Minimal invasive therapies for the treatment of symptomatic uterine leiomyomas - A multimodal approach

Eric Dorenberg, MD

Dept. of Radiology and Nuclear Medicine and
The Intervention Centre
Oslo University Hospital Rikshospitalet
Faculty of Medicine, University of Oslo
Contents
1. Acknowledgements
2. List of papers
3. Abbreviations
4. Background
   4.1. Leiomyomas
   4.2. Medical and surgical treatment options
   4.3. Uterine artery embolization
   4.4. High-intensity focused ultrasound
5. Aims of the thesis
6. Material
7. Methods
   7.1. Uterine artery embolization
   7.2. Contrast-enhanced ultrasound
   7.3. High-intensity focused ultrasound
   7.4. Magnetic resonance imaging
   7.5. Clinical evaluation
   7.6. Quality of life assessment
   7.7. Statistical methods
8. Summary of the results
9. General discussion
   9.1. Methodological considerations
   9.2. Uterine artery embolization
   9.3. MR-guided high-intensity focused ultrasound
10. Conclusions and future prospects
11. References
1. Acknowledgements

This work was carried out at the Department of Radiology and The Intervention Center at Oslo University Hospital, Rikshospitalet, University of Oslo, with participation from the Department of Gynecology, Oslo University Hospital.

I want to express my sincere gratitude to the following persons:

My main supervisor Professor Jarl Å. Jakobsen; his enthusiasm about new technologies was always an inspiration and his analytical talents helped to bring structure to this thesis.

My co-supervisor Per-Kristian Høl who played an important role in bringing back momentum to my work and made a great effort for making the dream of HIFU-equipment in Oslo come true.

Geir Hafsahl who gave me the privilege of sharing his vast knowledge and love to the field of interventional radiology – I could not have asked for a better teacher and mentor.

The co-authors at the department of Radiology: Professor Hans-Jørgen Smith and Knut Brabrand, both excellent teachers who were always willing to support me and made great contributions to the papers.

Professor Erik Fosse and the staff at The Intervention Center for offering an arena for the development of new therapies and outstanding practical help in performing trials. Special thanks to Frédéric Courivaud for excellent help during the HIFU trial.
All colleagues at the Department of Gynecology, namely Unni Kirste for taking the initiative to introduce UAE in Norway, Zarko Novacovic for collecting clinical data in paper I, Eva Ring and Kirsten Hald for having an open mind for interventional treatment of leiomyomas and supplying the patients without whom this thesis would not have been possible.

Rune Andersen and Tone Meyer, who together with Geir took care of the daily work, giving me time and space to complete this thesis.

Finally to my wonderful wife Dagny and our children Philip and Helene for all support, patience and love.
2. List of papers

This thesis is based on the following papers, which will be referred to by their roman numerals:

I. Dorenb erg EJ, Novakovic Z, Smith HJ, Hafsa hl G, Jakobsen JÅ. 
Uterine fibroid embolization can still be improved: observations on post-procedure MRI. Acta Radiol 2005; 46:547-553.


III. Dorenb erg EJ, Hol PK, Jakobsen JÅ, Ring E. Improved infarction rates in fibroids after the introduction of contrast-enhanced ultrasound during uterine artery embolization. Accepted for publication in Acta Radiologica.

### 3. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE</td>
<td>Contrast-enhanced</td>
</tr>
<tr>
<td>CEUS</td>
<td>Contrast-enhanced ultrasound</td>
</tr>
<tr>
<td>HIFU</td>
<td>High-intensity focused ultrasound</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MRgHIFU</td>
<td>Magnetic resonance-guided high-intensity focused ultrasound</td>
</tr>
<tr>
<td>NPV</td>
<td>Non-perfused volume</td>
</tr>
<tr>
<td>PVA</td>
<td>Polyvinyl-alcohol</td>
</tr>
<tr>
<td>TGM</td>
<td>Tris-acryl gelatin microspheres</td>
</tr>
<tr>
<td>UAE</td>
<td>Uterine artery embolization</td>
</tr>
<tr>
<td>UFE</td>
<td>Uterine fibroid embolization</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasonography</td>
</tr>
</tbody>
</table>
4. Background

Interventional radiology always seeks to develop minimal invasive procedures as an alternative to conventional, surgical methods. This thesis describes the introduction of two novel treatments of symptomatic, uterine leiomyomas in Norway.

4.1. Leiomyomas

Uterine leiomyomas are benign tumors arising from the smooth muscle cells of the uterus. Histologically they may also contain a varying amount of connective tissue. In the literature they are often referred to as fibroids; this thesis will use the terms leiomyoma or myoma. The prevalence of leiomyomas is high; in a pathology study of 100 specimens, Cramer et al (1) found myomas in 77 of them. Similar numbers were reported by Day et al. (2) who investigated 999 premenopausal women by ultrasound. They showed that the prevalence of leiomyomas increases with age and is race-dependent; in their material the prevalence of leiomyomas surpassed 80% in African-American women as compared to 70% in Caucasians. The formation of leiomyomas depends on hormonal production, and their size and number decreases after menopause (1). Clinical manifestations vary with the size and location of myomas. It is estimated that about 25% of all women will experience myoma related symptoms in their lifetime (3). These are usually classified in three distinct categories (4):
- Abnormal uterine bleeding
- Pelvic pressure and pain
- Reproductive dysfunction

The bleeding pattern most characteristic of leiomyomas is prolonged or excessively heavy menstruation, in some cases even leading to anemia. Excessive bleeding may cause substantial social embarrassment and loss of productivity (4). The increased size of the myomatous uterus may cause pressure to adjacent organs. Depending on the size and orientation of the uterus, and the location of the largest myomas, the direction of the pressure can vary, giving rise to different symptoms as constipation, urinary symptoms, bulking or pain. Especially submucous myomas and those causing distortion of the uterine cavity may affect fertility (5). Further, myomas have been shown to impact on pregnancy outcome with increased risk of miscarriages and birth complications (6-8).

4.2. Medical and surgical treatment options

Different hormonal agents are used for conservative treatment of leiomyomas. Especially hormone-releasing intrauterine devices have shown good results in reducing menorrhagia (9).

Hysterectomy has traditionally been the primary treatment of symptomatic leiomyomas and these benign tumors account for approximately one third of all hysterectomies in Western countries (10, 11). In 2000, of a total 4764
hysterectomies in Norway, approximately 2000 were done for leiomyomas (12). Despite the development of less invasive surgical methods, e.g. laparoscopic and transvaginal techniques, hysterectomy is associated with a substantial complication rate. In a report from Vestfold central hospital analyzing data from 315 hysterectomies with different techniques, Oma found an overall complication rate of 29% (13). In a large study including more 10,000 hysterectomies in Denmark, Møller et al. reported a complication rate of at least 18% (14).

Myomectomy, i.e. surgical removal of fibroids, is most frequently performed through an open, abdominal approach. Even if the procedure may cause substantial blood loss (15, 16), conversion to hysterectomy does not longer seem to be common (17). While laparoscopic myomectomy is technical difficult and therefore reserved to expert centers, hysteroscopic myomectomy is limited to a subgroup of submucous leiomyomas. Recurrence after open myomectomy is well documented and reported in at least 10% of cases (18). After laparoscopic myomectomy, recurrence rates are higher (19, 20).

On this background and given the benign nature of leiomyomas, it seems not surprising, that women increasingly want to play an active role in choosing therapies (21, 22) and embrace minimal invasive options. These patients’ preferences are an important factor for the success of new minimal invasive therapies for uterine leiomyomas.
4.3. Uterine artery embolization

In 1979, uterine artery embolization (UAE) was introduced as a new method to control post-partum hemorrhage (23). 16 years later, Ravina et al. suggested UAE as a new treatment for symptomatic leiomyomas (24). In their original paper on 16 women, most of them with serious menorrhagia, 11 patients experienced complete cure and only 2 patients had no symptom relief. For embolization, Ravina et al. used polyvinyl-alcohol particles, “gradually increasing the size of the particles until tumour blood flow was eliminated.” Finally, a fragment of gelfoam was left “in the trunk of the uterine artery to ensure stability of this devascularization.”

During the next five years, several authors adopted the technique and reported promising results (25-30). In 2001, Andersen et al. published the first Scandinavian paper on UAE (31): from January 1999 to May 2000, they treated 62 patients and were able to reproduce the results of other authors: a high technical success rate of 97%, relief or cure from menorrhagia in 96% and a low complication rate.

Based on the classification developed by the Society of Interventional Radiology (SIR), Spies et al. (32) published in 2002 in a study of 400 UAE procedures a periprocedural complication rate of 8.5%, including 1.25% serious adverse events. The reported complication rates and the suggested threshold from the quality improvement guidelines of SIR and its European counterpart Cardiovascular and Interventional Radiology Society of Europe (CIRSE) are given in Table 1.
Table 1. Complication rates and threshold as suggested by the quality improvement guidelines of SIR and CIRSE (33).

<table>
<thead>
<tr>
<th>Complication rates for UAE</th>
<th>Reported rate (%)</th>
<th>Suggested threshold (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient amenorrhea</td>
<td>5-10</td>
<td>10</td>
</tr>
<tr>
<td>Permanent amenorrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient &lt;45 years</td>
<td>0-3</td>
<td>3</td>
</tr>
<tr>
<td>Patient &gt;45 years</td>
<td>7-14</td>
<td>15</td>
</tr>
<tr>
<td>Transcervical myoma expulsion</td>
<td>0-3</td>
<td>5</td>
</tr>
<tr>
<td>Non-infectious endometritis</td>
<td>1-2</td>
<td>2</td>
</tr>
<tr>
<td>Endometrial or uterine infection</td>
<td>1-2</td>
<td>2</td>
</tr>
<tr>
<td>Deep venous thrombosis or pulmonary embolus</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Uterine necrosis</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Non-target embolization</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Using modern angiographic equipment with pulsed fluoroscopy and limiting the number of angiographic exposures as well as the use of oblique projections, the radiation dose from UAE can be kept below the threshold for temporary and permanent damage to the ovaries (34, 35).

In the early phase of UAE, almost simultaneously with the Danish group of Andersen et al., the gynecologists and radiologists at Oslo university hospital initiated the introduction of UAE in Norway resulting in paper I of this thesis. The technique of the procedure was adopted from earlier reports, but in accordance with evolving recommendation in the literature (36-39), magnetic resonance imaging (MRI) was chosen as modality for radiological follow-up.
MR imaging allows for volume measurements with high inter-observer reliability (37, 40). Omery showed that pre-operative findings at MRI might change the diagnosis and treatment strategy (39). With regards to radiological outcome after UAE, most early reports were interested in signal changes on MRI and volume reduction of leiomyomas (36, 37). Typically, the mean myoma volume reduction was in the range of 20-40% after 3 months and 40-70% at 12 months follow-up.

