAE is associated with shorter hospitalization and quicker return to work. Complication rates of UAE are low. These complications include post embolization syndrome (pain, nausea, vomiting and fever), persistent vaginal discharge, premature ovarian failure, vaginal expulsion of an infarcted fibroid, intrauterine infection, sepsis and death. Most of the observed complications are minor and occur during the first three months after UAE [8].

The most important outcomes of UAE are patient satisfaction, the reduction of symptoms and improvement of quality of life. The reported rates of satisfaction vary from 87% to 97%. The rates of symptom control range from 84% to 97% at 1 year after UAE and 73% to 89% at 5 years. Validated uterine fibroid symptom and quality of life questionnaires revealed significant improvements in fibroid symptoms and quality of life measures at up to 3 years after UAE [5].

Besides subjective patient measures, the outcome of UAE can be assessed objectively. The randomized Emmy trial showed a hysterectomy rate of 28.4% at 5 years after UAE [9]. These results show that it is extremely important to identify patients, who are unlikely to benefit from UAE and not to offer them this treatment option.

It has also been postulated that the percentage volume reduction in fibroids may predict long-term UAE outcome [10]. Some authors investigated the correlation between initial fibroid volume and its percentage reduction, however conflicting results were reported [11-13].

Objective

To evaluate the decrease in uterine fibroids volumes after UAE and its correlation with the initial volume of fibroids.

Material and methods

Patients

Premenopausal patients with symptomatic, intramural uterine fibroids qualified for UAE were included in the study. Diagnosis of uterine fibroids was established by history, clinical gynecological examination and transvaginal ultrasound. The patients were qualified for UAE according to the Society of Obstetricians and Gynaecologists of Canada Guidelines [14]. All patients underwent an ultrasound assessment of the dominant fibroid volume before and 3 months after UAE. Additionally, before UAE all patients underwent pelvic MRI to exclude concomitant pathologies that could be a contraindication for UAE.

Informed consent was obtained from each patient. The experimental protocol was accepted by a local bioethics committee.

Uterine artery embolization

Before UAE the patients were given prophylactic antibiotics (intravenous and intravaginal) and rectal diclofenac. Uterine artery embolization was performed by an interventional radiologist (Department of Interventional Radiology and Neuroradiology, Medical University, Lublin, Poland) through a single femoral artery puncture and bilateral catheterization of the uterine arteries with 4F catheters. Polyvinyl alcohol particles were administered until a complete stasis of contrast in both uterine arteries was observed. Pain was managed with PCA (patient controlled analgesia) morphine releasing pumps. Only patients with successful, bilateral embolization of the uterine arteries were qualified for the study.

Transvaginal ultrasound assessment of fibroids

All ultrasound examinations were performed by experienced sonographers on a Medison V20 Prestige ultrasound system equipped with a transvaginal volume transducer. The location of fibroids was determined on the basis of the location of the center of the tumor. The volume of the dominant fibroid was estimated using

an integrated VOCAL (Virtual Organ Computer-aided AnaLysis) imaging program. First a sagittal section in 2D grayscale mode was visualized and a 3D volume of the dominant fibroid was obtained. Then, starting from the sagittal view, the VOCAL program was used to define 6 consecutive planes (rotation step set at 30°) of the fibroid. In each plane a manual contour of the fibroid was drawn and the volume of the fibroid in cubic centimeters (cm^3) was obtained. Each patient underwent 2 ultrasound evaluations – before and 3 months after the procedure. Percentage reduction in fibroid volume was calculated. The association between pre-interventional fibroid volumes and percentage fibroid volume reductions was determined with the Spearman rank correlation test. P-values < 0.05 were considered statistically significant.

