Radiation Exposure During Uterine Fibroid Embolization (UFE): A Confounder-Controlled Comparison Between a State-of-the-Art Angiography Unit and a Conventional Angiography unit

Strahlenexposition während Uterusmyomembolisation (UME): Ein Störgrößen-kontrollierter Vergleich zwischen einem hochmodernen Angiografiesystem und einem konventionellen Angiografiesystem

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ZUSAMMENFASSUNG
Ziel Vergleich der Strahlenexposition zwischen einem modernen und einem konventionellen Angiografiesystem bei Patientinnen, die sich einer Uterusmyomembolisation (UME) unterzogen.

Material und Methoden Zwischen Januar 2009 und Dezember 2016 unterzogen sich in unserem Interdisziplinären Myomzentrum insgesamt 286 Patientinnen einer UME. Einschlusskriterien für die retrospektive Analyse waren eine erstmalige transarterielle Embolisation aufgrund symptomatischer Myome, die bilaterale Embolisation, Prozeduren mittels modernem (Gruppe 1) oder konventionellem (Gruppe 2) Angiografiesystem sowie bilateraler technischer Erfolg mit adäquatem Embolisationsendpunkt nach Injektion von Mikrosphären. Studienendpunkte waren Strahlenexposition, Major-Komplikationen, morphologischer Erfolg (MRT) und klinischer Erfolg (Fragebogen zur Lebensqualität). Die Kontrolle von Störgrößen erfolgte mittels Propensity Score Matching.

Ergebnisse Die Einschlusskriterien wurden von 58 (Gruppe 1) bzw. 177 (Gruppe 2) Patientinnen erfüllt. Nach Propensity Score Matching ergaben sich keine signifikanten Unterschiede zwischen Gruppe 1 (n = 46) und Gruppe 2 (n = 92) bezüglich Alter, Body-Mass-Index, Volumen des dominanten Myoms, Uterusvolumen, Fluoroskopiezeit und Embolisatmenge (je-weils p ≥ 0,10). Das Dosisflächenprodukt war in Gruppe 1 signifikant geringer als in Gruppe 2 (1159,0 cGycm² vs. 3123,5 cGycm²; p < 0,001), während die Major-Komplikationsrate (0 % in beiden Gruppen) und der Grad der Devaskularisation des dominanten Myoms (100 % in beiden Gruppen) vergleichbar waren (p > 0,99). Außerdem ergaben sich vergleichbare Ergebnisse bezüglich Schrumpfung des dominanten Myoms und des Uterus und der patientenberichteten Lebensqualität.
Introduction

Uterine fibroid embolization (UFE) has increasingly gained acceptance as a minimally invasive treatment for women with symptomatic uterine fibroids (also known as leiomyomas or myomas). Uterine fibroids are the most common benign tumors of the female reproductive system and a major cause of morbidity in women of childbearing age [1, 2]. The incidence of uterine fibroids is estimated between 20% and 40% of women in their reproductive age, and has been shown to reach 70% to 80% by the age of 50 years [1–3].

UFE involves the injection of microspheres via an angiographic catheter selectively positioned in the uterine arteries to cause devascularization with consecutive shrinkage of all fibroids [4, 5]. In the clinical routine, UFE is performed under fluoroscopy and angiography guidance. Since ovaries are sensitive to radiation, the hazards of ionizing radiation including carcinogenic effects and radiation damage are of great concern [6–8]. Studies have therefore analyzed the radiation dose applied during UFE and measures to reduce exposure [9–15]. Since most of these measures concern technical parameters, it has been hypothesized that state-of-the-art angiographic units are generally more appropriate than conventional units to reduce radiation exposure while maintaining image quality, low complication rates, and high clinical success [13].

To test this hypothesis, we retrospectively compared radiation exposure and outcome of patients who had undergone UFE under image guidance by either a state-of-the-art or a conventional angiography unit. Propensity score matching was used to assemble comparable study groups. The primary endpoint of our study was radiation exposure. Secondary study endpoints comprised technical outcome (major complication rate), morphological outcome, and clinical outcome (quality-of-life).