Three factors prompted us to investigate if the outcome of UAE could be improved by the use of contrast-enhanced ultrasound (CEUS) during the procedure:

- The problem of ovarian artery-to-uterine artery anastomoses
- The introduction of new particles for UAE
- Finding of incomplete devascularization in paper I

Already in 1999, collateral blood supply to leiomyomas arising from the ovarian arteries was identified as a cause of failure (41). Further case reports followed (42) and in 2002 Razavi et al. offered a classification of ovarian artery-to-uterine artery anastomoses (43) as shown in their illustration (Fig.1).
Fig.1. Classification of ovarian artery-to-uterine artery anastomoses. Illustration from Razavi et al. (43). In A) there is direct anastomosis with blood flow directed from ovaries to uterus, in B) no direct anastomosis between the arteries and in C) direct anastomosis with blood flow directed from uterus to ovaries.

In case A and C, there are direct anastomosis between both arteries, in A the ovarian artery contributes to the blood supply of the uterus, in C the blood flow is directed from the uterus to the ovaries. During UAE, the vascular resistance in the uterus will increase and eventually the blood flow in the anastomosis in A will stop or reverse. By forced injection of contrast in the uterine artery, both types of anastomosis, A and C, are likely to be detected at some point during the procedure. In case B however, there may remain an undetected blood supply to leiomyomas even after complete embolization of both uterine arteries. In 2003, Pelage published risk factors for the presence of collaterals between the ovaries and the uterus (44). Aortograms became part of the routine in many centers or were performed in presence of these risk factors (45). This was in contrast to the efforts of reducing the radiation dose from UAE, which was the concern of
several papers (34, 35). Therefore, eventually MR angiography was recommended for pre-UAE assessment of ovarian artery supply to leiomyomas (46).

After establishing the uterus in non-pregnant sheep as a pertinent model for UAE research, Pelage et al. (47) were able to demonstrate clumping of particles and occlusion of vessels of a wide range of size using PVA particles in an animal model (48) and established data on the size of the vessels relevant for sizing of particles (Fig. 2).

![Diagram of the uterus and leiomyomas with particle sizes](image)

**Fig. 2.** Drawing from Pelage et al. (49) illustrates the size of the uterine and ovarian vessels as well as the arterial plexus surrounding the leiomyomas.

With the introduction of calibrated microspheres as embolic agent for UAE, it became accepted that the procedure should aim at targeted occlusion of the arterial plexus surrounding the leiomyomas while minimalizing embolization of the ovaries and the normal myometrium (48, 50, 51). The angiographic endpoint of embolization was no longer complete cessation of flow, an endpoint that is
relatively easy to achieve and practiced by most investigators using PVA particles, but became more complex: embolization should be stopped when no residual hypervascularization of leiomyomas is visible, stasis is observed in the distal part and reduced flow achieved in the proximal part of the uterine artery (51). In our own, unpublished experience, this endpoint was difficult to achieve and a substantial number of procedures caused only incomplete devascularization of leiomyomas as judged by contrast-enhanced MRI at follow-up. This resulted in unsatisfying clinical results and rapidly decreasing referrals from gynecologists. In the same period of time, other authors recognized incomplete devascularization as an important reason for clinical failure of UAE and early recurrence of symptoms (38, 40).

The knowledge of these pitfalls in performing UAE led to the conception of using contrast-enhanced ultrasound during UAE as a mean to achieve complete devascularization of all fibroids, described in papers II and III.

4.4. High-intensity focused ultrasound

While embolization induces necrosis by ischemia, methods for focal ablation usually cause irreversible cell damage by temperature changes. Percutaneous methods as cryotherapy, radiofrequency and laser ablation have shown promising results in the treatment of symptomatic leiomyomas (52-59). However, these modalities still imply an invasive procedure, pain and the need for a recovery period.
Already in 1942, Lynn et al. considered potential biological applications of focused ultrasound (60, 61). The research in the following 20 years was concentrated mainly in neurosurgery (62-65), but its progress was restricted by technical limitations (66). During the 80's and 90's new devices for extracorporeal and transrectal applications were developed resulting in an increased interest in HIFU ablation of lesions of the liver, the kidneys and the prostate. In 2000, Vaezy et al. demonstrated in an animal model the ability of HIFU to ablate uterine leiomyomas (67). In all these applications, the image guiding was done by ultrasound. The work of a group at Harvard Medical Schools, in collaboration with General Electrics, established the technique of combining HIFU with MRI for guiding and simultaneous thermometry (68, 69). With the Harvard group in a leading role, several papers demonstrated the feasibility and safety of MR-guided HIFU ablation of uterine leiomyomas (70-73). In 2006, Stewart et al. presented mid-term results on 109 women treated with MRgHIFU for symptomatic uterine leiomyomas (74). 71% of the patients reported at least a 10 points improvement in the Symptom Severity Score (SSS) of the Uterine Fibroid Symptoms and Quality of Life questionnaire at 6 months. In their analysis of 359 patients followed for 24 months after MRgHIFU, the same group of authors concluded with a sustained symptom relief. Further, they found that the clinical effect was dependent on the size of the treated volume and recommended that the procedure should aim at a minimum of 20% of leiomyoma volume to be ablated. In a Japanese trial including 69 patients, Funaki et al. were able to reproduce promising clinical results (75). Two trials compared MRgHIFU to other treatment options: in a non-randomized study of Taran et al. (76), both hysterectomy and HIFU showed clinical efficacy, but there were less
complications and faster recovery in the HIFU group. The groups, however, had significant differences at baseline with more severe disease in the hysterectomy group. In 2010, Meng et al. (59) published the results of their comparison between MRgHIFU and radiofrequency ablation. In large leiomyomas they achieved higher ablation rates with radiofrequency than HIFU, in small myomas the results were similar.

All clinical trials mentioned above used the ExAblate system (In-Sightec, Haifa, Israel) in combination with 1.5 Tesla MR scanner from General Electrics Healthcare (Milwaukee, Wisc. USA). In 2009, Sonalleve, a new HIFU system developed by Philips Medical Systems (Vantaa, Finland), became commercially available and was CE marked in December of the same year. The system introduces a volumetric sonication method that produces volume ablations by steering the focal point along an inside-out spiral trajectory. This method was tested in several ex-vivo and in-vivo studies and is supposed to allow for faster ablation of larger volumes (77-80).
Fig.3. Image on the left shows HIFU table top with a round window under which the HIFU unit is mounted. On the picture to the right, a patient is placed in the prone position with the lower abdomen over the HIFU unit and the pelvis surrounded by a semi-flexible wrap-around-coil. (Both images from Philips Healthcare.)

In 2009, the Sonalleve MR-HIFU system was integrated in a 3 Tesla Philips Achieva MR scanner (Philips Medical Systems, Best, Netherlands) at The Intervention Center, Oslo university hospital. Paper IV describes the first experience with MR guided HIFU in Norway, and early results of the Sonalleve system in clinical practice.
5. Aims of the thesis

Uterine artery embolization (UAE) and MR-guided high-intensity, focused ultrasound (HIFU) ablation are minimally invasive treatment options for symptomatic, uterine fibroids. The aim of this thesis was to evaluate and – in a multimodal approach - to further develop these techniques during and after their introduction in Norway.

Specific objectives

1. To evaluate the efficacy of uterine artery embolization and the completeness of devascularization of uterine fibroids as assessed by changes in volumes and contrast-enhancement on MRI, and compared to clinical outcome.

2. To investigate the feasibility of using contrast-enhanced ultrasound during uterine artery embolization as a tool for finding the correct end-point of embolization.

3. To assess the infarction rate of uterine fibroids in patients that had undergone uterine artery embolization (UAE) assisted by contrast-enhanced ultrasound (CEUS).

4. To collect data on the feasibility and safety of the Sonalleve HIFU system (Philips Medical Systems, Vantaa, Finland) system in ablating uterine fibroids in a 3 Tesla magnet.
6. Material

All patients in this thesis were recruited at the Department of Gynecology at Rikshospitalet University Hospital (paper I-III) and in addition at the Department of Gynecology at Ullevål University Hospital (paper IV). After the fusion of all university hospitals in Oslo, both clinics now are parts of Oslo University Hospital, Oslo, Norway.

All patients were referred for treatment of symptomatic leiomyomas. The symptoms typically consisted of bleeding disorders (menorrhagia, menometrorrhagia), urinary symptoms (pollakiuria, urge incontinence) or pressure-related symptoms (pain, dyspareunia, bulging). Usually, there was a combination of symptoms.

The patients in all papers underwent gynecological examinations and contrast-enhanced MRI of the pelvis. Generally, we included women with symptomatic uterine fibroids, seeking uterine sparing treatment options. They all had a premenopausal hormonal state. Exclusion criteria in all studies were ongoing pregnancy, malignancy at cervical cytology, contraindications to MRI, lack of contrast-enhancement in dominant leiomyoma and pedunculated, subserosal fibroids.

Paper I describes 40 consecutive patients treated with UAE between January 1999 and May 2001. These were the first patients to undergo UAE in Norway. All patients had to be more than 30 years old; their mean age was 45 years (range 30-52 years). Only women with no desire of future pregnancy were offered UAE since this was a new, experimental treatment.
With increasing experience and published reports on pregnancies after UAE (81-83), also patients with a desire of future pregnancy and infertility as additional or even only symptom were treated with UAE during paper II and III. Also, the minimum age was lowered from 30 to 18 years.

Paper II prospectively included 10 consecutive patients treated between December 2004 and February 2006 with CEUS assisted UAE, while paper III retrospectively evaluated results from 30 of the following 40 patients who had undergone UAE between February 2006 and August 2009. The patients in paper II were 27 – 51 years of age (mean 38.7 years) similar to the patients in paper III (29 – 52 years, mean 41 years).

