**Background:** To investigate the long-term changes in health-related quality of life (HRQOL) after uterine artery embolization (UAE) for symptomatic fibroids, we conducted a prospective cohort study.

**Methods:** Eighty-two women completed the validated uterine fibroid symptom and QOL (UFS-QOL) questionnaire before UAE. Short-term results after a median of 8 months (range: 3–20) have been published previously. Patients were asked to complete the questionnaire again after a median of 6.3 years (range: 5–7.6). Secondary outcome measures were the frequency of additional surgical or endovascular procedures due to treatment failure and the menstrual status.

**Results:** A total of 4/82 patients (5%) were lost to follow-up. Of the remaining 78 patients, 11 underwent surgery or repeat UAE (hysterectomy $n=6$, myomectomy $n=1$, UAE $n=4$) at a median of 13 months (range: 5–70) after UAE. Two patients failed clinically but did not undergo a second intervention. The overall treatment failure rate 6 years after UAE was 17%. Clinical long-term follow-up regarding symptom control and quality of life was available in the remaining 65 patients. Symptom severity scores decreased from a median of 37.50 (quartile range, QR: 28.13–53.13) to 0.00 (QR: 0.00–10.94) ($P<0.001$), whereas the HRQOL total score increased from a median of 64.66 (QR: 46.34–79.10) to 100.00 (QR: 96.12–100.00) ($P<0.001$). Both scores also improved significantly compared with short-term results ($P=0.006$ and $P=0.041$). Permanent amenorrhea was observed in five patients at a median of 18 months (range: 10–46) after UAE and at a mean patient age of 50 years.

**Conclusions:** UAE leads to durable relief of fibroid-related symptoms and sustained improvement in HRQOL. After 6 years, clinical failure can be expected in 17%, and most of these patients require secondary invasive treatment.

**Key words:** uterine artery embolization / fibroids / long-term / quality of life

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**Introduction**

Since its first description in 1995 by Ravina et al., uterine artery embolization (UAE) has been demonstrated to be a safe and effective technique for treating symptomatic uterine leiomyomata (fibroids) (Ravina et al., 1995; Spies et al., 2001, 2005b; Walker and Pelage, 2002). Long-term studies with observational periods ranging from 3 to 6 years demonstrated rates of symptom control of ~70–90%, but also a recurrence with subsequent surgical or repeat endovascular intervention in up to 29% of patients (Spies et al., 2005a; Katsumori et al., 2006; Walker and Barton-Smith, 2006; Goodwin et al., 2008; Lohle et al., 2008). Few long-term studies incorporated validated outcome measures for assessing changes in symptoms and quality of life. In this prospective single-center cohort study, we administered the uterine fibroid symptom and quality of life (UFS-QOL) questionnaire and present long-term clinical follow-up data up to almost 8 years after UAE (Spies et al., 2002). Short- and mid-term results for the same cohort have already been published (Scheurig et al., 2006). To our knowledge, this is the first study prospectively evaluating the clinical long-term changes in symptom severity and health-related quality of life (HRQOL) at least 5 years after UAE with the use of a validated outcome measure.
Materials and Methods

Patient population

Between August 2002 and June 2004, 82 women with symptomatic uterine leiomyomata underwent UAE as an alternative to surgical treatment, either hysterectomy or myomectomy. All patients were seen by a gynecologist and interventional radiologist prior to study enrollment. Exclusion criteria and detailed demographic characteristics of this cohort have been published earlier (Scheuring et al., 2006). Table I briefly summarizes the baseline characteristics of the study population. All patients gave informed written consent and volunteered to participate in the follow-up examinations. The study was approved by the institutional review board, and permission to use the UFS-QOL questionnaire in an official German translation was granted by its authors and the Society of Interventional Radiology.

Embolization technique

UAE was performed using a transfemoral approach. After positioning the tip of either a 4F/5F endhole catheter or a coaxially advanced microcatheter in the horizontal segment of the uterine artery well beyond angiographically visualized cervicovaginal branches, free-flow particle embolization was realized with the use of 500–900 μm trisacryl gelatin microspheres (TGM) in 62 patients (Embosphere®, Biosphere Medical, Paris, France) or polyvinyl alcohol (PVA) particles in 20 patients (BeadBlock™, Biocompatibles, Farnham, UK or Contour-SE®, Boston Scientific, Natick, MA, USA). Embolization with TGM was carried out according to a limited embolization protocol with occlusion of the perifibroid plexus but preserved sluggish antegrade flow in the uterine arteries as the angiographic end-point.