Materials and Methods

Ethical Approval and Informed Consent

All procedures of this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Since this study was a retrospective audit of anonymized patient records, formal consent was not required.
Study Population
A total of 286 patients who underwent UFE in our Interdisciplinary Fibroid Center between January 2009 and December 2016 were evaluated. Predefined inclusion criteria for retrospective analysis were (1) first-time transarterial embolization for symptomatic uterine fibroids, (2) single-stage bilateral embolization from a right-sided transfemoral approach, (3) procedures applying either a state-of-the-art angiography unit (Artis Zeego Q; Siemens Healthineers, Erlangen, Germany) or a conventional unit (Axiom Artis; Siemens Healthineers, Erlangen, Germany), and (4) technical success with an adequate embolization endpoint in both uterine arteries as specified below. Patients who had previously undergone gynecological pelvic surgery or transarterial embolization for symptomatic adenomyosis were excluded. Because data were retrospectively collected, allocation of patients to Group 1 (state-of-the-art unit) or Group 2 (conventional unit) depended on the time of inclusion. The conventional unit was applied between January 2009 and October 2013 (Group 2) and then replaced by the state-of-the-art angiography unit in January 2014 (Group 1).

Study Design
Candidates for UFE were evaluated by our team, and the decision for UFE was based on the patient’s history, symptoms, and clinical examination, as well as on transvaginal ultrasound and laboratory analyses. Magnetic resonance imaging (MRI) including MR angiography and sagittal acquisitions was performed to verify the diagnosis, to rule out contraindications such as large pedunculated fibroids, and to plan critical procedural steps (e.g. definition of the optimal tube angulation for catheterization). In both study groups, UFE procedures followed the same protocol (see below).

The primary study endpoint was radiation exposure provided electronically by the angiography unit (DAP; cGy.cm²). Secondary study endpoints were the rate of post-embolization syndrome and major complications that occurred within one month after treatment as well as the morphological and clinical outcome. Complications were classified according to the Clavien-Dindo system [16]. In brief, this system defines five grades of treatment required to correct a specific complication (1: no intervention; 2: pharmacological treatment; 3: surgical intervention with or without general anesthesia; 4: life threatening; single or multiple organ dysfunction; 5: death of the patient). Major complications were defined by grades ≥ 3. Major complications were further classified according to the Society of Interventional Radiology (SIR) [17, 18] by the requirement of therapy, hospitalization of less or more than 48 hours, permanent adverse sequelae, and death.

The morphological outcome after UFE was evaluated by MRI including coronal and sagittal acquisitions after ≤ 6 weeks and 6 to 12 months. Devascularization was assessed by comparing MRI results obtained before and after UFE. The degree of devascularization of the dominant fibroid was rated on a 3-point Likert scale as described previously [19] (1: complete [100 %]; 2: almost complete [90 – 99 %]; 3: partial [≤ 89 %]).

As a clinical endpoint, quality-of-life was assessed in a questionnaire on the degree of dysmenorrhea, hypermenorrhea, dysuria, lower abdominal pain, dyspareunia, general fitness, and professional capacity (10-point scale; 1 = absent, 10 = maximum). General well-being was assessed on a 100-point scale (1 = absent, 100 = maximum). Questionnaires were obtained before (≤ 3 months) and after (6 – 12 months) UFE. After UFE, the questionnaire additionally asked about patient treatment satisfaction (10-point scale; 1 = absent, 10 = maximum).