Results

Sixty five patients with symptomatic, intramural uterine fibroids qualified for UAE were included in the study. All patients were premenopausal, the mean age was 43.1 ± 5.1 SD (range from 29 to 52 years). Before UAE, the median dominant fibroid volume was 101 cm^3 (range 23.6-610). At the three-month follow-up the median dominant fibroid volume decreased to 50.4 cm^3 (range 6.9-193.9) (Fig. 1). Median percentage reduction in fibroid volume three months after UAE was calculated at 50.1% (range 2.7-93.5). The Spearman correlation test between the initial dominant fibroid volume and percentage volume reduction showed a statistically significant, but relatively weak, positive correlation ($R = 0.33$; $p = 0.006$) (Fig. 2). Interestingly, smaller fibroids showed a great variability of fibroid volume reduction at 3 months after UAE, while larger fibroids showed a stable, predictable reaction to UAE (Fig. 2).
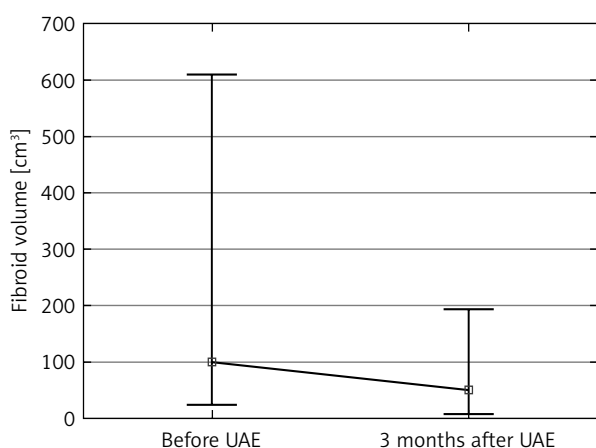
Discussion

In this study we performed an exploratory data analysis to determine the association between initial fibroid volume and fibroid volume reduction after UAE.

Our results show that uterine artery embolization results in an overall 50.1% reduction of fibroid volume at 3-month follow-up. This result is consistent with the findings reported in the literature [2, 12, 13, 15-18]. A summary of selected reports is presented in Table I.

At 2- to 6-month follow-up a 40-60% fibroid volume reduction was observed in most studies (Table I). This effect not only seems to be permanent, but also progresses with time. However, despite the fact that the overall fibroid volume reduction is similar in various studies, it has to be noted that there also is a great variability in fibroid volume reduction after UAE. In our study these values ranged from 2.7% to 93.5%, and other authors published similar results (Table I). For instance, in Sipola's *et al.* study at 6-month follow-up some fibroids were undetectable, but others have increased in size by even 43% [15]. Such variability may result from the presence of additional factors influencing UAE outcome.

Certainly the most important outcome of UAE is the improvement of the health-related quality of life. However, proper assessment of the impact of UAE on HRQOL requires long-term follow-up. Interestingly, Lohle *et al.* found that the percentage fibroid volume reduction during the first 12 months after UAE significantly correlates with patient satisfaction at long-term follow-up (mean: 54 months, range: 42-87) [10]. Therefore, we believe that the use of percentage fibroid volume reduction as a predictor of long-term UAE outcome is justified.

Fibroid volume is much more accurate in assessing the tumor mass than its largest diameter. A 10-cm spherical fibroid has a volume of 523 cm^3, while a 12-cm

Fig. 1. Median dominant fibroid volumes (cm^3) before and 3 months after uterine artery embolization (UAE). Asterisks represent minimal and maximal values
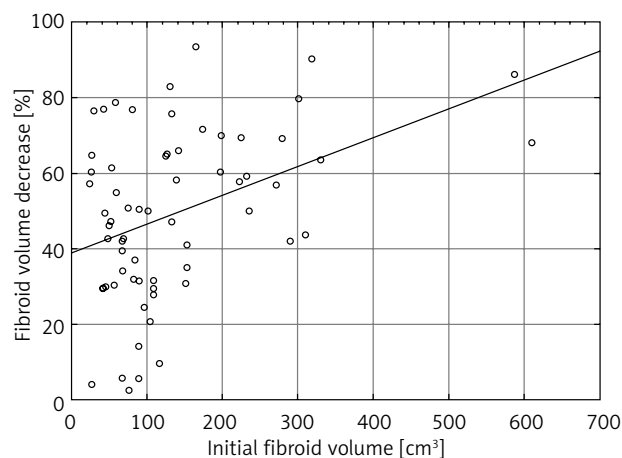

Fig. 2. Correlation between the initial fibroid volume and percentage volume decrease 3 months after UAE. The Spearman correlation test showed a statistically significant, positive correlation ($R = 0.33$; $p = 0.006$).

