

Acrylamido Polyvinyl Alcohol Microspheres for Uterine Artery Embolization: 12-month Clinical and MR Imaging Results

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PURPOSE: To report the 12-month clinical and magnetic resonance (MR) imaging results of an ongoing two-center registry involving acrylamido polyvinyl alcohol (PVA) microspheres for uterine artery embolization (UAE) for leiomyomas.

MATERIALS AND METHODS: A total of 69 patients underwent UAE with 500–700- μm , 700–900- μm , and 900–1,200- μm acrylamido PVA microspheres (BeadBlock). Thirty-three patients underwent UAE with a limited embolization (protocol A) and 36 patients underwent UAE with stasis as the angiographic endpoint (protocol B). Primary objectives were clinical efficacy measured by a leiomyoma-specific quality of life (QOL) questionnaire and infarction rate of leiomyomas on early contrast agent-enhanced MR imaging. Secondary objectives were in-hospital complications, patient satisfaction, and frequency of clinical failure.

RESULTS: Bilateral embolization was technically successful in 68 of 69 patients. A significant decrease ($P < .001$) in symptom severity and increase in health-related QOL was observed at 3 and 12 months with no significant differences between embolization protocols. However, contrast agent-enhanced MR imaging showed a significantly lower rate of completely infarcted leiomyomas in protocol A compared with protocol B ($P < .05$). Early clinical failures in patients treated according to protocol A were caused by incomplete tumor infarction. Minor complications occurred in five of 69 patients. Patient satisfaction was similar between protocols.

CONCLUSIONS: Acrylamido PVA microspheres are a clinically effective and safe embolic agent for UAE. The use of 500–700- μm spheres and a limited embolization results in an unacceptably high rate of failed tumor infarction. Superior imaging results and fewer repeat interventions can be achieved with use of 700–900- μm spheres and stasis as the angiographic endpoint.

J Vasc Interv Radiol 2008; 19:47–57

Abbreviations: PVA = polyvinyl alcohol, QOL = quality of life, UAE = uterine artery embolization

UTERINE artery embolization (UAE) has gained acceptance as an alternative treatment to surgery for symptomatic uterine leiomyomas. Different

embolic materials such as polyvinyl alcohol (PVA), gelating sponge, and tris-acryl gelatin microspheres have been used successfully for UAE (1–3).

Many reports on the success of UAE are based on studies of nonspherical PVA particles (1,4–6). However, nonspherical PVA particles have shown a tendency to clump and cause extensive arterial occlusion regardless of size in an animal model (7). Acrylamido PVA microspheres (BeadBlock; Biocompatibles, Farnham, UK) are precisely calibrated microspheres made of a PVA hydrogel dyed blue for better visualization. They are indicated for the treatment of hypervascular tumors and arteriovenous malformations and received approval for marketing in Europe in June 2003. The purpose of this

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The study was supported by a grant of Biocompatibles, Farnham, Surrey, UK. T.J.K. has served as an advisor to Biocompatibles and is currently an advisor to Terumo, and has received honoraria for presentations relating to the use of BeadBlock. None of the other authors have identified a conflict of interest.

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DOI: 10.1016/j.jvir.2007.08.019

Table 1
Demographic Characteristics of Study Population

Demographic Characteristics	Protocol A <i>n</i> = 33	Protocol B <i>n</i> = 36	<i>P</i> Value (<i>test</i>)
Median (range) age (y)	44 (34–52)	44.5 (33–53)	.691 (Mann-Whitney)
Presented symptoms			
Heavy menstrual bleeding	22 (67)	29 (81)	
Intermenstrual or menstrual pelvic pain	17 (52)	28 (78)	
Bulk-related symptoms	25 (76)	32 (89)	
Urinary frequency	10 (30)	17 (47)	
Pelvic pressure	15 (45)	28 (78)	
Backaches	5 (15)	7 (19)	
Limb pain	1 (3)	5 (14)	
Dyspareunia	2 (6)	5 (14)	
Hydronephrosis	1 (3)	0	
Constipation	5 (15)	9 (25)	
Dominant symptom			
Heavy menstrual bleeding	20 (61)	26 (72)	.592
Intermenstrual or menstrual pelvic pain	4 (12)	3 (8)	(χ^2)
Bulk related symptoms	9 (27)	7 (19)	
Median (interquartile range) uterine volume before UAE (cm ³)	612 (402–865)	467 (266–696)	.184 (Mann-Whitney)
Median (interquartile range) volume of dominant tumor before UAE (cm ³)	232 (80–360)	111 (51–242)	.041 (Mann-Whitney)
No. of tumors			
Single	10 (30)	9 (25)	.331
2–4	8 (24)	6 (17)	(χ^2)
≥5	15 (45)	21 (58)	
Location of dominant tumor*			
Subserosal pedunculated	1 (3)	2 (6)	.774
Subserosal	8 (24)	6 (17)	(χ^2)
Intramural	9 (27)	14 (39)	
Transmural	9 (27)	6 (17)	
Submucosal	5 (15)	7 (19)	
Submucosal pedunculated	1 (3)	1 (3)	
Evidence of adenomyosis on MR	2 (6)	6 (17)	

Note.—Values in parentheses are percentages unless otherwise specified.

* Defined as largest tumor on baseline MR imaging.

study was to analyze data of a prospective two-center registry with respect to safety and technical and clinical efficacy of acrylamido PVA microspheres for embolization of symptomatic uterine leiomyomas employing standardized clinical and imaging outcome measures.

MATERIALS AND METHODS

The study was performed at two centers. At each site, the institutional review board approved the protocol and informed consent was obtained from each patient for the UAE procedure, clinical data collection, and pre- and postinterventional contrast agent-enhanced magnetic resonance (MR) imaging.