Table I Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th>n</th>
<th>82</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [median (minimum–maximum)]</td>
<td>42.5 (33–63)</td>
</tr>
<tr>
<td>post-menopausal</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>67 (82%)</td>
</tr>
<tr>
<td>Bulk symptoms</td>
<td>47 (57%)</td>
</tr>
<tr>
<td>Severe dysmenorrhea</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>History of prior myomectomy</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Volume of uterus prior to UAE (ml) [median (25–75 percentile)]</td>
<td>325 (252–460)</td>
</tr>
<tr>
<td>Volume of dominant fibroid* prior to UAE (ml) [median (25–75 percentile)]</td>
<td>86 (28–177)</td>
</tr>
<tr>
<td>Number of fibroids</td>
<td></td>
</tr>
<tr>
<td>Singular</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>2–5</td>
<td>31 (38%)</td>
</tr>
<tr>
<td>More than 5</td>
<td>32 (39%)</td>
</tr>
<tr>
<td>Location of dominant fibroid*</td>
<td></td>
</tr>
<tr>
<td>Subserosal pedunculated</td>
<td>—</td>
</tr>
<tr>
<td>Subserosal</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Intramural</td>
<td>60 (73%)</td>
</tr>
<tr>
<td>Submucosal</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>Submucosal pedunculated</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

*Dominant fibroid defined as largest fibroid at baseline MR-imaging.

For spherical PVA particles (BeadBlock®, Contour-SE®), a more radical angiographic end-point, i.e. near stasis in the horizontal segment of the uterine artery, was chosen. The choice of the embolic agent was left to the discretion of the interventionalist. In our institution, UAE is performed as an inpatient procedure, and all women were admitted for further observation and sufficient analgesia with intravenous narcotics on the day of the procedure and non-steroidal anti-inflammatory drugs thereafter.

Clinical assessment

The self-administered UFS-QOL questionnaire comprises eight questions pertaining to the type and severity of symptoms, summarized in the Symptom severity score, and 29 questions on how the disease affects different aspects of the patient’s HRQOL (total score), subdivided into six subscale scores pertaining to concern, activities, energy/mood, control, self-consciousness and sexual function. Thus, a total of eight scores summarize the results of the questionnaire that refers to the three preceding months. Response options are presented as five-point Likert scales ranging from ‘not at all’ (1) to ‘a very great deal’ (5) in response to ‘how distressed were you by . . . ?’ for the symptom severity items (questions 1–8) and from ‘none of the time’ (1) to ‘all of the time’ (5) in response to the questions about HRQOL (questions 9–37).

The questionnaire was completed before UAE, and all patients were asked to complete it again at the time of follow-up via mail or telephone. According to the instruction by the authors, a subscale score was excluded from further analysis if more than 50% of the referring questions were not answered. Otherwise the missing value was imputed by the mean of the other subscale values. The UFS-QOL scores are normalized to a 100-point scale, with higher HRQOL indicating improvement in QOL and lower symptom scores indicating improvement in fibroid-related symptoms. Any surgical (hysterectomy, myomectomy) or endovascular intervention (repeat UAE) to control persistent or recurrent fibroid-related symptoms, such as menorrhagia, dysmenorrhea or bulk symptoms (see Table I), was recorded during the follow-up and defined as failure of embolization therapy in these women. The frequency of new permanent amenorrhea after UAE with an absence of menstrual bleeding for more than 6 months was documented with the date of the last menstrual period.

Statistical analysis

The demographic data of the study population were already analyzed and presented in a previous publication. According to non-parametric distribution, the results of the UFS-QOL questionnaire and its eight subscales before and after UAE are given with median and lower as well as upper quartiles (25th and 75th percentile). Changes within each score are presented with median and 95% confidence interval, and were tested for significance using Wilcoxon’s test for paired samples. For graphical illustration, the unpaired median score results of the UFS-QOL questionnaire of all three times of control are summarized in a radial plot with its 8 arms representing the 8 subscales of the questionnaire with 0 points in the centre of the plot and 100 points at the outer margin.

Additionally, all patients were stratified by age with one group of patients being younger than 40 years and the other being equal to or older than 40 years of age. Mann–Whitney test was performed to search for differences in clinical improvement assessed with the UFS-QOL questionnaire.

Kaplan–Meier analysis was used to determine the cumulative rates of treatment failure and subsequent re-intervention over time. Pearson’s χ² test and the Mann–Whitney test for unpaired samples was used to look for interrelations between the use of different particle types, TGM or PVA, and the clinical outcome regarding treatment failure as well as symptom severity and HRQOL. Statistical significance was accepted at P
Results

Bilateral UAE was technically successful in 80/82 (98%) patients. Two patients underwent unilateral embolization due to either absence of one uterine artery or previous surgical clipping on one side. No major complications, according to the classification system for complications of the Society of Interventional Radiology, were observed.