Since the treatment in paper IV again was of an experimental character, patients with desire of future pregnancy were excluded. Further, there were stricter inclusion criteria regarding size and position of the leiomyomas, which had to between 3cm and 12cm in diameter, and accessible for the HIFU beam, i.e. the ablation zone could not be deeper than 7cm from the skin level. The 7 patients included in this study were 44.6 years of age (range 39 – 51 years) and treated consecutively between January 2010 and March 2011.
7. Methods

7.1. Uterine artery embolization

Uterine artery embolization is an endovascular procedure, usually performed using standard angiographic equipment. In local anesthesia, the operator gains access to one or both common femoral arteries. Using pre-shaped catheters, the uterine arteries, which arise from the anterior division of the hypogastric artery, are intubated. Microcatheters are commonly used in order to overcome difficult anatomy and to minimize the risk of spasms. The catheter tip should be placed in the horizontal part of the uterine artery, avoiding embolization of cervicovaginal branches. Subtracted angiograms give an overview of the anatomy and help to depict anastomoses to the ovarian arteries. Under intermittent fluoroscopy, particles diluted in a mixture of saline and contrast agent are injected. Different types of particles suitable for UAE are commercially available. While gelatin sponge particles mainly are investigated in Asia (84), many Western centers use polyvinyl-alcohol (PVA) particles with good clinical results (83, 85). However, it has been shown that PVA particles can clump and form aggregates of larger particles giving a more proximal embolization that intended (48). Therefore, today many centers use spherical particles, e.g. tris-acryl gelatin microspheres. The embolization procedure aims at complete devascularization of all leiomyomas, the angiographic endpoint varies depending on the type of particles used. Because of possible redistribution of blood flow, the angiographic endpoint should be controlled 10 minutes after injection of particles. If embolization of the ovarian arteries is indicated, a catheter is placed in the proximal part of the vessel and particles injected from this position. Since the vessels supplying
ovarian tissue usually are smaller than 500 μm, many investigators prefer to use larger particles, e.g. 700-1200 μm, in order to prevent particles from entering the ovarian vasculature.

UAE procedures may cause considerable pain. While some centers perform UAE under epidural anesthesia, most operators control pain by intravenous administration of drugs, e.g. diazepam and ketobemidon. After the procedure, the patient is transferred for some hours to an intensive care unit until an adequate pain regimen is established. Usually patients are discharged from the hospital after 1-3 days and return to their normal activities within 1-3 weeks (86-88).

7.2. Contrast-enhanced ultrasound

The use of contrast media during ultrasound examinations has been an established technique in our department since the late nineties. Mainly used for detection and characterization of focal liver pathology, the use of contrast-enhanced ultrasound (CEUS) during uterine artery embolization was introduced at our institution in December 2004. We used SonoVue (Bracco, Milano, Italy) as contrast agent in all CEUS examinations in paper II and III. It consists of sulfur hexafluoride with a phospholipid shell, is administered intravenously and almost completely eliminated via the pulmonary route within 15 minutes. Since the gas-filled microbubbles act as a blood pool agent and have an immensely increased echogenicity as compared to surrounding tissue, they can be used to enhance
blood echogenicity in the assessment of blood flow in the vasculature. CEUS is capable of demonstrating even a very low degree of perfusion (89-91), but it requires ultrasound equipment with contrast specific imaging modes.

The incidence of side effects from ultrasound contrast agents is very low and allergic reactions are reported in less than 0.001% of cases (92, 93). Serious adverse events during CEUS mainly occurred in patients with severe coronary disease. Further, using low mechanical index and avoiding unduly long examination time, CEUS offers diagnostic information without additional radiation.

All CEUS examinations in this thesis were performed with an Acuson Sequoia 512 system (Siemens, Erlangen, Germany) with a 4C1 curved array probe. The contrast studies were carried out using contrast-specific software (Cadence) with low mechanical index and pulse inversion technique.

7.3. High-intensity focused ultrasound

HIFU ablation of leiomyomas can be performed on an outpatient basis. The procedure requires limited patient preparations and does usually not involve any post-procedural pain. A Foley catheter is mandatory to avoid moving of the uterus during the procedure due to filling of the bladder. A non-steroid anti-inflammatory drug and, if needed, a mild sedative are used as premedication. Additionally, a peripheral venous line is needed for delivery of MR contrast agent.

The process of transmitting energy to the tissue by ultrasound waves is called sonication. HIFU ablation consists of the consecutive heating of multiple, small
treatment cells, i.e. performing multiple sonications. In the Sonalleve system, the ultrasound emitter is a phased array 256-channel transducer, which is integrated in the MR tabletop as shown in Fig.3. In order to move the focus of the ablation, the transducer can to some degree be tilted in all directions by an electromechanical positioning system. The patient has to be placed in the prone position with the lower abdominal wall over the HIFU unit and the leiomyomas within the reach of the focus point, which in the current version of the Sonalleve system is maximum 10 cm from the transducer surface. It is important to avoid any air bubbles in the ultrasound path, therefore all hair between the umbilicus and the level of the symphysis has to be thoroughly removed. MR scans confirm the correct position of the patient and allow for detection of air at the skin level. The ablation is controlled from a separate console steering both the HIFU unit and the MRI scanner. On anatomic scans of the uterus, treatment cells are positioned. Safety margins to the bowel, bony structures the uterine serosa have to be kept and can limit the extent of the treatment. After choosing different ablation parameters, i.e. treatment cell size, energy level and ultrasound frequency, sonication of the different cells is performed. MR thermometry allows for almost real-time visualization of a temperature map in the treatment plan as well as in the near and far field. In case of unintended heating outside the treatment cell, the sonication can be immediately aborted by the operator or the patient. Additionally, integrated safety algorithms can prompt the system to stop sonication, e.g. in case of excessive heating or possible cavitation.

After the procedure, contrast-enhanced MR scans are obtained to show the non-enhancing volume as a result of the ablation. Usually patients are discharged after a few hours of clinical observation.
7.4. Magnetic resonance imaging

The capabilities of magnetic resonance imaging in soft-tissue characterization and differentiation, makes MRI to a valuable tool in imaging of the female pelvis. It allows for multiplanar imaging and can be combined with the application of contrast media for dynamic studies and assessment of tissue enhancement. In all papers of this thesis, contrast-enhanced MR imaging was carried out before the treatment and for follow-up at different time points. Pre-procedural MRI contributes to the verification of the diagnosis, enables characterization with regards to localization, number and contrast-enhancement, as well as volume measurement of leiomyomas. In addition, MRI is an important tool to judge the patient’s feasibility for HIFU therapy.

Follow-up studies in UAE trials are typically scheduled at 3 and 12 months. Examinations are usually performed in 1.5 Tesla scanners and often include sagittal and axial T2-weighted images as well as sagittal, contrast-enhanced fat-suppressed T1-weighted images.

In paper IV, MRI examinations were performed in a 3 Tesla scanner (Philips Achieva; Philips Medical Systems, Best, Netherlands) for screening prior to inclusion, immediately after HIFU ablation and at 30 days follow-up. During screening it is important to assess for bowel loops in the potential HIFU beam path, therefore the patients in our study were placed in a prone position simulating the position during treatment.

In their recommendations for reporting standards for uterine artery embolization trials, Goodwin et al. (94) suggest the following classification of
leiomyomas: pedunculated submucosal, broad-based submucosal or mixed submucosal / intramural, intramural, transmural, subserosal and pedunculated subserosal. In our first study that started before the publication of reporting standards, a more simple classification in submucous, intramural and subserosal leiomyomas was used. Pedunculated, subserosal leiomyomas were excluded from UAE. Early studies showed a greater volume reduction in submucous leiomyomas than in other locations (37, 95), but there are no reports on differences in clinical outcome and all not-pedunculated, symptomatic leiomyomas are generally accepted to be treated by UAE (96). Therefore, we continued to use the same, simplified classification of leiomyomas in paper II-IV.

The number of leiomyomas was given according to the recommendations of Goodwin et al. (94) grouped by single leiomyomas, 2-5 and more than 5 leiomyomas. In paper I, we also reported the number of patients with more than 10 myomas.

Both on pre-procedural and follow-up images, we assessed the volume of the uterus and the largest leiomyomas. In case of several equally large myomas, the one that was believed to contribute most to the patient’s symptoms was measured. For volume calculation of leiomyomas the formula of a prolate ellipse (length x depth x width x 0.523) was used. The uterine volume was measured by manually drawing the uterine area in each axial image with an electronic caliper and multiplying the sum of the areas by the distance between slices. HIFU ablation usually resulted in an irregularly shaped area of non-enhancement within the leiomyoma. The volume of this ablation zone was measured in the same way as the uterine volume.
Burn et al. (36) and Jha et al. (37) reported a poor relationship between the degree of contrast-enhancement of leiomyomas before UAE and subsequent volume reduction. However, there is general agreement that patients with exclusively non-enhancing leiomyomas will not benefit from the procedure. In this thesis, assessment of contrast-enhancement of leiomyomas was based on the presence or absence of enhancement; there were no attempts to quantify perfusion. On follow-up MR exams in paper I-III, we evaluated whether or not there was remnant contrast-enhancement in leiomyomas. In paper II, 4 different types of imaging outcome were established: type 1) describes complete lack of contrast-enhancement in all leiomyomas after UAE, type 2) is defined as remaining contrast-enhancement in parts of an otherwise non-enhancing leiomyoma, type 3) denotes a mosaic pattern with enhancing and non-enhancing leiomyomas, while type 4) describes a rare type of rim enhancement in the periphery of a myoma. In paper III the volume of the non-enhancing part of leiomyomas was independently assessed by two readers and expressed as a fraction of the total leiomyoma burden. The results were grouped in complete infarction (100%), almost complete infarction (90-99%) and incomplete infarction (<90%).

7.5. Clinical evaluation

All women who underwent minimal invasive treatment for symptomatic, uterine leiomyomas during this thesis had an outpatient consultation with a gynecologist at Oslo university hospital prior to treatment. Gynecologic examination including ultrasonography and Papanicolaou smear were done to confirm the diagnosis and
rule out malignancies. The patient’s symptoms were grouped in bleeding disorders (menorrhagia, menometrorrhagia), urinary symptoms (pollakisuria, urge incontinence) or pressure-related symptoms (pain, dyspareunia, bulging). For clinical follow-up, outpatient consultations were scheduled at 3 and 12 months (paper I-III). The clinical response was classified as complete cure, improvement, unchanged or worsened. Further, the gynecologist noted the patient satisfaction and whether she had undergone any additional treatment for leiomyomas. All clinical data were collected by review of the patients’ hospital files.

7.6. **Quality of life assessment**

The Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire was introduced by Spies et al. (97) in 2002 and is a validated tool for assessment of leiomyoma related symptoms. It consists of 37 questions with 5 possible answers to each question, ranging from “not at all” to “a very great deal”. The answers are translated into a score from 1 to 5. The first 8 questions relate to the severity of symptoms and can be used to calculate a transformed symptom severity score (tSSS):

\[
tSSS = \frac{(\text{raw score questions 1-8}) - 8}{32} \times 100
\]

A Norwegian version of the UFS-QOL was used in paper IV. For inclusion in the study the patients should have a tSSS above 40. At 30-days follow-up with MRI,
all patients were again asked to fill in the questionnaire. The UFS-QOL score and the tSSS were calculated for all patients at both time points.