Patient Population

Between January 2004 and December 2005, 69 patients with an indica-

tion for surgical treatment of symptomatic leiomyomas presented for UAE as an alternative to surgery at the two participating centers and were enrolled in the registry. Median patient age was 44 years (range, 33–53 y). Detailed characteristics of the study population are given in **Table 1**. All patients were initially seen by a gynecologist who established the diagnosis of symptomatic uterine leiomyomas and the indication for surgical treatment. Each patient was also counseled by an interventional radiologist experienced in UAE for leiomyomas and underwent MR imaging to confirm the presence of uterine leiomyomas, assess the extent of disease, and exclude other pathologic processes.

Selection Criteria

Entry criteria included age at least 30 years, presence of leiomyoma on

MR imaging and ultrasonography, and leiomyoma-related symptoms that warranted therapy, such as heavy menstrual bleeding, pelvic pain, pelvic pressure, urinary frequency, backaches, limb pain, dyspareunia, hydronephrosis, and constipation. Exclusion criteria included previous UAE, participation in any other investigational device or drug study, pregnancy or desire to conceive within the next 12 months, suspected gynecologic malignancy or pelvic inflammatory disease, known contrast agent allergy, abnormal serum creatinine level, and coagulopathy. Anatomic criteria for exclusion were uterine volume smaller than 250 cm³, pedunculated leiomyomas with a vessel stalk smaller than 50% of tumor diameter, hysteroscopically resectable tumors without concomitant intramural and/or subserosal tumors, and dominant adenomyosis. Symp-

tomatic postmenopausal patients receiving hormone replacement therapy and patients with evidence of concomitant minor focal adenomyosis in the presence of dominant leiomyoma disease were not excluded. All eligible patients were asked to complete a validated leiomyoma-specific symptom and quality of life (QOL) questionnaire, the Uterine Fibroid Symptom Severity and QOL (UFS-QOL) questionnaire (8).

Procedure

The embolization procedures were performed with a unilateral or bilateral femoral access. Through 4-F or 5-F catheters placed in the internal iliac artery, a microcatheter with a 2.8-F tip (Renegade Hi-Flo; Target Therapeutics/Boston Scientific, Natick, Mass; or Embocath; Biosphere Medical) was advanced into the uterine artery in a coaxial fashion in all cases. The embolic material was prepared by adding a total volume of 5 mL of normal saline solution and 10 mL of nonionic contrast medium (various manufacturers) to a prefilled 5-mL syringe containing 2 mL of the embolic agent.

Two different embolization protocols were used in the registry: in protocol A (limited embolization endpoint; $n = 33$), embolization was performed by slowly injecting 500–700 μm acrylamido PVA microspheres (BeadBlock) during free flow. The angiographic endpoint was occlusion of the perifibroid plexus and sluggish flow in the ascending segment of the uterine artery, leaving the transverse segment and cervicovaginal branches patent (9). Initially, 500–700- μm microspheres were used. If flow had not slowed to the desired endpoint after administration of a total of three vials (6 mL), the particle size was increased to the next larger size (ie, 700–900 μm or 900–1,200 μm) and embolization continued until the endpoint was achieved.

In protocol B (embolization to near-stasis; $n = 36$), 700–900- μm acrylamido PVA microspheres (BeadBlock) were used from the beginning. The endpoint for embolization in protocol B is best described as stasis, with the main uterine artery remaining patent, but with negligible residual flow toward the uterus. As a rule of thumb, the uterine artery had to be visualized

under fluoroscopy for at least 10 cardiac beats after contrast agent injection, indicating minimal antegrade flow. This endpoint corresponds to an angiographic image of a patent horizontal segment with absent flow in the ascending segment of the uterine artery. Similar to protocol A, the particle size was increased in protocol B to the next larger size (ie, 900–1,200 μm) if the endpoint was not reached after administration of 6 mL of acrylamido PVA and embolization was continued until the desired endpoint was reached.

In both protocols, the embolization endpoint was always checked after waiting approximately 5 minutes, and additional microspheres were injected if necessary until the endpoint was stable.

The two embolization endpoints were verified across the sites for all four operators. Before the study, exemplary digital angiographic runs of the two endpoints were available to the four operators. The endpoint of embolization was checked for every case by the second operator at each center to verify adherence to the protocol. All four operators were interventional radiologists with more than 4 years experience with the procedure.

After embolization, the presence of possible collateral flow via the ovarian artery was identified by abdominal aortography and selective ovarian arteriography with or without ovarian artery embolization performed at the discretion of the four operators.

Protocol A was used for UAE in the first 33 consecutive patients treated at both centers (16 patients at center 1 and 17 patients at center 2). Thereafter, protocol B was used in the following 36 patients (20 patients at center 1 and 16 patients at center 2).

Each patient was admitted to the hospital. Patients received a Foley catheter and were routinely given antibiotics on the day of the intervention. Pain management consisted of intravenous application of opioids and nonsteroidal antiinflammatory drugs according to hospital treatment scheme.

MR Imaging

All patients were scheduled to undergo baseline unenhanced MR imaging and contrast agent-enhanced MR imaging at two time points for follow-

up: within 24–72 hours after UAE and at 3-month follow-up. Patients treated according to protocol A underwent additional contrast agent-enhanced MR imaging at 6- and 12-month follow-up. MR imaging was performed on a 1.5-T scanner (Magnetom Vision or Magnetom Symphony; Siemens Medical Systems, Erlangen, Germany; Intera; Philips Medical Systems, Eindhoven, The Netherlands) with use of a torso phased-array coil. After an initial localization scan, breath-hold fat-saturated T1-weighted transaxial gradient-recalled echo images and sagittal and transaxial T2-weighted turbo spin-echo images covering the uterus were taken. The volume of the uterus and of the dominant leiomyoma (largest tumor before therapy), the number of leiomyomas per patient (single, 2–4, ≥ 5) and the location of the dominant tumor were determined. Based on the location of the center of the leiomyoma, dominant leiomyomas were defined as being subserosal pedunculated, subserosal, intramural, transmural, submucosal, or submucosal pedunculated according to a modification of the Society of Interventional Radiology (SIR) Reporting Standards for UAE (10). Volumes were determined by measuring the maximum extent of the uterus and dominant leiomyoma in three planes and multiplying the product by 0.5233 according to the ellipsoid volume formula (11). After UAE, unenhanced and gadolinium-enhanced fat-saturated T1-weighted gradient-recalled echo images were obtained in the transaxial and sagittal planes.