Tab. I. Summary of studies investigating fibroid volume decrease after uterine artery embolization

Authors	Follow-up	Fibroid volume decrease (range)	Reference
Present study	3 m	50.1% (2.7-93.5%)	Present study
Firouznia *et al.*, 2008	12 m	67.3% ± 23.0 SD	12
Naguib *et al.*, 2010	3 m	52.6% (12.8-96.7%)	13
Sipola *et al.*, 2010	6 m	44% ± 31 (−43-100%)	15
deSuoza *et al.*, 2002	30 min. 1 m 4 m	6.0% ± 8.1 SD 22.3% ± 17.5 SD 36.7% ± 26.5 SD	16
Hirst *et al.*, 2008	6 m	47.3% ± 36.2 SD	2
Burn *et al.*, 2000	2 m 6 m	40% (6-100%) 59% (6-100%)	26
Jha *et al.*, 2000	3 m	40.4% ± 35.8 SD	27

m – month, min. – minute, SD – standard deviation

fibroid – 904 cm^3. Moreover, finding the largest diameter is more user-dependent and irregular tumors are not described properly by this parameter [19].

In our study we have used the VOCAL 3D to estimate fibroid volume. Undoubtedly this method is more difficult and time consuming than the ellipsoid formula (V = Π/6 × height × width × length), and requires using a volume transducer and dedicated software. On the other hand, 3D volumetry appears to be more precise, especially for the assessment of irregular tumors. We did not identify any studies comparing these ultrasound methods in pre-UAE assessment of fibroids. However, Radeleff *et al.* compared the ellipsoid formula and 3D volumetry in the preinterventional MRI assessment of submucosal fibroids to predict the risk of fibroid expulsion after UAE [20]. Fibroid volumes obtained by the ellipsoid formula and by 3D volumetry were not significantly different. Interestingly, a statistically significant difference between the volume of expelled and non-expelled fibroids was found only by 3D volumetry, which may justify the use of 3D volumetry and supports the view that this technique is more accurate in estimating fibroid volume [20].

We have found that larger fibroids tend to decrease to a greater extent after UAE. Studies investigating the correlation between initial fibroid volume and percentage fibroid volume decrease are summarized in Table II. Interestingly, in available studies either no correlation between the initial fibroid volume and percentage volume decrease was found [12, 15-17, 21] or a negative correlation between these parameters was observed [11, 13, 18]. This is in contrast with the results obtained in our study. Considering the complex pathophysiology of fibroids, this may be due to the presence of additional factors influencing the outcome of UAE.

One of the proposed factors influencing the outcome of UAE is the location of fibroids. Some authors demonstrated that submucosal fibroids shrink to a greater ex-

tent after UAE than intramural and subserous fibroids [11, 13, 18]. Pedunculated subserosal fibroids are less likely to reduce in volume and are more often associated with no clinical improvement after UAE [22]. This phenomenon may be caused by the distribution of embolic particles, which are located mainly in the inner parts of the myometrium [23]. Other authors did not find any correlation between fibroid location and the outcome of UAE [12, 16]. However, in deSouza's study the majority of included fibroids were intramural (thirty four), with only seven submucosal, three subserous and one cervical fibroid. Possible correlations might have therefore been difficult to show. Nevertheless, in our study we included only intramural fibroids to exclude the possible influence of fibroid location on the imaging outcome of UAE. In all studies summarized in Table II the authors included subserous, intramural and submucosal fibroids in various numbers, which may have had an impact on the correlation between the initial fibroid volume and percentage volume reduction and may explain the discrepancy between those studies and our results. It has to be stressed that submucosal fibroids tend to cause symptoms very early and are usually smaller than other types of symptomatic fibroids. Considering the fact that due to embolic particle distribution, submucosal fibroids tend to shrink more after UAE, this can explain the correlations observed by other authors (Table II).

It has also been suggested that increasing age is negatively correlated with fibroid volume reduction after UAE [18]. The authors have found that for every decade increase in the patient age, the volume reduction decreased by 13% [18]. This, considering the estrogen-dependent pathogenesis of fibroids, is probably explained by the decreasing level of estrogens. It has been established that estrogens increase blood flow in uterine vessels by causing vasodilatation. That it is why at a histological level, the reduction of estrogen levels

Tab. II. Summary of studies investigating the correlation between initial fibroid volume and percentage fibroid volume decrease after uterine artery embolization