7.7. **Statistical methods**

For comparison of uterine and leiomyoma volumes before and after treatment, we used paired-samples t-tests. Statistical significance of differences between subgroups was evaluated with Chi-square tests. A significance level of 0.05 was used for all tests.

Statistical analysis in paper I was performed using SPSS for Windows (SPSS, Chicago, Ill, USA, version 12.0.1). In papers III and IV we used Prism 5 for MAC OS X (Graph Pad Software Inc, San Diego, California, USA, version 5.0c).
8. Summary of the results

Paper I

40 women with symptomatic uterine leiomyomas underwent bilateral uterine artery embolization. UAE was technically successful in 38 patients. The mean uterine volume was 929 ml before the procedure and decreased in average by 46.2 % at 12 months. Submucosal leiomyomas showed a higher volume reduction (56.1%) than intramural (51.3%) and subserosal (43.9%) leiomyomas. After UAE, MRI showed no enhancement of myomas in 30 patients. In this group the average volume reduction of the uterus was 42.7% at 6 months. In 8 patients post-procedural MRI revealed partially remaining vascularization of leiomyomas despite angiographically complete embolization of the uterine arteries. In these patients the uterine volume decreased in average by 27.7%, significantly less than in the first group (p<0.05). There was significant improvement of symptoms in the majority of patients, but slightly lower in patients with partially remaining vascularization of myomas.

Paper II

In this prospective study of 10 consecutive women undergoing UAE, we successfully performed both the embolization procedure and CEUS during embolization in all patients. In four cases injection of particles was continued based on the findings at CEUS despite angiographically complete embolization. In one patient, final CEUS correctly predicted incomplete devascularization of
leiomyomas. In another patient, a contrast-enhancing outer rim of the leiomyoma was misinterpreted at CEUS. Overall the results of CEUS imaging at completion of UAE correlated well with the findings at MRI.

**Paper III**

30 patients that had undergone uterine artery embolization assisted by CEUS were included in this retrospective study. All UAE and CEUS procedures were technically successful. In 5 cases the endpoint of embolization was adjusted based on findings at CEUS. In 3 patients additional embolic agent was injected in the uterine arteries, in 2 patients also the ovarian arteries were embolized. In one patient, CEUS correctly predicted incomplete devascularization of leiomyomas. The mean volume shrinkage of dominant leiomyomas was 39.8% after 3 months and 59.8% after 12 months. There was complete infarction of all myoma tissue in 97% of patients at 3 months and 96% of patients at 12 months. At 3 months after UAE, complete cure or significant symptom relief was reported in 96%, 88% and 94% of patients suffering of bleeding disorders, urinary dysfunction and pelvic pain respectively. No major complications were observed.

**Paper IV**

7 women with symptomatic uterine fibroids were treated with MR guided HIFU ablation. The procedure was technically feasible in all patients. An average of 19 sonications were performed during each procedure. Mainly, treatment cells sized 8 mm and 12 mm were used. Of a total 130 treatment cells, 86 cells were aborted
either by the user, the patient or the system. However, the maximum temperatures in completed and aborted sonication cells did not differ significantly and was in average just above 68°C. We needed in average 135 minutes for positioning, planning and treatment. The non-perfused volume after treatment ranged from 1 to 27 ml and was unchanged or decreased in all but 1 patient at 30 days follow-up. Two patients reported clinical benefit while 2 patients had a higher symptom severity score at 30 days. There were no major adverse events.
9. General discussion

In this thesis we have shown that UAE was successfully introduced in an early period and we were able to reproduce the good clinical and radiological results published by others. Contrast-enhanced ultrasound was suggested as an additional tool to improve UAE technique without increasing the radiation dose. CEUS proved feasible to be performed during UAE procedures and changed the endpoint of embolization in about one fifth of cases. Patients treated by CEUS-assisted UAE had a high rate of completely infarcted fibroids. The Sonalleve HIFU system was technically feasible in a 3 Tesla setting and we were able to induce areas of non-enhancement consistent with thermal ablation in all patients.

9.1. Methodological considerations

In 2005, Moss published in Cardiovascular and Interventional Radiology an article with the title “Uterine fibroid embolization: more evidence is required” (98). He compared standards required in the development of a new drug to those that commonly are accepted when introducing new procedures or devices in interventional radiology (Table 2). Moss points out the weakness of evidence required before new methods or devices are accepted by the interventional community.
Table 2. Outline in the phases of drug development (10 years) and the development of UAE (2-4 years) (98).

<table>
<thead>
<tr>
<th>Phases in drug development</th>
<th>Phases in development of UAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal studies</td>
<td>Humans</td>
</tr>
<tr>
<td>Phase 1 trials (healthy volunteers)</td>
<td>Small series published</td>
</tr>
<tr>
<td>Phase 2 trials (pharmacokinetic studies)</td>
<td>Procedure rapidly accepted and dramatic increase of numbers</td>
</tr>
<tr>
<td>Phase 3 trials (large clinical RCTs)</td>
<td>Promotion by world wide web</td>
</tr>
<tr>
<td>Medical congress agency</td>
<td>US registry launched</td>
</tr>
<tr>
<td></td>
<td>Death reported (London)</td>
</tr>
<tr>
<td></td>
<td>RCTs launched</td>
</tr>
<tr>
<td></td>
<td>Guidelines published</td>
</tr>
<tr>
<td></td>
<td>Animal work published</td>
</tr>
</tbody>
</table>

RCT=randomized controlled trial

When UAE was introduced in Norway in 1998, only few trials on the safety and efficacy of the procedure had been published. It is debatable whether a randomized controlled trial (RCT) should have been planned or it was appropriate to collect the early Norwegian experience in a single-arm prospective trial. The study design in papers II and IV with a small number of patients is appropriate for collection of safety and feasibility data of new procedures.

In paper III, it would obviously be interesting to have a control group, possibly perform a randomized controlled trial comparing results after UAE with and
without the assistance of CEUS. On the other hand, this would raise the following concerns: in a prospective trial aiming at complete devascularization of all leiomyomas, the well described, but hardly standardized endpoint of embolization opens for a bias towards more aggressive embolization. Secondly, the use of CEUS during UAE has an educational effect and thus the two study groups would have to be treated by different operators or at different institutions, which again could impact on the results.

Besides the study design, the lack of a standardized method to collect clinical data in paper I-III is an obvious restriction. The UFS-QOL questionnaire used in paper IV had not yet been developed, but the use of a validated questionnaire as the SF-36 and objective measures for assessment of specific symptoms would have been advantageous. Evaluating the safety of a new treatment, the 30-days morbidity rates should be investigated. This was done in paper IV, but not systematically in paper I.

Further, in papers I and II there was no second, blinded reader of the MR examinations. However, other publications have shown excellent inter-observer agreement for the calculation of volumes of the uterus, myoma volumes and percentage of perfused leiomyoma (40, 99). CEUS examinations had to be read immediately, as the continuation of the procedure depended on the result. In this setting it was practically not possible to include a second reader.

The study published in paper IV was sponsored by Philips Medical Systems. Even if no personal grants were given to any of the investigators, the possible bias in industry-sponsored trials has to be taken into consideration.
9.2 Uterine artery embolization

In their article “Quality improvement guidelines for uterine artery embolization for symptomatic leiomyomata”, Hovsepian et al. (100) gave an overview on the results of early UAE trials (Table 3).

The results of paper I mirror the international experience: high clinical response especially to menorrhagia and a volume reduction of dominant leiomyomas of more than 50%. One case of an infected, submucosal leiomyoma leading to acute hysterectomy was the most serious complication we encountered in our UAE experience and was reported in paper I. Pelvic infection must be expected in 1-2% of cases and may, if untreated, result in lethal sepsis (101).

Overall, the complication rate in UAE in papers I-III was low and within the thresholds suggested by the Cardiovascular and Interventional Radiology Society of Europe (100). However, as described in the last chapter, due to study design our complication rate may have been underestimated.
Table 3: Over view over the results of early UAE trials (91).

<table>
<thead>
<tr>
<th>Ref</th>
<th># of pts.</th>
<th>Duration of follow-up</th>
<th>Menorrhagia improved</th>
<th>Pressure/pain improved</th>
<th>Mean fibroid volume reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchins et al 1999 (26)</td>
<td>305</td>
<td>12 months</td>
<td>92 %</td>
<td>92 %</td>
<td>48 %</td>
</tr>
<tr>
<td>Goodwin et al 1999 (102)</td>
<td>60</td>
<td>16 months</td>
<td>90 %</td>
<td>93 %</td>
<td>49 %</td>
</tr>
<tr>
<td>Ravina et al 1999 (103)</td>
<td>184</td>
<td>29 months</td>
<td>90 %</td>
<td></td>
<td>50-100%</td>
</tr>
<tr>
<td>Siskin et al 2000 (29)</td>
<td>49</td>
<td>6 months</td>
<td>88.5 %</td>
<td></td>
<td>47.5 %</td>
</tr>
<tr>
<td>Pelage et al 2000 (30)</td>
<td>80</td>
<td>6 months</td>
<td>94 %</td>
<td></td>
<td>52 %</td>
</tr>
<tr>
<td>Brunereau et al 2000 (104)</td>
<td>58</td>
<td>12 months</td>
<td>93 %</td>
<td></td>
<td>51 %</td>
</tr>
<tr>
<td>McLucas et al 2001 (105)</td>
<td>167</td>
<td>6 months</td>
<td>82 %</td>
<td></td>
<td>52 %</td>
</tr>
<tr>
<td>Andersen et al 2001 (31)</td>
<td>62</td>
<td>6 months</td>
<td>96 %</td>
<td>70 %</td>
<td>68 %</td>
</tr>
<tr>
<td>Spies et al 2001 (106)</td>
<td>200</td>
<td>21 months</td>
<td>90 %</td>
<td>91 %</td>
<td>60 %</td>
</tr>
<tr>
<td>Katsumori et al 2002 (84)</td>
<td>60</td>
<td>12 months</td>
<td>100 %</td>
<td>100 %</td>
<td>70 %</td>
</tr>
<tr>
<td>Walker &amp; Pelage 2002 (83)</td>
<td>400</td>
<td>17 months</td>
<td>84 %</td>
<td>79 %</td>
<td>64 %</td>
</tr>
<tr>
<td>Pron et al 2003 (107)</td>
<td>538</td>
<td>3 months</td>
<td>83 %</td>
<td>77 %</td>
<td>42 %</td>
</tr>
<tr>
<td>Paper I</td>
<td>40</td>
<td>12 months</td>
<td>100 %</td>
<td>89 %</td>
<td>55 %</td>
</tr>
</tbody>
</table>
In the aforementioned article by Moss, the author asks why almost every publication quotes uterine volume and how it reduces following embolization. He answers: “Because radiologists can measure it easily, so we do it. But does it correlate with symptoms, and does it indicate the fibroid is dead and no longer growing? No, it does not.” He cites the study by Pelage on long-term outcome after UAE (40), showing that incomplete leiomyoma infarction occurs in up to one third of patients with continued growth of the viable part of the myoma. This is in line with the results in paper I where we found contrast-enhancement on MRI in parts of the leiomyomas in 27% of patients. There was also a tendency towards poorer clinical outcome in this subgroup of patients, a finding that later has been confirmed in other publications (108-111). Therefore the technical goal of UAE has to be complete devascularization of all leiomyomas. The introduction of new embolic agents showed the difficulty of reaching this goal. Different angiographic endpoints had to be defined for different types of embolic agent in order to secure acceptable results (112-114). Still, there remains the possibility of residual blood supply to leiomyomas through ovarian collaterals. Paper II and III show that CEUS can be performed during UAE and very high rates of completely infarcted leiomyomas can be achieved. Unfortunately, the infarction rate is not part of the reporting standards for UAE trials (94), which makes a comparison of the infarction rates difficult. However, the studies actually reporting leiomyoma infarction rates use the same or a similar grading of infarction rates as we did in paper III. In these studies complete devascularization of all leiomyomas is typically reported in about 80% of patients as compared to 97% in our material. Interestingly, the difference is in
the range of the number of patients in whom the endpoint of the procedure was adjusted (18% in paper II and III) based on the finding at CEUS. In all of them, additional particles were injected in the uterine arteries; in 2 patients also the ovarian arteries were embolized. The potential advantage of this proceeding has to be weighted against the risk of complications.