Postprocedural Image Analysis

All contrast agent-enhanced image sets were assessed by two radiologists with more than 8 years of experience in MR imaging with the use of a digital workstation that allows interactive image analysis. Infarction of fibroid tissue was defined as lack of enhancement in two imaging planes. The percentage of infarction for all leiomyomas (overall infarction rate of tumor load) was initially graded in 10% increments from 0% to 100%. The final percent infarction of tumor load after UAE was determined by averaging the midpoints of the range for each assignment between two blinded readers. For further analysis, these results were summarized in four catego-

ries: 0%–49%, 50%–89%, 90%–99%, and 100% infarction of fibroid tumor load. Unenhanced T1-weighted gradient-recalled echo images served to differentiate between persistent perfusion of fibroid tumor tissue and hyperintense hemorrhagic necrosis (12). All comparisons were made on an intraindividual basis. For analysis of changes in the infarction rate in protocol A over time, the only patients compared were those who had undergone contrast agent-enhanced MR imaging at 24–72 hours and at 3-, 6-, and 12-month follow-up.

Clinical Follow-up

Clinical follow-up included the UFS-QOL questionnaire and assessment of patients' satisfaction. The self-administered UFS-QOL, a 37-question leiomyoma-specific symptom and QOL questionnaire that yields a symptom score and a QOL score, was completed by all study patients before UAE and again at each follow-up visit. In protocol A, clinical follow-up was available at 3, 6, and 12 months after UAE. In protocol B, clinical questionnaires were available at 3- and 12-month follow-up in a limited number of patients enrolled at one center.

The questionnaire comprises eight questions pertaining to the type and severity of symptoms and 29 questions regarding the patient's health-related QOL. The questions refer to the 3 preceding months. The eight symptom items (questions 1–8) are summarized in a symptom severity scale. The 29 health-related QOL items are subsumed under six subscales pertaining to concern, activities, energy/mood, control, self-consciousness, and sexual function, and together represent the health-related QOL total score. Symptom severity subscale, health-related QOL subscales, and health-related QOL total score result in a total of eight scores. If a patient failed to answer a question, the corresponding subscale was excluded from analysis, whereas all other subscale scores were included. The mode of calculation of the scores is described in detail elsewhere (8).

Patients' satisfaction was assessed on a five-point Likert scale that included the following categories: "very satisfied," "satisfied," "unsure," "dissatisfied," and "very dissatisfied."

Clinical failure was defined as an unchanged or worsened symptom score at 12-month follow-up or secondary interventions to treat persisting leiomyoma-related symptoms. Patients lost to follow-up were also counted as cases of clinical failure.

All adverse events during hospitalization and as long as 3 months after the intervention were recorded as major or minor according to the SIR classification system (13). After 3 months, only complications that required therapeutic interventions were recorded. Minor complications were defined as those that required nominal therapy, including additional hospital observation. Major complications were adverse events that resulted in unanticipated increase in level of hospital care, required surgical or other major intervention, or resulted in permanent injury. Surgical and/or radiologic interventions to control persistent leiomyoma-related symptoms were recorded during follow-up of patients, and UAE was regarded as a therapeutic failure in these women.

Statistical Analysis

Descriptive statistics, including mean, median, minimum, maximum, 25th and 75th percentiles, and 95% CIs where appropriate, were used to summarize the continuous variables in this study. The age distributions of groups A and B were compared by Mann-Whitney *U* test for unpaired samples to identify any significant differences. The Pearson χ^2 test was used to identify differences between group A and B with regard to the number of leiomyomas, the localization of the dominant leiomyoma, presence of adenomyosis, and clinical symptoms before treatment.

Volumes.—Uterine and dominant tumor volumes were compared between groups before and after embolization therapy with the Mann-Whitney *U* test. The Wilcoxon test for paired samples was applied to test changes in volume after UAE for statistical significance within each group. The percentage volume reduction is given as median with 95% CI and illustrated graphically.

UFS-QOL.—The results of each UFS-QOL score before and after UAE are given as medians with 25th and 75th percentiles. The UFS-QOL was analysed with the Wilcoxon test for paired samples to compare the scores

before UAE with the results after 3 and 12 months, respectively. In addition, the achieved scores at 3- and 12-month follow-up were tested similarly. Comparison of the scores before UAE as well as after 3- and 12-month follow-up between groups A and B was made with the Mann-Whitney *U* test for unpaired samples.

Statistical significance was accepted at a *P* value less than .05. Statistical analysis was performed with the SPSS software package (version 13.0.1; SPSS, Chicago, Ill).

RESULTS

Baseline values of patients treated according to embolization protocol A versus protocol B did not differ significantly regarding age, symptoms, size of the uterus, number of leiomyomas, and location of the dominant tumor at baseline. The volume of the dominant tumor was significantly greater (*P* = .041) in patients of protocol A and a larger percentage of patients treated according to protocol B showed evidence of adenomyosis on MR imaging before therapy.

Bilateral UAE was technically successful in all 33 patients treated according to protocol A and 35 of 36 patients treated according to protocol B. In one patient treated per protocol B, only unilateral access to the uterine artery was achieved as a result of tortuous anatomy and spasm. In each protocol, one patient was found to have an ovarian artery collateral supply that was embolized after clinical failure 3 months after UAE in the case in protocol A and at the time of initial UAE in protocol B. During delivery of acrylamido PVA via the microcatheters, catheter occlusion occurred in three of 36 patients treated according to protocol B but could be managed without exchanging the microcatheter. No catheter occlusion occurred in patients treated according to protocol A. The number of patients receiving acrylamido PVA particles of a given size, the respective amount per particle size, and the combined amount of particles used in each protocol are summarized in **Tables 2** and **3**. In the majority of patients treated according to protocol A, particles larger than 500–700 μm were needed to complete the embolization.