Uterine Fibroid Embolization Procedures
Seven interventional radiologists (A – G) conducted UFE procedures. UFE was performed either with epidural anesthesia or with superior hypogastric nerve block. Since hypogastric nerve block was recognized as a safe and effective approach for pain control, application of epidural anesthesia for UFE became increasingly rare in our center. After pre-medication (250 mg prednisolone, 4 mg ondansetron, 1.25 mg midazolam, 1 g novamine, and 7.5 mg piritramide) and local anesthesia of the right groin (20 – 40 ml ultracain 1 %), the femoral artery was punctured and a 4 or 5 F vascular sheath was inserted. The main stem of the left iliac artery was catheterized under fluoroscopy (pelvic angiography preset, 4 or 7 pulses/s [depending on image quality], field-of-view [FOV] of 22 cm, tight collimation, no tube angulation), either with a 4 F Cobra 2 catheter or a 5 F RUC catheter, each in combination with a soft guidewire. Intravenous analgesia was maintained with 15 mg piritramide over a period of 90 minutes. In patients undergoing epidural anesthesia, the patient controlled anesthesia (PCA) started at this time and continued for at least 24 hours. To identify the uterine artery, digital subtraction angiography (DSA) acquisition was performed (pelvic angiography preset, FOV of 22 cm, frame rate of 1 image/s, optimal tube angulation with free projection of the origin of the uterine artery according to MR angiography [usually 45 ± 5 degrees], contrast material volume of 10 – 12 ml at 3 – 5 ml/s). After selection of the appropriate frame as a reference image, the uterine artery was catheterized applying an overlay or a roadmap technique with a 2.7 F coaxial microcatheter. Repetitive intra-arterial spasmolysis (0.25 mg Nitro) was routinely performed. The adequate embolization position was verified (DSA acquisition: pelvic angiography preset, FOV of 22 cm, frame rate of 1 image/s, no tube angulation, contrast material volume of 5 – 8 ml at 1.5 – 1.8 ml/s). For prominent collaterals to the ovary, the technique was adapted for example by a deeper embolization position or the use of larger microspheres to avoid collateral embolization. Coil embolization of the ovarian artery was never performed. Subsequently, in patients undergoing superior hypogastric nerve block, the skin below the belly was anesthetized (5 ml ultracain 1 %), and a 21 G Chiba needle was positioned at the front of the L5 / S1 intervertebral space under fluoroscopy (pelvic angiography preset, 4 or 7 pulses/s [depending on image quality], FOV of 22 cm, tight collimation). After verification of the correct needle position by fluoroscopy (pelvic angiography preset, 4 or 7 pulses/s [depending on image quality], FOV of 22 cm, tight collimation) in two projections (no tube angulation and 90 degree tube angulation), two different medications were administered (1: 50 – 100 mg bupivacaine-hydrochloride [10 – 20 ml carbostesin 0.5 %]; 2: 75 – 150 mg ropivacaine-hydrochloride [10 – 20 ml ropivacaine 7.5 mg/ml]). Microspheres with 700 ± 250 and/or 900 ± 250 μm were injected...
until stasis (Embozene Microspheres; Boston Scientific, Marlborough, USA). The amount of microspheres was documented. Imaging of stasis, defined as stagnation of the flow in the uterine artery for at least 5 s, was performed with fluoroscopy (pelvic angiography preset, 4 or 7 pulses/s [depending on image quality], FOV of 22 cm, tight collimation). Another DSA acquisition demonstrated devascularization 5 minutes after the last microsphere injection (pelvic angiography preset, FOV of 22 cm, frame rate of 0.5 image/s, no tube angulation, contrast material volume of 4 ml at 1 ml/s). The surrogate of an adequate embolization endpoint was the lack of forward-flow of the contrast material column within the uterine artery (stasis) for at least 10 s. After removal of the microcatheter, the main stem of the right internal iliac artery was catheterized under fluoroscopy (pelvic angiography preset, 4 or 7 pulses/s [depending on image quality], FOV of 22 cm, tight collimation, no tube angulation) by using the Waldman loop technique. Embolization of the right uterine artery was carried out as described. For patients undergoing superior hypogastric nerve block, one further medication was injected after completion of right-sided embolization (75 – 150 mg ropivacaine-hydrochloride [10 – 20 ml ropivacaine 7.5 mg/ml]). Finally, the catheters and sheath were removed, and the groin was compressed. Aftercare included further intravenous medications (250 mg prednisolone [once a day], 4 mg ondansetron [repetitive as required], 1 g novamine [repetitive as required], and 7.5 mg piritramide [repetitive as required]).

### Statistics

Categorical data were summarized as percentages (frequencies), and continuous data were summarized as median (interquartile range), if not otherwise specified. Groups were compared using the chi-square and the Wilcoxon rank sum test. To account for unobservable confounders that were likely to be associated with both the use of the Artis Zeego Q and a decreased DAP, a matched-controlled analysis using high-dimensional propensity scores was performed. High-dimensional propensity scores were generated by logistic regression analysis with Firth’s penalized likelihood [20]. The model included age, body-mass index (BMI), volume of the dominant fibroid, volume of the uterus, volume of the injected microspheres, fluoroscopy time, and interventional radiologist. Patients in Group 1 (cases) were matched by high-dimensional propensity score, using a greedy matching algorithm, to patients in Group 2 with a 1-to-2 matching ratio [21]. A two-sided P-value of ≤ 0.05 was considered to indicate statistical significance. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, USA) or Prism software version 6.00 (GrafPad Software, LaJolla, USA).