In the literature, there have been reports of uterine necrosis following UAE (115-117). The question has been raised whether infection of a necrotic leiomyoma was the true reason of hysterectomy it the first report by Godfrey et al. (115), but the authors rejected this suggestion (118). In 2010, Scheurig-Muenckler et al. showed that uterine ischemia is common after UAE, but usually resolves completely in all patients (119). Another complication of too aggressive embolization might be non-target embolization of other organs, especially the ovaries. Transient amenorrhea as a consequence of UAE has been desribes up to 14% of cases and may be caused by non-target embolization. Permanent amenorrhea, however, is rare and seems to be age-related (120, 121). Two small series on ovarian artery embolization as a supplement to UAE (122, 123), have shown excellent clinical response and did not indicate an increased risk of ovarian failure.

In summary, during the introduction of UAE in Norway, we were able to reproduce good mid-term results with a low risk profile. Based on the common finding of incomplete infarction of leiomyomas after UAE, the use of CEUS is suggested as a valuable tool in order to improve the radiological outcome.
9.3. **MR-guided high-intensity focused ultrasound of leiomyomas**

The introduction of MR-guided HIFU ablation of uterine leiomyomas in paper IV is special. In addition to describing the introduction of this technique in clinical use in Scandinavia, it also reports one of the earliest clinical experiences with a new HIFU system and the unusual combination of HIFU and a 3 Tesla scanner.

We were able to perform sonications and induce areas of non-enhancement on follow-up MRI in all patients. The only complication in our series was a minor skin burn that was probably caused by insufficient hair removal and resolved spontaneously. This is in accordance with the low complications rates reported in the literature (59, 124, 125). Minor skin burns are encountered in 5-7% of patients (74, 124) and usually do not require any treatment, but there has been a report on a full thickness skin burn from HIFU treatment (126).

It is common that the patients experience some pain during the procedure. This is usually related to heating of the skin or bony structures in the ultrasound path, or caused by the rather uncomfortable position that the patients have to keep during the procedure. The latter problem might be overcome in future generations of devices with a more ergonomic design of the tabletop. Further, it will be necessary to decrease the time used for the procedure. This was one of the anticipated advantages of the Sonalleve system. We were not able to achieve significantly shorter treatment times than previously reported in the literature, but considering the small sample size and the obvious need for a learning period, no conclusions can be drawn so far. The same applies for the disappointingly small size of the non-enhancing volume at follow-up MRI. Stewart et al. recommend that the ablated volume should be at least 20% of the leiomyoma
In their report on 359 patients, this was achieved in only 43% of them. In a recent publication, LeBlang et al. (128) report in 80 patients a substantially higher rate of non-perfused volume using protocols that allow greater ablation volumes than in earlier studies that were restricted by limitations given by the FDA. LeBlang et al. found in 147 leiomyomas an average non-perfused volume of 55% of the myoma volume after HIFU treatment. However, of a total of 204 leiomyomas in the 80 women, 57 could not be treated. If the non-perfused volume would be reported similarly to the infarction rate in UAE trials, it would certainly be less than 50% and closer to the results from Stewart et al. (127) who report the NPV as a fraction of the total leiomyoma burden. This latter report is the only publication showing midterm results at 24 months. They conclude with sustained relief if the NPV is over 20% of total leiomyoma volume. This interpretation of the data however has been questioned (129), and a potential bias of the authors who have made a major contribution to the development of both the specific device and the technique, has to be ruled out by further studies in different centers. Also our study has been sponsored by the industry, but none of the investigators has received any grants or has any commercial interest in the Sonalleve system.

Having in mind the increased risk of recurrence of leiomyoma related symptoms in women with incomplete infarction rates after UAE, it seems reasonable to assume a substantial recurrence rate in women undergoing MRgHIFU ablation. However, the advantages of short recovery time and low complication rates may possibly justify the need for further or repeated therapy.
10. Conclusions and future prospects

Conclusions

Uterine artery embolization is a safe and feasible method for the treatment of symptomatic uterine leiomyomas. The procedure can be performed with very high technical success rates while serious adverse events are rare. The vast majority of patients and especially those with bleeding disorders can expect to experience symptom relief or complete cure.

Using PVA particles for UAE, about one out of 4 procedures will result in partial infarction of the total fibroid burden. This seems to impact on the clinical outcome and may lead to the need of further treatment in the long term.

Contrast-enhanced ultrasound can be performed during UAE procedures. The results of CEUS can play a role in finding the correct endpoint of embolization.

High infarction rates were achieved after the introduction of CEUS during UAE procedures.

The Sonalleve MR-HIFU system can induce areas of non-enhancement in leiomyomas, consistent with thermal ablation. No serious adverse events occurred in our 7 patients.

Future prospects

In the future the treatment of uterine fibroids by hysterectomy may be replaced by more minimal invasive approaches.

UAE is to be considered as an excellent treatment option of leiomyomas. This status will be challenged by the continued development of less invasive, surgical methods. In order to increase acceptance of UAE among gynecologists and the knowledge among patients, there will be a continued need for comparative trials.

Future studies should clarify the potential role of CEUS during UAE procedures. These studies should aim at comparing infarction rates achieved with and without the routine use CEUS during UAE and assess the potential, clinical
benefit of CEUS. The possibility of reducing the radiation dose from UAE by using 
CEUS instead of angiography for endpoint assessment also deserves further 
investigations. Further, CEUS should be considered as adjunctive tool in the 
assessment of new embolic agents for UAE. A potential benefit of CEUS can also 
be evaluated for other embolization procedures, e.g. liver embolization.

The clinical long-term efficacy of MR-guided HIFU ablation of leiomyomas has 
still to be proven and compared to other treatment options. This could also aid in 
the establishment of guidelines for which patients are the optimal candidates for 
HIFU. Even if recurrence rates may prove to be high and sustained symptom 
control may require repeated procedures, the non-invasiveness of HIFU with no 
post-procedural pain and almost immediate return to work, may make it to the 
treatment option preferred by the patients.

Among all available treatment options, HIFU is the only one that doesn’t interfere 
with the myometrium. Therefore HIFU may gain importance in the treatment of 
women with a desire of future pregnancy

Regarding the Sonalleve system, larger trials should be conducted in order to 
differentiate between limitations given by user inexperience and those of the 
system. Technical improvements are likely to improve the accuracy in the 
prediction of the estimated treatment volume, contribute to shorten the 
treatment time and increase the number of feasible patients.
11. **References**


Improved infarction rates in fibroids after the introduction of contrast-enhanced ultrasound during uterine artery embolization

Abstract

Background: In order to achieve sustained symptom control and minimize the risk of recurrence, uterine artery embolization (UAE) should aim at complete infarction of all fibroids.

Purpose: To retrospectively evaluate the infarction rate of uterine fibroids in patients that had undergone uterine artery embolization (UAE) after the introduction of contrast-enhanced ultrasound (CEUS) during UAE procedures at our institution.

Material and Methods: 30 patients treated with UAE between February 2006 and August 2009 were included. MR images obtained before, at 3 months and 12 months after the procedure were reviewed. We evaluated volume changes in dominant fibroids as well as the infarction rate of all fibroids in each patient. Clinical results were evaluated by reviewing the medical records. The study was approved by the institutional review board.

Results: CEUS was technically successfully performed during the UAE procedure in all patients. In 5 cases the endpoint of embolization was adjusted based on findings at CEUS. The mean volume shrinkage of dominant fibroids was 39.8% after 3 months and 59.8% after 12 months. There was complete infarction of all fibroid tissue in 97% of patients at 3 months and 96% at 12 months. No major complications were observed.

Conclusion: After the introduction of CEUS during UAE procedures in our institution, high infarction rates were achieved.

Key Words: Leiomyoma, Fibroids, Uterine artery embolization, contrast-enhanced ultrasound
The clinical efficacy of uterine artery embolization (UAE) for the treatment of symptomatic uterine fibroids has been shown in numerous trials through the past decade (1-3). The infarction of fibroids results in immediate softening and eventually shrinkage, contributing to the intended symptom relief. The technical goal of the procedure is to induce complete infarction of all fibroid tissue. Incomplete infarction of fibroids is associated with less favorable clinical outcome in the short term (4,5). Further, it is known that incomplete infarction may result in re-growth of the fibroids with recurrence of symptoms, typically after 3 to 5 years (4).