Table 2
Size and Amount of Particles Used per Embolization Protocol

	Acrylamido PVA Particles Used			Total
	500–700 μm	700–900 μm	900–1,200 μm	
Protocol A				
No. of patients	33	18	5	33
Mean (95% CI) amount (mL)	6.9 (5.7–8.2)	5.5 (3.9–7.0)	7.2 (0.5–13.9)	10.8 (8.0–13.7)
Protocol B				
No. of patients	–	36	8	36
Mean (95% CI) amount (mL)	–	8.9 (7.5–10.3)	8.9 (0–20.5)	10.6 (8.1–13.1)

Complications

During the hospital stay, five complications occurred in five patients, all of which were minor (four SIR class A, one SIR class B). Patients treated according to protocol A (ie, limited endpoint) and protocol B (ie, embolization to stasis) were equally affected. Two patients developed a rash attributable to specific medications that resolved spontaneously. One patient had a small groin hematoma and another had a temporary increase of serum creatinine after the procedure. One patient experienced prolonged pain (>48 hours) after the procedure, which necessitated prolonged intravenous analgesia.

Four patients had complications that required intervention after UAE after discharge from the hospital. One patient had an emergency room visit for leiomyoma expulsion that required assisted removal. Three patients required antibiotic treatment for infectious discharge. One woman had two episodes of infectious discharge with *Streptococcus hemolyticus* and *Staphylococcus aureus*. All infections resolved with antibiotic treatment. Two patients experienced spontaneous expulsion of tumors and another three experienced sloughing of tumor material that stopped without the need for additional treatment before the follow-up visit 3 months after UAE. Three patients reported temporary amenorrhea at 3-month follow-up with resumption of menstruation by the 6-month follow-up visit. Three patients developed permanent amenorrhea (lasting >12 months) reported at 3-, 6- and 12-month follow-up, respectively.

Table 3
Combined Size and Amount of Particles between Embolization Protocols

Protocol/Particle Size (μm)	No. of Pts.	Mean (95% CI) Amount (mL)
Protocol A		
500–700	15	4.7 (3.1–6.3)
500–900	13	12.4 (9.7–15.0)
500–1,200	5	25.2 (19.5–30.9)
Protocol B		
700–900	28	8.6 (6.9–10.3)
700–1,200	8	17.7 (8.3–27.0)

Clinical Outcome

Analysis of UFS-QOL.—**Figure 1** shows the number of patients available for analysis of the UFS-QOL during the course of the study. Patients treated according to protocols A and B showed a significant ($P < .001$) decrease in symptom severity and a significant ($P < .001$) increase in health-related QOL measured 3 and 12 months after UAE with acrylamido PVA (**Table 3**). Minor differences were seen in QOL subscales between patients undergoing embolization according to protocol A versus protocol B.

Analysis of Intraindividual Changes in the Symptom Severity Subscore per Protocol.—Thirty patients treated according to protocol A completed the questions on symptom severity within the UFS-QOL before and 3 months after UAE. Ten of 30 patients (33%) had an unchanged or worsened symptom severity score (absolute difference, 0–24 score points) at 3-month follow-up. For 24 patients, questionnaire data were available at 12-month follow-up. Twenty patients had already shown an improvement at 3-month follow-up also showed improved scores at 12-month follow-up, with a tendency toward better results compared with

3-month follow-up (**Table 3**). Another five of those 10 patients with unchanged or worsened symptoms at 3-month follow-up had improved scores at 12-month follow-up compared with baseline, one patient’s score had further worsened, and four did not return the relevant pages of the UFS-QOL.

At 12-month follow-up, 32 of 33 patients treated according to protocol A gave information on secondary interventions to treat persistent leiomyoma-related symptoms after UAE.

Three repeat interventions (three repeat UAE, one UAE in combination with ovarian artery embolization) were performed after 3-month follow-up because of persisting tumor-related symptoms. Repeat UAE in these three cases was performed 4–6 months after initial UAE because symptoms did not improve and persistent tumor perfusion (<60% infarction of tumor load) was noted on the 3-month follow-up contrast agent-enhanced MR imaging. Ovarian artery embolization and repeat UAE were performed 4 months after UAE because of collateral ovarian artery supply to leiomyomas identified at the time of initial UAE and lack of clinical

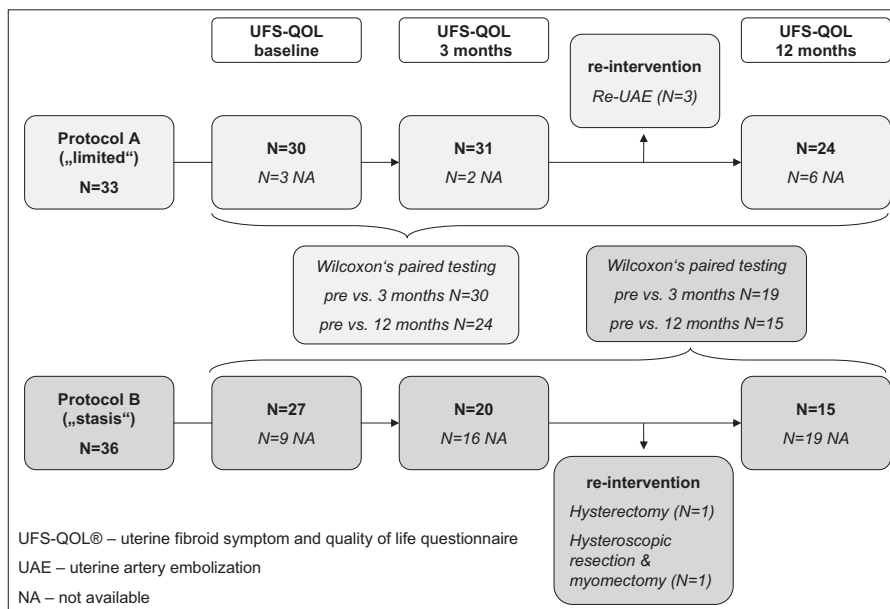


Figure 1. Clinical follow-up of study patients.

improvement together with progressive growth of noninfarcted tumors on follow-up contrast agent-enhanced MR imaging. In summary, in a total of eight of 33 patients (three with repeat interventions, one with unchanged/worsened symptom severity score, four lost to follow-up) treated according to protocol A, initial UAE was regarded as a clinically failed procedure.