<table>
<thead>
<tr>
<th>Group 1 (n = 58 patients)</th>
<th>Group 2 (n = 177 patients)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Age (years)</td>
<td>45.0 (39.8 – 48.0)</td>
<td>46.0 (43.1 – 48.8)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>25.8 (22.4 – 29.5)</td>
<td>24.1 (22.0 – 27.8)</td>
</tr>
<tr>
<td>Dominant fibroid (volume, cm³)</td>
<td>52.7 (23.7 – 178.6)</td>
<td>60.0 (17.2 – 134.9)</td>
</tr>
<tr>
<td>Uterus (volume, cm³)</td>
<td>301.0 (194.5 – 453.8)</td>
<td>308.6 (191.6 – 517.2)</td>
</tr>
<tr>
<td>Injected microspheres (volume, ml)</td>
<td>5.7 (5.2 – 8.2)</td>
<td>5.3 (3.7 – 8.0)</td>
</tr>
<tr>
<td>Fluoroscopy time (min.)</td>
<td>11.5 (9.3 – 13.8)</td>
<td>12.1 (9.5 – 17.6)</td>
</tr>
<tr>
<td>Procedures (per radiologist)</td>
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<td>32</td>
</tr>
<tr>
<td>Radiologist A</td>
<td>2</td>
<td>32</td>
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<tr>
<td>Radiologist B</td>
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<td>64</td>
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<td>25</td>
</tr>
<tr>
<td>Radiologist D</td>
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<td>37</td>
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<tr>
<td>Other radiologist</td>
<td>14</td>
<td>19</td>
</tr>
</tbody>
</table>

BMI: body-mass index; Group 1: state-of-the-art angiography unit (Artis Zeego Q); Group 2: conventional angiography unit (Axiom Artis).

BMI: Body-Mass-Index; Gruppe 1: hochmodernes Angiografiesystem (Artis Zeego Q); Gruppe 2: konventionelles Angiografiesystem (Axiom Artis).
Results

Patient Characteristics and Propensity Score Matching

Out of 286 patients who underwent UFE in our institution, 58 (Group 1) and 177 (Group 2) patients were included in the retrospective analysis. Patient characteristics and procedural parameters (▶ Table 1) were then adjusted for confounders by propensity score matching to generate homogeneous groups of 46 (Group 1) and 92 (Group 2) patients for final analysis (▶ Table 2; ▶ Fig. 1).

Outcome Parameters

Technical Endpoints

The DAP was significantly and almost 3-fold lower when a state-of-the-art angiography unit was employed during UFE (Group 1: 1159.0 cGycm² [638.9 – 1319.0] vs. Group 2: 3123.5 cGycm² [1578.0 – 4532.5]; p < 0.001). Importantly, the respective fluoroscopy time did not significantly differ between Group 1 and Group 2 (p = 0.80; ▶ Table 2). No major complications according to both Clavien-Dindo and SIR classification occurred in either group (p > 0.99 between groups). As expected, all patients of both groups developed post-embolization syndrome (p > 0.99), which could be managed effectively by applying intravenous medica-