In total, 4/82 (5%) patients were lost to a long-term clinical follow-up: one because of hysterectomy for endometrial cancer 6 years after UAE at the age of 51 years, and the other three were not available for follow-up interviews. The remaining 78 patients were subject to further long-term analysis. Of these, 11 patients underwent a second intervention due to clinical failure, either surgical or repeat endovascular; after a median of 13 months (range: 5–70 months), resulting in a cumulative rate according to Kaplan–Meier analysis of 14.6% after 70 months (5.8 years) (Fig. 1). Seven patients underwent surgical treatment after a median of 20 months (range: 6–70 months), in six cases hysterectomy and in another myomectomy at first but later also hysterectomy due to insufficient symptom control. Repeat UAE was performed in 4/78 (5%) patients after a median of 9.5 months (range: 5–13 months). Two additional patients failed clinically after UAE with no relevant symptom alleviation. One woman was scheduled for hysterectomy at the time of writing after failed clinically after UAE with no relevant symptom alleviation. One woman was scheduled for hysterectomy at the time of writing after a median of tolerating the predominantly bulk-related symptoms, which never really changed after UAE. The second woman chose not to undergo an already scheduled repeat UAE despite treatment failure. She was 55 years of age at the time of her first UAE and after initial treatment failure experienced alleviation of symptoms with the onset of her menopause and under hormone replacement therapy with a combination of estradiol and norethisterone acetate (Activelle®, Novo Nordisk Pharma Ltd., Mainz, Germany) 1 year later. The above-mentioned 13/78 patients (17%) who either did not benefit from embolization therapy or even underwent further surgical or endovascular procedures to control their symptoms were classified as clinical failures of UAE. The remaining 65 patients were included in the analysis of the UFS-QOL questionnaire. Figure 2 additionally summarizes the course of patient selection in a comprehensive flow chart.

Pearson’s χ² test showed no significant interrelationship between the chosen particle type, either trisacryl gelatin micropheres or PVA particles, and treatment failure (P = 0.382).

New permanent amenorrhea was observed in 5/65 (8%) patients at a median of 18 months (range: 10–46) after UAE, the patients being 40–61 years of age (mean: 50) at that time.

Analysis of the UFS-QOL questionnaire

In the course of this study, the clinical short-term outcome was assessed at a median of 8 months (range 3–20 months; interquartile range: 9 months) and the long-term outcome at a median of 6.3 years (range: 5–7.6 years; interquartile range: 0.95) after UAE. Tables II and III list the questionnaire scores after the short- and long-term follow-up for the paired samples. The symptom severity and HRQOL total scores improved significantly from baseline to short-term follow-up (P < 0.001) to a median score of 10.94 (quartiles: 6.25–25.00) for the symptom severity and 93.97 (quartiles: 83.62–99.14) for overall HRQOL. The long-term follow-up data showed a significant improvement in comparison with both the baseline values (P < 0.001) and the short-term follow-up data, significant for the symptom severity (P = 0.006), concern (P = 0.020), control (P = 0.004) and sexual function subscale (P = 0.004) as well as for the HRQOL total score (P = 0.041). The median symptom severity score reaches the lower and the median quality of life scores the upper border of the score range of 100 points. Changes between the short- and long-term assessment are displayed in Table IV. Figure 3 allows a direct comparison of the median score results at baseline and both short- and long-term control in one radial plot.

The comparison of the symptom severity and the overall HRQOL score with respect to the particle type used, either TGM or PVA, revealed no significant difference (P = 0.647, P = 0.994). Stratifying our patient population by age [younger than 40 years (n = 48) versus equal to or older than 40 years (n = 48)], we observed no significant difference in clinical response on UAE regarding the symptom severity (P = 0.215) and the overall HRQOL (P = 0.645) at the last available follow-up.

Repeat UAE

Of the 13 patients with clinical treatment failure caused by insufficient fibroid infarction after UAE, four chose to undergo a second UAE instead of attempting a surgical approach. These patients were followed up similarly to the patients without treatment failure after a median of 5.2 years (range: 4.8–6.3) and presented with marked clinical improvement. The symptom severity score decreased from a median of 57.82 (range: 51.88–71.88) to 0.00 (range: 0.00–0.00); the HRQOL total score increased from a median of 59.05 (range: 11.21–70.69) to 100.00 (range: 88.79–100.00). However, due to the very small sample size, the observed changes did not
achieve significance (symptom severity score: \( P = 0.109 \), HRQOL total score: \( P = 0.068 \)).