Twelve-month UFS-QOL follow-up and clinical data for patients treated according to protocol B were available at only one treatment center. Twenty patients completed the questions on symptom severity within the UFS-QOL before and 3 months after UAE. Three of 20 patients (15%) had an unchanged or worsened symptom severity score (absolute difference, 2–9 points) at 3-month follow-up. At 12-month follow-up, one of those three patients had improved scores and one patient had a worsened score compared with baseline. One patient did not return the relevant pages of the UFS-QOL. Two of 20 patients had undergone a repeat intervention (one hysteroscopic leiomyoma resection combined with myomectomy and one hysterectomy) within 12-month follow-up. Hysteroscopic resection in one case was performed 6 months after UAE as a result of persisting prolonged men-

orrhagia and intermittent spotting. A contrast agent-enhanced MR study performed at 3-month follow-up had shown infarction of all tumors, but submucous tumor material had shifted into the uterine cavity and was considered to be the cause of the menstrual abnormality. Myomectomy was performed in addition to hysteroscopic resection according to the patient's wish. This case was not considered a failure of the UAE procedure but a rare but typical sequela of UAE necessitating further invasive treatment. Hysterectomy was performed 4 months after UAE in one patient because of suspected leiomyosarcoma based on rapid recurrent growth of a 90% infarcted single tumor at 72-hour contrast agent-enhanced MR imaging with nearly 90% viable tissue observed at subsequent 3-month follow-up. Pathologic specimen examination revealed no malignant tissue.

None of these repeat interventions were performed as a treatment for persistent leiomyoma-related symptoms after UAE.

In summary, in two of 20 patients (one with unchanged/worsened symptom severity score and one lost to follow-up) treated according to protocol B who completed 12-month clinical follow-up, initial UAE was regarded as a clinically failed procedure.

Patient Satisfaction with the Results of UAE

Patient satisfaction did not differ significantly between patients treated per protocol A versus protocol B. Twenty-seven of 28 patients without repeat interventions treated according to protocol A showed a response at 3- and 12-month follow-up. At 3-month follow-up, 13 of 27 patients (48%) reported they were very satisfied, six (22%) were satisfied, six (22%) were unsure, two (7%) were dissatisfied, and none were very dissatisfied. At 12-month follow-up, a significant change ($P = .026$) toward a higher rate of satisfaction could be observed, with 14 of 27 patients (52%) being very satisfied, 12 (44%) satisfied, none unsure, none dissatisfied, and one (4%) very dissatisfied.

A subgroup of 15 patients treated in one center according to protocol B answered the items on satisfaction at 3- and 12-month follow-up. At 3-month follow-up, eight of 15 patients (53%) treated according to protocol B reported they were very satisfied, five (33%) were satisfied, two (13%) were unsure, none were dissatisfied, and none were very dissatisfied. The answers were unchanged at 12-month follow-up.

MR Imaging Findings

Sixty-eight of 69 patients (99%) treated with acrylamido PVA completed 24–72-hour contrast agent-enhanced MR imaging. Three-month contrast agent-enhanced MR imaging follow-up was completed by 32 of 33 patients (97%) treated according to protocol A and 33 of 36 patients (92%) treated according to protocol B. The results of contrast agent-enhanced MR imaging with respect to the infarction rate at 24–72 hours and 3 months after UAE for patients treated according to protocols A and B are compared in Figure 2.

A significant difference in percentage infarction of the leiomyoma load was observed between the two protocols at 24–72 hours ($P < .011$) and 3 months ($P < .003$) after UAE in favor of protocol B. Only two patients (6%) treated according to protocol B, compared with seven (22%) for protocol A, had an infarction rate less than 90%. At 3-month follow-up, the percentage

of patients with incomplete infarction of tumor tissue after treatment according to protocol A increased disproportionately compared with patients treated according to protocol B.

Additional contrast agent-enhanced MR imaging after 6 and 12 months for infarction of leiomyoma load was completed by 22 of 33 patients (67%) treated according to protocol A (Fig 3). In patients with 100% infarction of tumor load at 24–72-h contrast agent-enhanced MR imaging, no increase in perfused (ie, vital) tumor tissue was observed at further follow-up. Differences in the number of patients with 100% infarction of tumor load between follow-up time points are explained by expulsion or sloughing of uninfarcted tumor tissue leading to a higher number of patients with 100% infarction technically or differences in the assessment by the reviewers between these time points. In patients with partially infarcted leiomyomas at 24–72 hour contrast agent-enhanced MR imaging, there was a clear trend toward a lower infarction rate of tumor load over time, indicating growth of viable tumor tissue.

Although baseline uterine and dominant tumor volume were greater in patients treated according to protocol A, volume changes of the uterus and dominant leiomyoma at 3-month follow-up were significant for patients in protocols A and B in both groups (Table 4). Percentage volume reduction of the uterus was greater for patients treated according to protocol B, whereas percentage volume reduction of dominant leiomyomas was greater for patients treated according to protocol A. However, these differences were not significant. The development of uterine and dominant tumor volumes of patients treated according to protocol A on 3- and 12-month follow-up MR imaging is illustrated in Figures 4 and 5. A continuous and significant decrease in uterine and dominant leiomyoma volume was observed over time.