Morphological Endpoints

Morphological outcome was assessed in two MRI examinations performed after ≤ 6 weeks and 6 to 12 months. The first MRI examination revealed complete devascularization in all but three cases, as indicated by an average devascularization score of 1.0 (1.0 – 1.0) in both groups (p > 0.99 between groups). These three patients (Group 1: one patient; Group 2: two patients) underwent a second UFE in the meantime, and control MRI examinations at < 4 weeks after UFE demonstrated complete devascularization of the dominant fibroid. The second MRI after 6 to 12 months demonstrated significantly reduced volumes of the dominant fibroid and the uterus in both groups. In Group 1, the volumes of the dominant fibroid and the uterus significantly declined from 126.3 cm³ (40.8 – 345.6) and 343.6 cm³ (214.7 – 1160.0) before UFE (n = 46) to 19.9 cm³ (10.2 – 64.5) and 234.2 cm³ (89.2 – 464.1) after 6 to 12 months (n = 12; p = 0.0005 in each comparison). Likewise, in Group 2, the volumes of the dominant fibroid and the uterus significantly declined from 105.3 cm³ (11.1 – 243.0) and 383.1 cm³ (236.8 – 590.2) before UFE (n = 92) to 15.2 cm³ (2.9 – 77.2) and 179.5 cm³ (87.8 – 372.6) after 6 to 12 months (n = 36; p < 0.0001 in each comparison).
There were no significant differences between Group 1 and Group 2 in absolute and relative values of dominant fibroid and uterus shrinkage (Fig. 2). At 6 to 12 months after UFE, the relative shrinkage of the dominant fibroid and the uterus in Group 1 (74.1% [58.4–90.7%], 57.1% [30.7–68.1%]) only marginally differed from that in Group 2 (57.7% [26.8–90.5%], 55.6% [39.7–71.0%]; p = 0.32 and p = 0.58 for the comparison of dominant fibroid shrinkage and uterus shrinkage, respectively). Figure 3 exemplarily shows MRI examinations of one patient in Group 1 before (Fig. 3a) and 8 months after UFE (Fig. 3c), demonstrating complete devascularization of the dominant fibroid as well as the reduced volumes of the dominant fibroid, the smaller fibroids, and the entire uterus. Superselective DSA of the uterine artery shows the embolization position with opacification of multiple arterial feeders (Fig. 3b).

Clinical Endpoints
Out of 138 patients included after propensity score matching, 24 (Group 1) and 46 (Group 2) patients completed the questionnaires on quality-of-life before and after UFE. At ≤3 months before UFE, only slight differences between study groups were observed in the degree of dyspareunia (Group 1 [1.0 (1.0–3.0)] vs. Group 2 [3.0 (2.0–4.0)]). Importantly, the survey further revealed that UFE improved the degree of dysmenorrhea, hypermenorrhea, dysuria, general fitness, and professional capacity in both study groups (Fig. 4). In Group 1 (Fig. 4a), dyspareunia additionally improved after UFE from 3.0 (1.0–5.0) to 1.0 (1.0–2.0) while the degree of lower abdominal pain did not change. In Group 2 (Fig. 4b), the degree of dyspareunia did not change while the degree of lower abdominal pain improved from 2.0 (2.0–5.0) to 1.0 (1.0–1.0). The degree of general well-being improved in both groups and was equally high after 6 to 12 months (Group 1: 80.0 [70.0–90.0]; Group 1: 85.0 [70.0–90.0] with 100 = maximum). Likewise, maximum treatment satisfaction rates were obtained at 6 to 12 months after UFE (median [interquartile range] in both groups: 10.0 [9.0–10.0] with 10 = maximum).
Discussion

Here, we demonstrated that a state-of-the-art angiography unit has the potential to significantly reduce the radiation exposure of patients undergoing UFE when compared to a conventional angiography unit. Complication rates remained equally low. Morphological and clinical success as well as patient satisfaction were equally high with both angiography units. The radiation dose was...
reduced almost 3-fold by the state-of-the-art unit, and complete devascularization of the dominant fibroid – an imaging biomarker for symptom control and re-intervention – was observed in all patients. Within one month after UFE, no major complications occurred. After 6 to 12 months, there were no significant differences between the study groups regarding shrinkage of the dominant fibroid and the uterus and the patient-reported quality-of-life.

Appropriate measures for radiation reduction during pelvic angiography are of utmost importance. Effective measures include optimized source-object, source-image, and object-image distances, the avoidance of magnification and oblique projections, tight collimation to the relevant anatomy, the use of pulsed fluoroscopy with decreased image frequency, and the use of low frame rates or even last-image-hold to document angiographic endpoints [9, 13]. Flat panel detectors improve image quality while reducing radiation exposure, and pre-interventional optimization of the tube angle by 3D-reconstructed contrast-enhanced MR angiography helps to avoid conventional survey aortography [11, 22, 23]. In particular, angiography units allowing the selection of lower pulse rates during fluoroscopy contribute to a significant reduction in the overall fluoroscopy time and the radiation dose exposure of patients undergoing UFE [9, 24]. In the Artis Zeego Q angiography unit (Group 1), radiation dose has been further reduced by copper prefiltration and automatic exposure control. Copper prefiltration significantly reduces the proportion of low energy quanta of the discrete X-ray spectrum of the tube, and the automatic exposure control additionally adjusts the X-ray tube voltage, tube current, exposure time, and focal spot size.