**Discussion**

UAE has proved to be a safe and effective treatment alternative with a low rate of periprocedural complications and significant improvement of fibroid-related symptoms in many observational and comparative studies (Razavi et al., 2003; Siskin et al., 2006; Hehenkamp et al., 2008; Hald et al., 2009; Freed and Spies, 2010; Spies et al., 2010). Based on good and consistent scientific evidence, the American College of Obstetricians and Gynecologists judged the procedure as a safe and effective option for appropriately selected women who wish to retain their uteri (ACOG, 2008). However, hysterectomy still
represents the first-line treatment for this benign condition when medical therapy fails. In the USA, the rate of hysterectomy for uterine leiomyomas among all other reasons only decreased by 1% from 33.4% in the surveillance period from 1988 through 1993–32.4% in the period from 2001 through 2005 (Lepine et al., 2002). We observed that previously the fibroid disease was constantly dominating the women’s thoughts and perception of life circumstances, and the alleviation after UAE results in a quite positive attitude toward their quality of life despite minor problems that may bother women without a similar history. The long-term results of the prospective multicentre longitudinal FIBROID registry published after a follow-up interval of 3 years summarizes the clinical data of almost 1300 patients, showing similar results with a rate of major reintervention, i.e. hysterectomy, myomectomy or repeat UAE, adding up to 14.4% and highly significant improvement in quality of life in the remaining women (Goodwin et al., 2008). The authors also observed significant improvements when comparing the score results obtained after 6 and 12 months with the long-term follow-up data after 3 years. Popovic et al. (2009) published data of a small patient cohort of 39 women after a mean follow-up of 7 years using a comparable questionnaire with emphasis on the patients’ quality of life, which, similarly to our study and the FIBROID registry, showed highly significant improvements. However, all data, including the baseline quality of life information, were obtained retrospectively. Both studies, in addition, were only in nearly all subscales of the questionnaire, with the median subscale scores now corresponding to the lower border of the score range regarding symptom severity and the upper border for the scales pertaining to the impact on quality of life. Spies et al. pointed out that especially the subscales ‘Concern’ and ‘Control’ are most affected by symptomatic uterine fibroids. They deal with the inconvenience and anxiety caused by the unpredictable onset and intensity of menses, and the subsequent feeling of losing control over one’s health and future scheme of life. Whereas the median of the ‘Concern’ subscale already reached the upper border of 100 points after the short-term follow-up, the ‘Control’ subscale showed the least improvement at that time but was nevertheless comparable with the level of the healthy control group of the validation study. However, this subscale experienced the greatest and again highly significant (P = 0.004) improvement when comparing the short- and long-term follow-up. This seems to reflect the process of gaining confidence and self assurance, which may not be complete after a couple of months as most of these women have a long history of suffering. Another interesting observation is the positive overreaction in all score results after the long-term follow-up, relevantly exceeding those of the healthy control group in the study by Spies et al. It may be argued that previously the fibroid disease was constantly dominating the women’s thoughts and perception of life circumstances, and the alleviation after UAE results in a quite positive attitude toward their quality of life despite minor problems that may bother women without a similar history.

<table>
<thead>
<tr>
<th>UFS-QOL subscale</th>
<th>n</th>
<th>Short-term follow-up median (quartiles)</th>
<th>Long-term follow-up median (quartiles)</th>
<th>Difference median (95% CI)</th>
<th>P-value (Wilcoxon’s test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom severity</td>
<td>56</td>
<td>9.38 (3.91–24.22)</td>
<td>0.00 (0.00–11.72)</td>
<td>6.25 (0.00–9.38)</td>
<td>0.006</td>
</tr>
<tr>
<td>Concern</td>
<td>57</td>
<td>100.00 (77.50–100.00)</td>
<td>100.00 (100.00–100.00)</td>
<td>0.00 (–5.00 to 0.00)</td>
<td>0.020</td>
</tr>
<tr>
<td>Activities</td>
<td>56</td>
<td>96.43 (83.03–100.00)</td>
<td>100.00 (93.75–100.00)</td>
<td>0.00 (–3.57 to 0.00)</td>
<td>0.091</td>
</tr>
<tr>
<td>Energy/mood</td>
<td>56</td>
<td>92.86 (79.46–100.00)</td>
<td>100.00 (90.18–100.00)</td>
<td>0.00 (–7.15 to 0.00)</td>
<td>0.089</td>
</tr>
<tr>
<td>Control</td>
<td>57</td>
<td>90.00 (85.00–100.00)</td>
<td>100.00 (97.50–100.00)</td>
<td>–5.00 (–10.00 to 0.00)</td>
<td>0.004</td>
</tr>
<tr>
<td>Self-consciousness</td>
<td>57</td>
<td>100.00 (91.67–100.00)</td>
<td>100.00 (100.00–100.00)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.204</td>
</tr>
<tr>
<td>Sexual function</td>
<td>58</td>
<td>93.75 (75.00–100.00)</td>
<td>100.00 (100.00–100.00)</td>
<td>0.00 (–12.50 to 0.00)</td>
<td>0.004</td>
</tr>
<tr>
<td>HRQOL total</td>
<td>51</td>
<td>95.69 (83.62–99.14)</td>
<td>100.00 (93.10–100.00)</td>
<td>–3.45 (–6.90 to 0.00)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