DISCUSSION

In the United States 140,000–180,000 hysterectomies are performed for uterine fibroid tumors each year, accounting for one third of all hysterectomies per-

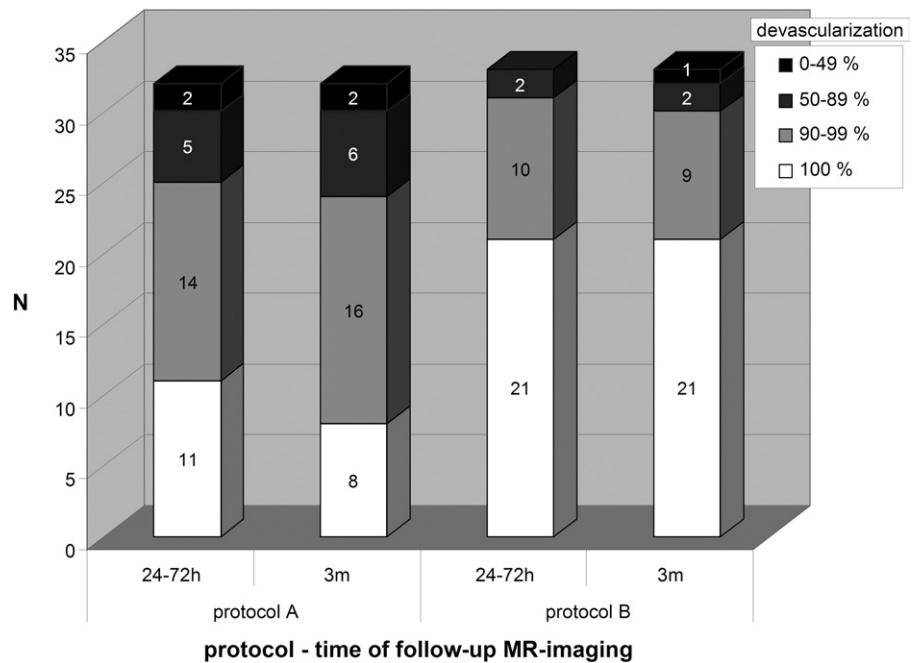


Figure 2. Intra-individual comparison of infarction rate of fibroid tumor load on contrast agent-enhanced MR imaging per protocol at 24–72 hours and 3-month follow-up.

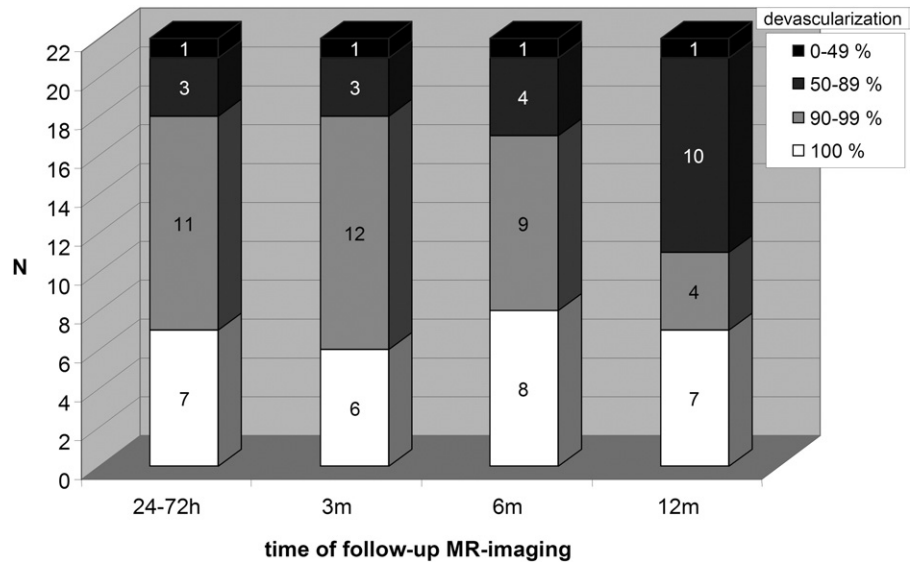


Figure 3. Intra-individual comparison of infarction rate of fibroid tumor load on contrast agent-enhanced MR imaging in patients treated by protocol A (ie, limited embolization) with follow-up available at 24–72 hours and 3, 6, and 12 months.

formed in middle-aged women (14,15). In the United Kingdom, women have a one-in-five chance of having a hysterectomy by the age of 55 years, with 90% being performed for a benign condition, most likely uterine leiomyomas (16,17). Although hysterectomy is the definite

treatment for uterine leiomyoma, many patients would like to avoid major surgery and look for permanent alleviation of symptoms rather than surgical cure from this benign disease (18). UAE has been proven to be a safe and effective treatment alternative to surgery for

Table 4
Comparison of Changes in Health-related QOL and Symptom Severity of Patients Treated by Protocol A versus Protocol B