According to a recent radiological and gynecological expert meeting on UFE, the DAP should lie below 5000 cGycm² for pulsed fluoroscopy units [25]. Several studies have recently investigated approaches to meet this requirement, resulting in DAPs between 2440.0 ± 1900.0 cGycm² (mean ± SD) and 4577.0 (2342.0 – 6813.0) cGycm² (mean and 95% CI) [9, 11, 13, 25 – 27]. In addition, substantial experience of radiologists performing UFE has shown to decrease the fluoroscopy time needed for uterine artery catheterization [24]. Moreover, strict adherence to protocols established to limit exposure as well as the use of modern angiographic units has been shown to reduce radiation dose during UFE [13, 24]. In our study, UFE procedures in both groups followed the same protocol, and propensity score matching ensured comparability of patient characteristics and procedures. With UFE performed under image guidance by a conventional angiography unit, patients were exposed to an average DAP of 3123.5 cGycm², which lies in the range of recently published values [9, 11, 13, 23, 26 – 28]. In contrast, image guidance by a state-of-the-art angiography unit reduced this radiation exposure almost 3-fold. Since the analysis of both study groups was controlled for potential confounders, we can assume that this additional reduction is based primarily on the technical advances of modern angiography units.

This study has limitations. First, UFE procedures were not fully standardized (e.g. pulse rates and mapping techniques [road map or overlay]; type of patient analgesia [PCA vs. hypogastric nerve block]). Second, dominant fibroid shrinkage was the surrogate endpoint for treatment success, which might disregard the significance of the patient’s symptoms. However, we believe that there is no benefit to assessing multiple fibroids instead of a single representative one, but we cannot make any assertion as to whether reduced radiation exposure during UFE influences rates of fibroid-related symptoms in the long term. Third, successful shrinkage of the dominant fibroid and the uterus was demonstrated after 6 to 12 months, but a more specific examination schedule might have resulted in different results. Finally, pre-treatments such as myomectomy were not considered in the propensity score calculation. However, our study was designed to assess the radiation exposure during UFE, the rate of major complications, the degree of devascularization, and the quality-of-life in the short term. Further evaluations are now planned to assess long-term fibroid-related symptoms.

In conclusion, a state-of-the-art angiography unit has the potential to reduce radiation exposure in patients undergoing UFE without increasing the risk of major complications while achieving comparable morphological and clinical success.

**CLINICAL RELEVANCE**
- UFE is a safe and effective minimally invasive treatment for the control of fibroid-related symptoms such as reduced quality-of-life.
- Since UFE is performed under X-ray control, radiation exposure needs to be minimized.
- A state-of-the-art angiography unit has the potential to reduce radiation exposure in patients undergoing UFE.
- The reported dose reduction does not seem to negatively affect major complications or morphological and clinical success.

**ABBREVIATIONS AND ACRONYMS**
- BMI: body mass index
- DAP: dose-area product
- DSA: digital subtraction angiography
- FOV: field-of-view
- MR: magnetic resonance
- MRI: magnetic resonance imaging
- PCA: patient controlled anesthesia
- UFE: uterine fibroid embolization

**Conflict of Interest Disclosures**

SOMMER CM, KLAPP-OLIGER M, SCHLETT CL, EERPENBACH S, THOMAS K, HATOOP A AND KURZ PP REPORT THE FOLLOWING DISCLOSURES: NOTHING TO DISCLOSE REGARDING THIS STUDY.

VOIGT W REPORTS THE FOLLOWING DISCLOSURES: EMPLOYEE OF SIEMENS HEALTHINEERS, ERLANGEN, GERMANY.

RICHTER GM REPORTS THE FOLLOWING DISCLOSURES: SPEAKER FOR SIEMENS HEALTHINEERS, ERLANGEN, GERMANY AS WELL AS TECHNICAL AND FINANCIAL SUPPORT FROM SIEMENS HEALTHINEERS, ERLANGEN, GERMANY.
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