CI, confidence interval; HRQOL, health-related quality of life; UFS-QOL, uterine fibroid symptom and quality of life questionnaire.

Figure 3 Radial plot with symptom severity and quality of life scores at each time of control.
able to present a response rate of a little over 60%, leaving a large portion of patients uncontrolled.

Treatment failure does not necessarily result in surgery, as we were able to show in four patients who agreed to undergo repeat UAE, which resulted in symptom control in all patients at the long-term follow-up. The most important predictor of clinical outcome is the infarction rate of the fibroid load, which can be influenced by several factors during UAE, such as difficulties in catheterization, arterial spasm precluding free-flow embolization, choice of embolic material and embolization end-point, or collateral fibroid supply, e.g. via an enlarged ovarian artery. All of these factors result in fibroid portions remaining viable and leading to growth and finally recurrence of clinical symptoms (Kroencke et al., 2010). Repeat embolization therapy should be considered in patients with recurrent symptoms.

The effect of UAE on ovarian reserve and future fertility still is a topic for which currently no definitive results are available. In our study population, 8% experienced permanent amenorrhea, indicating the onset of menopause. The mean age was 50 years, which is the typical age of entering menopause in the average female population (Greendale et al., 1999). All but one woman were older than 45 years by the time of UAE, and the onset of menopause might have occurred coincidentally. The youngest patient entering menopause was 39 years at the time of UAE and was menopausal one year later. Retrospective evaluation of the procedural details and clinical information revealed no obvious reason for this particular course. The natural chance of entering menopause in such early age in the general population is about 1% with an age range from 40 to 58 when the final period generally happens. Such early or even premature menopause has been associated with low socioeconomic status, long history of smoking, age at menarche, parity, BMI and others, factors that unfortunately were not systematically measured in from our patients. Current studies confirm that embolization therapy has no adverse effect on the ovarian reserve in patients younger than 40 years (Tropeano et al., 2004, 2010). Accordingly, in a long-term observational study with 211 patients, Katsumori et al. (2008) reported no onset of permanent amenorrhea in patients under the age of 40 throughout the 6-year study period. The FIBROID registry documented the largest proportion of permanent amenorrhea after UAE with 28.6%, almost 80% of the women being older than 45 years, but also 5.5% being younger than 40 years (Goodwin et al., 2008). The stratification of our study population by age (younger than 40 versus equal to or older than 40) revealed no differences in clinical outcome.

One limitation of our study is the small sample size. However, we were able to obtain the clinical follow-up in over 95% of patients, corroborating the reliability of the information presented here. Another limitation is the chosen study design without randomization to a control group or surgical treatment. This was caused by the patients confirmed wish to undergo UAE as an alternative to surgery when presenting in our department, which conflicts with any randomized protocol. Our results are therefore helpful in evaluating the long-term effect of UAE, which was the intention of the study, but has to be viewed with caution when comparing them to results of studies on other treatment options. Well-designed randomized studies with comparable end-points are needed to compare the outcome of currently available treatment options.

We conclude from the results of this study that UAE proved to be an effective treatment option for patients suffering from symptomatic uterine leiomyomata, otherwise facing surgery, with remarkable improvement of their previously impaired HRQOL and an acceptable failure rate after a long-term follow-up.

**Authors’ roles**

The authors contributed substantially in the following ways: C.S.-M. conception and design, data acquisition, statistical analysis, manuscript editing, critical discussion and manuscript revision. A.L. conception and design, data acquisition, critical discussion and manuscript revision. V.F. data acquisition and manuscript revision. M.M. data acquisition and manuscript revision. B.H. conception and design, critical discussion and manuscript revision and T.J.K. conception and design, data acquisition, critical discussion and manuscript revision, performed all interventional procedures presented in this manuscript.

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