Regardless its clinical importance, the degree of fibroid infarction achieved during UAE is not part of the reporting standards for UAE procedures. It has, however, been reported in several trials, and especially in those dealing with new particles and endpoints used for UAE (6-8). A series of 40 UAE patients (9) showed that in 38 patients who were embolized with polyvinyl alcohol (PVA) particles until complete cessation of flow in the uterine arteries, only 75% had complete infarction of all dominant fibroids at MRI follow-up at 3 months. When introducing tris-acryl gelatin microspheres (TGM) with an altered endpoint of embolization, defined as the “pruned-tree appearance” which indicates embolization of the perifibroid plexus, we experienced increased numbers of patients with remnant vascularization of fibroids. According to our own, unpublished data, in about half of the 33 patients of this early experience with spherical particles, less than 90% of their total fibroid burden was infarcted. Therefore in 2004, we introduced the use of contrast-enhanced ultrasound (CEUS) during the UAE procedure, in order to secure complete devascularization of all fibroid tissue. After an initial report on the first 10 patients in 2006 (10), CEUS has whenever available been used during UAE procedures at our institution.

The purpose of this study was to retrospectively evaluate the post-UAE infarction rate of fibroids after the introduction of CEUS during UAE procedures at our institution.

**Material and Methods**

This retrospective study was approved by the institutional review board, written informed consent was not required.
We retrospectively identified 40 consecutive patients who between February 2006 and August 2009 had undergone UAE for symptomatic fibroids at our institution. In 30 patients CEUS was performed during the procedure, in 10 patients the ultrasound equipment was not available. The mean age of the patients was 41 years (range 29 to 52 years). All patients had been scheduled for contrast-enhanced MRI before and after UAE at 3 and 12 months. Routinely, MR examinations were performed using a 1.5T unit (Magnetom Vision Plus, Siemens, Erlangen, Germany) and included sagittal and axial T2-weighted turbo spin-echo (TSE) images as well as sagittal contrast-enhanced fat-suppressed T1-weighted images. As intravenous contrast agent 0.1 mmol/kg body weight of gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma AG, Berlin, Germany) was used. All available MRI studies were identified and findings classified according to the reporting standards for UAE trials. We assessed on the pre-UAE MRI the number of fibroids, as well as the location and volume of the dominant fibroid. The location was classified as submucosal, intramural, or subserosal. For calculation of volumes the formula for a prolate ellipsoid (length x width x height x 0.523) was used. If more than one dominant fibroid was present, we evaluated the largest one, or the fibroid that was believed to contribute most to the patient’s symptoms.

On follow-up MR examinations, volume measurements were repeated for the same fibroid as pre-UAE. Infarction of fibroids was defined as absence of contrast-enhancement on T1-weighted MR images on follow-up as compared to baseline imaging. Infarction rate was defined as fraction of infarcted fibroid in percent of fibroid volume. The rate of infarction was independently evaluated visually by two readers and assigned to 3 groups: group A) complete lack of contrast enhancement in all fibroid tissue (100% infarction rate), group B) infarction rate of 90-99%, meaning less than 10% of fibroid tissue showing contrast-enhancement and group C) defined as more than 10% of fibroid tissue showing evidence of contrast-enhancement (less than 90% infarction rate). Fibroids smaller than 10mm were noted, but excluded from the analysis of infarction rate. In case of disagreement between the two readers, the decision was based on consensus.

All UAE procedures were performed by the same interventional radiologist (ED), using bilateral approach with microcatheters and tris-acryl glycerin particles sized between 500 and 900 microns. The endpoint of embolization, evaluated angiographically 10 minutes after injection of particles, was sluggish forward flow in the ascending part of the uterine artery.
with visible opacification during 5 to 10 heart beats after injection of 2 ml of contrast media. If the intended endpoint was reached, contrast-enhanced ultrasound was carried out.

Ultrasound images were recorded using an Acuson Sequoia 512 system (Siemens, Erlangen, Germany) with contrast-specific software (low-mechanical index and pulse inversion technique). All ultrasound examinations were performed by transabdominal scanning. The sterile cover was lifted to give access to the lower abdominal region while keeping the puncture sites sterile and 2.4 ml of contrast agent (SonoVue, Bracco, Milan, Italy) were injected in a cubital vein followed by 10 ml of saline. The whole uterus was scanned during the arterial phase while storing multiple 10 s video clips. By visual assessment, findings were categorized in presence or absence of any residual, arterial enhancement. If CEUS showed complete lack of contrast-enhancement in fibroids, the procedure was ended. In case of remnant contrast-enhancement, embolization was continued until near stasis of flow in the uterine arteries. If CEUS then still gave evidence of remnant arterial enhancement of fibroids, an aortography was obtained to depict collaterals from the ovarian arteries. If these were accessible for selective catherization, a microcatheter was placed proximally in the vessel and particles injected slowly until cessation of flow in the distal part of the vessel supplying the uterus. If further embolization was technically impossible despite remnant contrast-enhancement at CEUS, the procedure was ended. We noted the results of the last CEUS in each patient and the number of procedures where CEUS altered the end-point of embolization. Prior to UAE, the operator informed all patients about the potential course of the procedure and obtained the patients’ consent for the use of CEUS and – if indicated – ovarian embolization.

Clinical data were evaluated by reviewing the patients’ medical records. For each patient we assessed former invasive therapies for symptomatic fibroids, symptoms at time of UAE, and clinical effect at 3 and 12 months follow-up, graded as complete disappearance of symptoms, improvement, unchanged or worsening.

For statistical analysis of changes in fibroid volume paired t-tests were performed using Prism 5 for MAC OS X (Graph Pad Software, Inc., San Diego, CA, USA, version 5.0c). Significance was defined as p less than 0.05.
Results

The baseline characteristics of the study population are shown in Table 1. Pre-UAE MRI was available for all patients. The vast majority of patients had less than 5 fibroids, with dominant tumor mainly in a submucosal or intramural location.

All UAE and CEUS procedures were technically successful. In 5 patients (17%), the endpoint of embolization was adjusted based on finding at CEUS. Embolization was continued through uterine arteries in all 5 of them, in two patients, we performed additional embolization of the ovarian arteries. In 27 patients the final CEUS examination showed complete devascularization of all fibroid tissue (Fig. 1). In 2 patients, CEUS suggested slight, late enhancement in the periphery of a dominant fibroid. In both patients, angiography showed near complete stasis of flow in the uterine arteries and at aortography only small ovarian arteries without evidence of collateral supply to the fibroids were identified (Fig. 2). In one patient, CEUS revealed significant contrast-enhancement in large parts of her fibroids despite complete embolization of both uterine and ovarian arteries. The procedure was ended at that point.

Contrast-enhanced MRI examinations were available for 29 patients at 3 months follow-up after UAE and 26 patients at 12 months. One patient was satisfied with the clinical result and did not want to undergo further MRI examinations, 3 patients were lost to radiological follow-up.

At baseline, the median volume of the dominant fibroid was 120 cm$^3$ with an interquartile range from 66 to 238 cm$^3$. The median volume (interquartile range) of the dominant fibroid was 75 cm$^3$ (41-160) and 41 cm$^3$ (19-143) at 3 and 12 months respectively. The mean volume shrinkage of dominant fibroids was 39.8% after 3 months and 59.8% after 12 months (p<0.001, Table 2).

We observed complete infarction of all fibroid tissue in 28 of 29 patients (96.6%) after 3 months and 25 of 26 patients (96.2%) after 12 months (Table 2). This included the two cases where CEUS suggested slight, late enhancement in the periphery of a dominant fibroid. None of the patients that had complete infarction after 3 months showed evidence of revascularization after 12 months.
The patient with remnant contrast-enhancement at CEUS despite uterine and ovarian embolization, had infarction of less than 90% of fibroid tissue at both 3 and 12 months.

Typically, patients presented with a combination of symptoms with heavy menstrual or intermenstrual bleeding as main complaint. 5 women had earlier undergone myomectomy. Clinical follow-up data are available for 26 patients at 3 months and 23 patients at 12 months. Three months after UAE, complete cure or significant relief of symptoms was reported in 96%, 88% and 94% of patients for bleeding, urinary dysfunction and pelvic pain respectively. These results were sustained at 12 months follow-up (Table 2). Two women underwent UAE as last option for treatment of infertility, one of them gave birth to a healthy child within one year after embolization.

Discussion

In the current study we observed complete devascularization of all fibroids on MRI examination at 3 months follow-up in 97% of all patients. This includes 4 patients were the endpoint of embolization was adjusted because CEUS gave suspicion of remnant vascularization despite the fact that the angiographically intended endpoint had been achieved.

While most publications report 100% infarction rates in less than 80% of patients (4-8,11-14), we were able to achieve complete infarction in almost all patients at three months (Table 3). Some of the cited publications show the results of high volume centers using well-established embolic agents. Since our center only has a low number of UAE patients, performing in average one UAE procedure per month, we assume that the use of CEUS contributed to the good imaging results.

At 12 months follow-up none of the patients that had shown complete infarction of all fibroids at 3 months had evidence of revascularization of fibroids. This is in accordance with earlier published results in the literature (4,5) and emphasizes the value of early imaging follow-up
after UAE procedures. In one patient CEUS correctly predicted incomplete devascularization of fibroids after embolization of both uterine and ovarian arteries without possibility of further injection of particles. In such situations, the patient might seek alternative treatment options at an earlier stage than if she had to wait for several months until referred to follow up MRI.

In 2 patients CEUS gave suspicion of slight, late enhancement in the periphery of a dominant fibroid. Both these fibroids showed complete lack of contrast enhancement at MRI after 3 months. A similar finding at early MRI of slight rim enhancement that disappears after 3 months has also been described by other authors (11) and is believed to represent edema and dilated lymphatic vessels (15,16). This finding can be difficult to separate from true peripheral fibroid enhancement (10). The importance of this early slight enhancement needs to be further investigated.

During the study period, 10 patients underwent UAE without CEUS assistance. In our experience, CEUS had an educational effect on judging the endpoint of UAE on angiography and thereby had an influence also on those procedures where the advanced ultrasound equipment needed for CEUS was not available. Therefore we think it is not appropriate to compare this subgroup of patients to the CEUS group and chose to exclude them from this analysis.

CEUS examination during UAE can be performed fast and is technically easy. Due to the enlargement of the uterus, the access for transabdominal ultrasound is usually excellent. The preparation of the ultrasound equipment, the patient and the ultrasound contrast agent can be done during the 10 minutes waiting period that should be kept between the injection of particles and the angiographic control. After a short pre-contrast examination of the uterus, remnant enhancement of fibroids can be seen within 1-2 minutes after administration of contrast agent. Thus, CEUS usually adds only few minutes to UAE procedures. The benefit of CEUS during UAE procedures has to be weighted against this increased costs and procedure time. Even if others might not embrace our model of routinely using CEUS during UAE procedures, CEUS still can be a useful tool for difficult cases, during the learning of UAE or during the evaluation of new embolic agents.
Our study has several limitations. The possible benefit of complete infarction has to be weighted against the risk of an increased complication rate. Too aggressive embolization might lead to unintended infarction of myometrium or ovaries and especially cause increased pain (17). In our retrospective study, there was no standardized collection of data regarding complications and clinical outcome; neither did we have a control group. Even if our results did not indicate an increased complication rate, a more thorough evaluation of this issue is needed. The number of patients in our study was low and even if we achieved high infarction rates, the design of this retrospective evaluation allows no conclusion regarding the effect of CEUS on infarction rates.