UFS-QOL Subscale	No. of Pts.	Median (IQR) before UAE	No. of Pts.	Median (IQR) 3 Months after UAE	No. of Pts.	Median (IQR) 12 Months after UAE	P Values*
Protocol A (limited)							
Symptom severity	30	42.2 (31.3–49.2)	31	25.0 (15.6–37.5)	23	15.6 (6.3–31.3)	<.001; <.001; .023
Concern	30	77.5 (48.8–96.3)	31	90.0 (70.0–100.0)	24	97.5 (85.0–100.0)	.014; .005; .088
Activities	30	67.9 (45.5–86.6)	31	82.1 (71.4–96.4)	24	92.9 (83.0–100.0)	.004; <.001; .020
Energy/mood	29	60.7 (41.1–78.6)	31	78.6 (64.3–92.9)	24	92.9 (71.4–100.0)	.002; <.001; .073
Control	28	62.5 (50.0–75.0)	31	80.0 (70.0–90.0)	24	97.5 (86.3–100.0)	.001; <.001; .055
Self-consciousness	30	70.8 (56.3–83.3)	31	83.3 (75.0–100.0)	24	100.0 (91.7–100.0)	.001; <.001; .011
Sexual function	30	75.0 (46.9–100.0)	30	81.6 (62.5–100.0)	23	100.0 (75.0–100.0)	.028; .002; .596
HRQL total	27	64.7 (51.7–79.3)	30	81.5 (67.7–92.5)	23	94.0 (86.2–98.3)	.001; <.001; .053
Protocol B (stasis)							
Symptom severity	27	53.1 (40.6–59.4)	20	18.8 (10.2–33.6)	15	15.6 (6.3–31.3)	<.001; .001; .310
Concern	27	65.0 (30.0–80.0)	20	95.0 (90.0–100.0)	15	95.0 (85.0–100.0)	<.001; .001; .435
Activities	27	53.6 (32.1–75.0)	19	85.7 (75.0–96.4)	15	96.4 (82.1–100.0)	.001; .001; .159
Energy/mood	27	60.7 (46.8–71.4)	20	80.4 (68.8–96.4)	15	85.7 (71.4–100.0)	<.001; .001; .507
Control	27	65.0 (45.0–85.0)	20	85.0 (80.0–95.0)	15	90.0 (80.0–95.0)	.001; .004; .570
Self-consciousness	27	66.7 (58.3–83.3)	20	91.7 (75.0–100.0)	15	91.7 (75.0–100.0)	.005; .010; .538
Sexual function	26	75.0 (50.0–87.5)	19	87.5 (75.0–100.0)	14	87.5 (75.0–100.0)	.003; .016; .429
HRQOL total	26	61.2 (45.0–75.9)	18	84.5 (76.5–94.8)	14	92.2 (77.4–95.9)	.001; .001; .553

Note.—HRQOL = health-related QOL; IQR = interquartile range.

* Before UAE vs 3 months after UAE; before UAE vs 12 months after UAE; 3 months after UAE vs 12 months after UAE, respectively.

Table 5
Changes in Uterine and Dominant Leiomyoma Volume per Protocol at 3-month Follow-up

Outcome	No. of Pts.	Median (IQR) before UAE	No. of Pts.	Median (IQR) 3 Months after UAE	Median (95% CI) Volume Reduction (%)	P Value (Wilcoxon test)
Uterus						
Protocol A	33	612 (402–865)	32	449 (229–554)	27 (19–37)	<.001
Protocol B	36	467 (266–696)	34	301 (176–426)	36 (26–45)	<.001
Dominant leiomyoma						
Protocol A	33	233 (80–360)	32	97 (34–191)	50 (39–55)	<.001
Protocol B	36	111 (51–242)	34	85 (27–165)	40 (19–51)	<.001

Note.—Values provided in cm³ where applicable; IQR = interquartile range.

women with symptomatic leiomyomas (19–22).

Different embolic agents have been used for UAE for leiomyomas, and a diversity of outcome measures have been used to date. To obtain comprehensive validated data on clinical and imaging outcomes after UAE with acrylamido PVA for uterine fibroid tumors the UFS-QOL questionnaire, as well as standardized contrast agent-enhanced MR imaging, were prospectively employed in the current registry. Comparing embolization protocols A and B regarding clinical outcome measures, no substantial difference with respect to symptomatic improvement, health-related QOL, and patient satis-

faction with treatment results was found. There were no major complications during hospital stay and follow-up. Typical sequelae of UAE such as tumor sloughing and expulsion were observed at a frequency comparable with those in previous case series.

However, a difference between embolization protocols regarding repeat interventions to treat persisting tumor-related symptoms was observed. Repeat interventions in patients treated according to protocol A (ie, limited embolization endpoint) became necessary within 6 months after initial UAE, and these early failures were clearly linked to incomplete infarction of tumors. Infarction percent-

ages of tumor load in the three cases treated again by UAE according to protocol A were 20%–29%, 50%–59%, and 40%–49% at 3-month follow-up contrast agent-enhanced MR imaging. Persistent perfusion of leiomyomas could not be attributed to spasm in any case. Collateral ovarian artery supply of a large subserosal tumor was present in one case and treated at the time of repeat UAE. However, in addition to the uninfarcted tumor supplied by the ovarian artery, multiple tumors were also uninfarcted in this patient and dysmenorrhea and menorrhagia persisted. In addition, a decrease in the rate of infarction of tumor load could be observed over time in

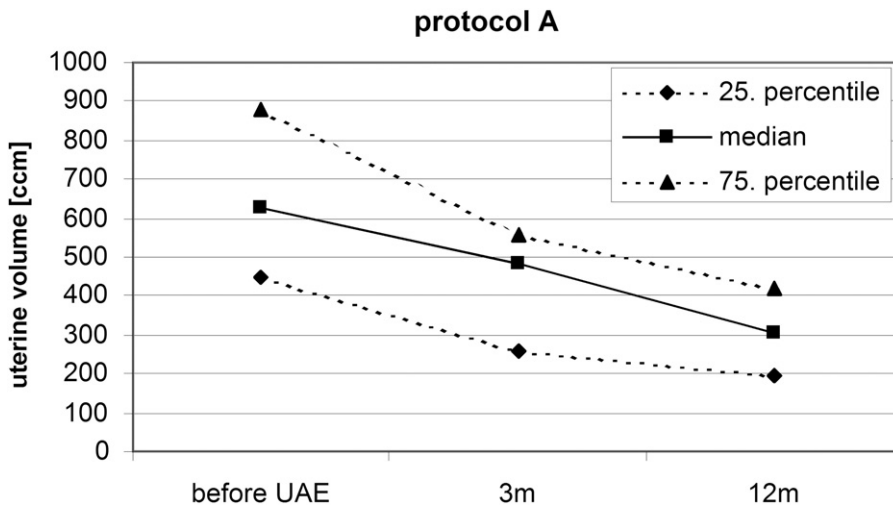


Figure 4. Changes in uterine volume in patients treated according to protocol A (ie, limited embolization) on 3- and 12-month follow-up MR imaging.