Authors	No. of patients (fibroids)	Patient age (range)	Initial dominant fibroid volume/size	Follow-up	Correlation between initial fibroid volume and percentage fibroid volume decrease	Reference
Present study	65	44 (29-52)	101 cm^3 (23.6 -610)	3 m	↑	Present study
Sipola *et al.*, 2010	52	47.9 (38-59)	66 mm (33-100)	6 m	0	27
Firouznia *et al.*, 2008	101	36.9 (20-49)	274.3 cm^3 (9.1-2618.2)	12 m	0	24
deSuoza *et al.*, 2002	11 (45)	40 (29-48)	89.9 cm^3 (0.6-434)	4 m	0	28
Spies *et al.*, 2002	200	NP	NP (9-2173)	12 m	↓	23
Hecht *et al.*, 2011	11 (28)	43	47 cm^3 (18-182)	6 m	0	35
Burn *et al.*, 2000	18 (32)	39 (28-53)	340 cm^3 (15-1383)	6 m	0	30
Jha *et al.*, 2000	31 (125)	45.2 (31-53.8)	69.4 cm^3	3 m	↓	31
Naguib *et al.*, 2010	28 (84)	48 (37-57)	51.6 cm^3 (0.72-371.1)	3 m 12 m	↓ ↓	25

↑ – positive correlation, ↓ – negative correlation, 0 – no correlation, m – month, NP – not presented

may result in vascular effects similar to those of UAE [18]. Therefore, it seems reasonable to assume that the effect of UAE may be less pronounced in postmenopausal patients. For this reason, in our study we included only premenopausal patients. Interestingly, Lohle *et al.* investigated the effects of UAE in 92 premenopausal patients aged 25 to 53 (mean age: 43) and did not find an association between patient age and UAE outcome [10]. This may suggest that not the patient age itself, but the menopausal status is the determinant of successful UAE. It has to be noted that in our study we included only premenopausal patients. In most of the studies summarized in Table II, the menopausal status of participating patients was not defined. Considering the fact that in some of those studies, the patient age exceeded 50 and ranged even up to 59 [13, 15, 17, 18], it can be suspected that postmenopausal patients were included. This may be another factor explaining the discrepancy between our results and available studies.

Another conclusion drawn from the analysis of studies shown in Table II is the variability of included fibroid volumes. In Hecht *et al.*'s study, median fibroid volume was almost seven times smaller than in Burn *et al.*'s report. The largest fibroid in Sipola's study was estimated at 2618 cm^3, while in Hecht's study – at 182 cm^3. Therefore, direct comparisons of the results of these studies may not be justified.

The possible explanation for the association between initial fibroid volume and its percentage reduction after UAE is the differences in vascularization between large and small fibroids. In early studies using pigment or radiopaque dye injections it has been shown that small fibroids are less vascular than myometrium, while larger fibroids were more vascular. These find-

ings were confirmed by color Doppler ultrasound studies, which showed that vascularization of fibroids was largely dependent on the tumor size [24]. Some studies have also attempted to correlate fibroid vascularization with the outcome of UAE. For instance, in a group of 20 patients Harman *et al.* demonstrated that high pre-UAE vascularity (evaluated by power Doppler ultrasonography) was associated with greater fibroid volume reduction [25]. On the other hand, deSouza *et al.* did not find a significant correlation between initial fibroid perfusion and volume reduction after UAE [16].

It is generally accepted that patients qualified for UAE should undergo an MRI scan. However, it may be reasonable to perform initial 3D-ultrasound assessment of fibroids before qualifying the patient for MRI and finally UAE, to estimate the possible outcome of UAE and identify patients, who are unlikely to benefit from UAE. Such approach may decrease the number of unnecessary MRIs and improve the overall cost-effectiveness of the procedure. Moreover, 3D-ultrasound seems to be a perfect tool for follow-up after UAE. It is relatively cheap and available, estimates fibroid volumes comparably to MRI and allows the assessment of fibroid vascularization [19, 25].

Conclusions

Many factors may influence the outcome of UAE. These factors, such as menopausal status, fibroid location, initial fibroid volume and fibroid vascularization, should be taken into consideration when planning studies investigating the outcome of UAE. Our results show that in premenopausal patients with intramural

fibroids greater volume reductions can be expected in the case of larger fibroids. Further research is needed, especially investigating the correlation between fibroid vascularity and outcome of UAE.

Disclosure

Authors report no conflicts of interest.

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