In conclusion, in our retrospective evaluation of 30 patients that had undergone CEUS during UAE, we found that CEUS changed the endpoint of embolization in 17% of patients. After 3 months, 97% of patients showed complete infarction of all fibroids on follow-up MRI. Further studies should be conducted to assess the influence of CEUS on infarction rates and verify a clinical benefit.
Table 1

Baseline characteristics of the study population. Values are in numbers and median with percentage (%) or range in parentheses.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients age in years (range)</td>
<td>41 (29-51)</td>
</tr>
<tr>
<td>Presented symptoms</td>
<td></td>
</tr>
<tr>
<td>heavy menstrual or intermenstrual bleeding</td>
<td>27 (90%)</td>
</tr>
<tr>
<td>pelvic pain</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>urinary frequency</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Median (interquartile range) volume of dominant fibroid before UAE (cm³)</td>
<td>120 (66-238)</td>
</tr>
<tr>
<td>No. of fibroids</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>14 (47%)</td>
</tr>
<tr>
<td>2-4</td>
<td>14 (47%)</td>
</tr>
<tr>
<td>≥5</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Location of dominant fibroid</td>
<td></td>
</tr>
<tr>
<td>Submucosal</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Intramural</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Transmural</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Subserosal</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

Table 2

Main results at 3 and 12 months follow-up

<table>
<thead>
<tr>
<th></th>
<th>3 months after UAE</th>
<th>12 months after UAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>volume reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dominant fibroid</td>
<td>39.8% *</td>
<td>59.8% *</td>
</tr>
<tr>
<td>complete infarction at MRI</td>
<td>28 of 29 patients</td>
<td>25 of 26 patients</td>
</tr>
<tr>
<td></td>
<td>(96.6%)</td>
<td>(96.2%)</td>
</tr>
<tr>
<td>complete cure or relief from symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>96 %</td>
<td>95 %</td>
</tr>
<tr>
<td>urinary dysfunction</td>
<td>88 %</td>
<td>86 %</td>
</tr>
<tr>
<td>pelvic pain</td>
<td>94 %</td>
<td>86 %</td>
</tr>
</tbody>
</table>

* p<0.001
Table 3

Infarction rate of fibroids in recently published trials

<table>
<thead>
<tr>
<th>Study and year</th>
<th>Ref.</th>
<th>Infarction rate</th>
<th>Embolic agent</th>
<th>MR follow-up</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelage et al, 2004</td>
<td>(4)</td>
<td>71% 29% *</td>
<td>PVA</td>
<td>3 months</td>
<td>Dominant fibroids evaluated</td>
</tr>
<tr>
<td>Spies et al, 2005</td>
<td>(6)</td>
<td>73% ** 29% **</td>
<td>TAGM  SPVA</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Katsumori et al, 2007</td>
<td>(11)</td>
<td>64% 33% 2%</td>
<td>Gelatin sponge</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>Siskin et al, 2008</td>
<td>(12)</td>
<td>67% 4% 29%</td>
<td>SPVA</td>
<td>1 month</td>
<td></td>
</tr>
<tr>
<td>Galvez et al, 2008</td>
<td>(13)</td>
<td>59% 41% *</td>
<td>PVA</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>Kroencke et al, 2008</td>
<td>(7)</td>
<td>25% 50% 25%</td>
<td>a-PAVM</td>
<td>3 months</td>
<td>limited embolization aggressive embolization</td>
</tr>
<tr>
<td>Kroencke et al, 2010</td>
<td>(5)</td>
<td>63% 27% 9%</td>
<td>a-PAVM</td>
<td>24-72 hours</td>
<td></td>
</tr>
<tr>
<td>Worthington-Kirsch et al, 2010</td>
<td>(8)</td>
<td>52% 28% 20%</td>
<td>TAGM, SPVA, a-PAVM</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Smeets et al, 2010</td>
<td>(14)</td>
<td>60% 31% 8%</td>
<td>PFcHM</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Current paper</td>
<td></td>
<td>97% 3% 0%</td>
<td>TAGM</td>
<td>3 months</td>
<td></td>
</tr>
</tbody>
</table>

Note: PVA- polyvinyl alcohol particles; TAGM – tris-acryl gelatin microspheres; SPVA – spherical polyvinyl alcohol particles; a-PVAM – acrylamido polyvinyl alcohol microspheres; PFcHM – polyzene F-coated hydrogel microspheres

* only numbers for groups B and C together available
** only numbers for groups A and B together available
Fig. 1 A: Ultrasound images obtained at the end of UAE procedure. On contrast-enhanced ultrasound (right) the fibroid is sharply delineated and shows no evidence of contrast-enhancement. Note high-echogenic spots representing gas artifacts on both images. B: Contrast-enhanced, sagittal MR image confirms complete infarction of fibroid at 3 months follow-up.
Fig. 2 A: On B-mode image (left) the embolized fibroid (arrows) has increased echogenicity with some high-echogenic spots and is surrounded by low echogenic myometrium. On contrast-enhanced ultrasound (right) the fibroid shows no evidence of contrast enhancement centrally, but there are no sharp margins. Contrast-enhancement in the periphery (arrows) is suspected. Note arterial enhancement of myometrium. B: At 3 months follow-up (B) contrast-enhanced MRI shows complete infarction of the fibroid.
References


High-intensity focused ultrasound ablation of uterine fibroids using the Sonalleve system in a 3 Tesla scanner – first clinical assessment

Abstract

Introduction

The purpose of this study was to evaluate the feasibility and safety of the Sonalleve high-intensity focused ultrasound (HIFU; Philips Healthcare, Vantaa, Finland) system in ablating uterine fibroids in a 3 Tesla magnet.

Material and methods

Seven women with symptomatic uterine fibroids were included in this study. HIFU treatment was performed according to the manufacturer’s recommendation; the procedure duration was limited to 3 hours and the upper limit for ablation volume was 50% of fibroid volume. Technical data describing the HIFU procedures were collected. On MR images at baseline, immediately after ablation and on 30 days follow-up, we evaluated the size of the uterus and dominant fibroid, as well as the volume of the ablation zone. To assess potential short-term clinical response, all patients were asked to complete the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire before and 30 days after treatment. All peri- and postprocedural adverse events were recorded.

Results

The procedure was technically feasible in all patients. The median number of sonications performed during each procedure was 20 (range 2–27), the maximum temperatures in both completed and aborted sonication cells was about 68°C. The median time needed for the procedure was 156 minutes (range 95-164). The non-perfused volume after treatment ranged from 1 to 27 ml and was unchanged or decreased in all but 1 patient at 30 days follow-up. There were no major adverse events.

Conclusion

The Sonalleve system is safe and feasible for MR-guided HIFU ablation of uterine fibroids in a 3 Tesla magnet.
Introduction

Several minimally invasive treatment options for uterine fibroids have emerged during the last years. While uterine fibroid embolization and percutaneous thermal ablation methods such as cryotherapy or radiofrequency ablation still involve an invasive procedure and may cause substantial pain during and after the procedure, ablation by high-intensity focused ultrasound (HIFU) offers a virtually painless and truly non-invasive treatment. Several trials have reported promising short- and mid-term results and serious adverse events seem to be rare (1-3). The vast majority of trials dealing with MR-guided HIFU (MRgHIFU) of uterine fibroids used the ExAblate HIFU system (ExAblate 2000, InSightec, Haifa, Israel). Philips Healthcare (Vantaa, Finland) has the recent years developed the Sonalleve HIFU system, which was CE marked in December 2009. At our institution, the Sonalleve MR-HIFU system was integrated in a 3 Tesla Philips Achieva MR scanner (Philips Healthcare, Best, The Netherlands). The purpose of this trial was to do the first clinical evaluation of the safety and technical efficacy of the Sonalleve – HIFU system in a 3 Tesla MR.

Material and Methods

This study was approved by the regional ethics committee.

All patients were recruited among women referred to the department of gynecology at our hospital for treatment of symptomatic uterine fibroids. Patients who sought minimally invasive treatment options and who, based on gynecologic ultrasound examination, seemed suitable for MRgHIFU-treatment were asked to complete the first eight questions of the standardized Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire (4). If the transformed symptom severity score (tSSS) was over 40, they were referred to screening MRI at the Intervention Center. Screening examinations were performed with patients in the prone position in the same 3T MR that was used for HIFU treatment. Imaging included axial and sagittal T1 and T2 weighted images, including contrast-enhanced T1-weighted sequences of the pelvis. As intravenous contrast agent 10-
15ml of gadoteric acid 279.32 mg/mL (Dotarem, Guerbet, Roissy, France) was used. For inclusion in this trial, the patient had to be at least 18 years of age, with a weight below 140kg, and a premenopausal hormonal state. Only contrast-enhancing fibroids, larger than 3cm and smaller than 12cm, and uterus under 24 weeks in gestational size and without heavy calcifications could be considered for treatment. Exclusion criteria were desire for future pregnancy, significant systemic disease, suspicion of malignancy at cervical cell assessment, other pelvic disease as endometriosis or ovarian tumor, hematocrit below 25%, extensive scarring along the lower, anterior abdominal wall and positive pregnancy test on treatment day.

**HIFU therapy system**

The Intervention Center at our hospital is a research unit dedicated to the development of new technology and minimal invasive therapies. Since 2008 the Intervention Center has used a Philips Achieva 3 Tesla MR (Philips Healthcare, Best, The Netherlands) in which, in 2009, the Sonalleve HIFU system was integrated. The system consists of a HIFU therapy console, used for planning and treatment as well as post-treatment operations; further a generator cabinet and a patient tabletop unit which houses the electromechanical transducer positioning system, the phased array 256 channel ultrasound transducer and integrated radiofrequency coils. On our system, the deepest available HIFU focus location was 10 cm from the surface of the transducer, without the use of electronic deflection. Philips uses volumetric techniques that allow heating of treatment cells of 4, 8, 12 or 16mm in diameter (5, 6). For each treatment cell, the user can select the ultrasound frequency (1.2 or 1.4 MHz) and the power with an upper limit of 200W. Ablation can be done using treatment cells or feedback cells. In treatment cell mode the system delivers a certain power during a pre-calculated duration in order to achieve the calculated sufficient thermal dose of 240 EM. In feedback cell mode, the system adjusts the heating duration until the calculated thermal dose has been delivered. In both modes, temperature higher than 85°C measured in the planned treatment region will stop the sonication. Feedback sonication mode is supposed a safer method in order to prevent overheating. The system displays two-dimensional temperature data overlaid on anatomical images.
temperature map has a temporal resolution of 4 seconds acquiring 3 images at the focus point in the coronal plane, one in the sagittal plane and one image of the near field and far field each. For each cell the estimated treatment volume is calculated assuming an ellipsoid shape. The diameter is derived from the coronal thermometry images and the length from the sagittal slice. Additionally, different parameters that monitor e.g. cavitation or undesired heating are displayed.