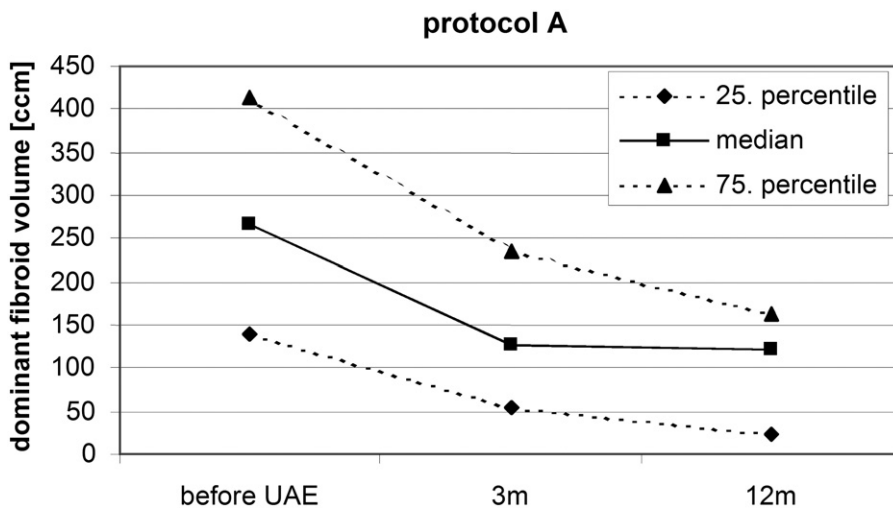


Figure 5. Changes in dominant leiomyoma volume in patients treated according to protocol A (ie, limited embolization) on 3- and 12-month follow-up MR imaging.

patients treated according to protocol A, indicating regrowth of tumors as a result of vital fibroid tissue not infarcted by UAE.

In contrast to these findings, the two cases that necessitated repeat interventions treated according to protocol B (ie, embolization to stasis) were not considered clinical failures. Case one had a 90% infarcted tumor at 24–72-hour contrast agent-enhanced MR imaging, but there was rapid regrowth of the noninfarcted portion at 3-month follow-up and hysterectomy was performed because of a suspected leiomyosarcoma. Case two had a 100% infarcted

tion rate of tumor load at 24–72-hour and 3-month follow-up. Successful hysteroscopic resection of a completely infarcted leiomyoma that had shifted into the uterine cavity and caused irregular menstrual bleeding was performed. Additional myomectomy of two infarcted tumors was performed only according to the patient’s wish but was not considered a causative treatment.

Our imaging results clearly indicate that the use of 500–700- μm acrylamido PVA microspheres and a limited angiographic endpoint leads to a higher rate of noninfarcted tumors compared with a protocol

employing 700–900- μm acrylamido PVA microspheres and stasis as the angiographic endpoint. Moreover, the analysis of consecutive contrast agent-enhanced MR imaging in a subset of patients treated according to protocol A highlights that incomplete leiomyoma devascularization leads to regrowth of perfused (ie, vital) fibroid tissue over time. Although this may have no clinical impact for the majority of patients on a short-term basis, it seems likely that patients with incomplete tumor infarction are at a higher risk for clinical failure. Uninfarcted tumors have been identified as a major factor for early and late clinical failure after UAE (23–26). Our limited experience support this observation, although the number of patients and follow-up time within this registry do not allow definitive conclusions.

The significant differences in infarction rate between protocols A and B may be explained by the different size of the particles, the different angiographic endpoint used, or a combination of the two. Our initial approach was based on our experience with other spherical agents such as tris-acryl gelatin microspheres. Use of microspheres of similar size with the use of the same limited endpoint has been shown to result in favorable clinical and imaging results (27,28). We therefore used acrylamido PVA spheres of a similar size (500–700 μm) and with a limited embolization endpoint. In 23 of 33 patients (70%) treated according to protocol A, additional larger spheres were necessary to reach the endpoint after the injection of 6 mL of 500–700- μm spheres at least on one side. In contrast, larger spheres were needed to reach the endpoint in only eight of 36 patients (22%) treated according to protocol B. Additionally, with a less aggressive endpoint in protocol A (ie, limited embolization) than in protocol B (ie, embolization to stasis), one might expect that a smaller amount of acrylamido PVA spheres is needed to reach this endpoint. However, the average amount of embolic agent used per patient was similar. Animal data indicate that acrylamido PVA microspheres in the size range of 500–700 μm penetrate deeper than tris-acryl gelatin microspheres of similar size (29). These

findings may explain why partial infarction of tumors was more often seen in patients treated according to protocol A versus protocol B if 500–700- μm acrylamido PVA do not sufficiently occlude the peripheral plexus vessels of fibroid tumors or migrate distally after delivery. Therefore, the size of the spheres rather than the embolization endpoint seems to be the major determinant of the significant differences in infarction rate of tumor load observed between treatment protocols. This assumption is supported by the results of a prospective trial of acrylamido PVA microspheres for UAE presented by Dhand et al (30). Although stasis was the angiographic endpoint during this trial, which used only 500–700- μm acrylamido PVA microspheres, only 54% of patients treated had tumor necrosis of 25%–89% at 3 months follow-up.

In summary, UAE with acrylamido PVA microspheres in a size range of 500–1,200 μm is safe and results in a favorable clinical outcomes at mid-term follow-up based on UFS-QOL scores. However, the use of 500–700- μm acrylamido PVA microspheres and a limited embolization approach resulted in an unacceptable rate of uninfarcted fibroid tissue and repeat interventions resulting from leiomyoma regrowth. Our results highlight the value of contrast agent-enhanced MR imaging to determine the efficacy of an embolic agent to infarct uterine leiomyomas. A significant better infarction rate of targeted tumors was achieved when using 700–900- μm acrylamido PVA spheres and stasis as the angiographic endpoint. Long-term follow-up is needed to determine if a better infarction rate translates into fewer clinical failures and repeat interventions. In addition, randomized studies are needed to compare the efficacy of acrylamido PVA microspheres with other embolic agents regarding infarction rate, complication rate, and long-term clinical outcome.

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