Pretreatment evaluation

On pre-treatment MRI, we evaluated the number of fibroids as well as their location, classified as submucous, intramural, subserosal or pedunculated subserosal. Volume measurement of the uterus were performed by summation of manually outlined areal on axial slices and volume measurements of dominant fibroids by using the formula of a prolate ellipse (length x width x depth x 0.523). Prior to treatment, all patients completed the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire.

MRgHIFU procedure

All procedures were performed on an outpatient basis. The patients were asked to thoroughly shave all hair between the umbilicus and the level of the symphysis. A Foley catheter was inserted in order to avoid moving of the uterus during the procedure due to filling of the bladder. The patients received a non-steroid anti-inflammatory drug and, if needed, a mild sedative as premedication. Additionally, a peripheral venous line was established for delivery of MR contrast agent. Vital signs such as blood pressure, heart rate, respiration rate, and oxygen saturation were recorded. The patients’ temperature was recorded for use as the baseline temperature reference of the treatment. In the MR suite, the patients were placed on the HIFU patient table in a prone position with lower abdominal wall over the prepared HIFU-unit and a semi-flexible wrap-around RF receive coil around the pelvis. If necessary the patients’ position was corrected after anatomic imaging in order to place the target volume of the ablation in the treatable reach of the HIFU-
unit. The patients were given a stop button and instructed on how to use it. After skin bubble detection scan (high resolution GRE sequence), 3 sequences were acquired:

- Sagittal Segmented 3D RARE (MSh TSE) with scan duration= 04:54, FOV (mm)= 250x250x141, pixel size (mm)= 1.49x1.57x3, TR/TE (ms)= 1700/165, number of profiles/shot=67, SENSE factor 2 and BW (Hz) =452.9.
- Sagittal 3D SPGR (T1w FFE) with scan duration= 01:39, FOV= 220x240x100, pixel size= 1.25x1.50x2.5, TR/TE=2.70/1.20, flip angle (FA)= 7, SENSE factor 1.5 and BW= 864.6.
- Coronal fat suppressed 3D SPGR (SPAIR T1w-TFE) with scan duration 03:45, FOV= 260x260x100, pixel size= 1.10x1.16x2.50, TR/TE=6.9/3.4, FA=10, SENSE factor 2 and BW=210.7.

3D Multi-planar reconstruction was used for treatment planning in the HIFU console software environment. The target volume to be treated was marked using different views. The largest fibroid believed to cause symptoms was targeted. The total treated volume of all fibroids was not to exceed 250 ml or 50\% of their volume. Treatment cells were placed in the tissue while avoiding any surgical clips or scars and with the focal point respecting a 1.5 cm margin of the uterus serosa and a 4 cm margin of the gut, the bladder or any boney structures. Electronic markers were placed in order to detect patient movement during the course of the HIFU procedure (Fig. 1). A test-sonication at low energy levels was performed, and based on the temperature rise measured by MR thermometry, the energy required for effective ablation was calculated. Multiple treatment cells were placed, in the first patients with partial overlap, later in the trial close to each other without overlap. Sonication was to be interrupted by the operator, if any safety related irregularity in the MR thermal imaging, either too high tissue temperature (focal region temperatures >80°C) or excessive heating (temperatures > 47°C) of a tissue outside of the treating volume or no or only slight heating in the intended region, was observed. If the patient stopped the treatment because of pain, the cause of the pain was identified before moving on with the procedure. If needed, the treatment plan was altered, e.g. by changing the direction of the ultrasound beam in order to avoid pain from bone structures in the ultrasound path. After completion of the ablation, the two latter MR sequences were acquired without
and with Gadolinium contrast injection. The total time with the patients in an unchanged, prone position was limited to 3 hours. Procedure-related data as number of sonications, cell size, procedure time, applied energy and maximum temperature were recorded. During the study period, there were 2 software updates of the HIFU equipment. In the versions used for the last 4 patients, the system calculates an estimated treatment volume, which was compared to post-procedural MR findings.

Posttreatment evaluation

On MR images obtained immediately and 30 days after treatment, volume measurements of uterus and fibroids were repeated. Any new, non-enhancing part of the fibroids was assumed to represent the coagulation necrosis caused by the ablation, and is hereafter called non-perfused volume (NPV). The NPV was measured in the same manner as the uterine volume and was compared to the predicted treatment volume on thermal map imaging (Fig. 2). All patients were contacted by telephone after 1, 2, 3, 7, 14 and 30 days. They were asked about type and strength of pain or discomfort which was graded on a 10 points scale, the need for pain medication, the time point for return to normal activities and any adverse events. At 30 days, all patients were asked to answer the UFS-QOL questionnaire. Further, we recorded whether the patient had undergone other treatments for fibroid related symptoms.

Results

7 patients were treated between January 2010 and March 2011. Their mean age was 44.6 years (range 39-51) and their mean transformed symptom severity score was 47. All patients had one dominant fibroid with a mean diameter of 8.2 cm (range 5.2 – 11), situated in an intramural (n=5) or submucous (n=2) position. The mean fibroid and uterine volume at baseline was 271 cm³ and 563 cm³ respectively.
One patient was scheduled twice for HIFU treatment. In the first attempt, bowel loops between the uterus and the abdominal wall made sonication impossible. The second time, she was successfully treated after having been brought to a Trendelenburg position for 20 minutes immediately before the procedure. In our second patient, a scar after cesarean section that primarily was not believed to impact on treatment, turned out to limit the possible beam path and only 2 sonication cells could be performed.

Table 1 gives an overview over the main data regarding the procedures. In average, 19 sonlications were performed in each patient with an average of 13 cells sized 8mm and 6 cells sized 12mm. Almost exclusively feedback cells were used. Of a total of 130 cells treated in this study, 44 cells were completed and 86 cells were aborted, either by the user (n=39), the patient (n=17) or the software (n=30). The main reason for user or software abort was potential heating outside the treatment cell detected on thermal map images. The main reason for patient abort was skin heating. There was no statistical difference in maximum temperatures in completed and aborted treatment cells (mean ±SEM 68.05 °C ±0.086 and 68.13 °C ±1.73). The median time that the patients were kept in the prone position was 156 minutes (range 95 – 164); the median treatment time i.e. from the first to the last sonication was 104 minutes (range 23 – 112). In 6 patients a contrast-enhanced MR was performed 30 days after the HIFU treatment. Table 2 shows the treatment volume estimated by the software in the last four patients, as well as the NPV as measured on contrast-enhanced MRI immediately and 30 days after the procedure. In 3 patients the NPV was smaller than the estimated treatment volume. There was no statistically significant change in fibroid or uterine volume 30 days after the procedure; in one patient the NPV was larger at 30 days than immediately after treatment.

There were no major complications related to the procedures. One patient suffered a small 1st degree skin burn that was believed to be caused by insufficient hair removal and resolved uneventfully within 2 weeks. All patients returned to their daily activities within 2 days. During the follow-up period, none of the patients reported pain related to the therapy or used any pain medication. Only 4 of 7 patients completed the UFS-QOL questionnaire at 30 days. The average HRQL
score was unchanged (54); the transformed symptom severity score was unchanged in 1 patient, decreased by 10% in another patient and increased by more than 100% in the remaining two patients. By the end of the study, 3 patients had undergone hysterectomy and 2 patients had been treated by uterine artery embolization for fibroid related symptoms.

Discussion

In this first clinical study of 7 patients, treated with the Sonalleve HIFU system in a 3T MR, we were able to perform sonications and induce areas of non-enhancement within the fibroids in all patients. This is in accordance with other publications, especially the early trials using the ExAblate 2000 system (7, 8). Contrast-enhanced MR images did not reveal any unintended lesions and there were no major adverse events. First-degree skin burns resolving spontaneously as described in one of our patients, are reported to occur in about 5% of all cases (9) using other equipment. In their report on 109 patients, Stewart et al (9) reported one case of temporary sciatic nerve damages, further there has been one case report describing a full thickness skin burn requiring surgical repair in the literature (10). Thus, the frequency of serious adverse events in HIFU ablation of uterine fibroids is low and seems even to decrease with increased operator experience (1). In addition it seems uncommon that patients experience any pain after the treatment.

The goal of HIFU ablation is to induce coagulation necrosis with successive relief of symptoms. In order to achieve sustained symptom relief the NPV should be as large as safely achievable. Earlier studies found a significant difference in radiological and clinical outcome between patients with a NPV higher than 20% as compared to those with a NPV below 20% (1, 11). Our trial describes the feasibility of a new HIFU device in a 3 Tesla setting. We were not able to induce a non-enhancing volume as large as 20% of the fibroid volume in any of our patients. Therefore, the lack of clinical response is expected. In some patients parts of the fibroids were out of the reach of our system in which the maximum depth of the focus point was 10 cm from the transducer surface.
In their initial phase 1 report on the ExAblate 2000 system, Tempany et al. (8) described a poor correlation between the pre-treatment planned volume, the non-enhancing volume on MRI and the findings in the specimen at pathologic analysis. In 4 of their 6 patients they found the non-enhancing volume on MRI to be larger than the presumed treatment volume. This was the case only in one of our 7 patients, who also was the only patient where the NPV was larger after 30 days than immediately after treatment. However, both her fibroid and uterine volume had increased in the same time frame. The estimation of the treatment volume is limited by the current spatial resolution of thermometry and the assumed shape of the treated area that might be substantially different from the actual result. Further technical developments are believed to decrease the difference between the NPV and the estimated treatment volume.

86 of 130 sonications were aborted, mostly because of true or suspected near field heating. However, abortion usually occurred towards the end of sonication, independently whether the patient, the operator or the system stopped sonication. Consequently, there were no significant differences in maximum temperature in completed and aborted cells.

One of the limits of widespread use MR guided HIFU fibroid treatment in busy radiological departments, is the long treatment time. By introducing a new technique of volumetric heating, the Sonalleve system targets at shortening the procedures. However, according to this preliminary study, the treatment times are in concordance to reports in the literature. Typically, it took 2.5 hours from the patient was placed in the prone position until contrast media was injected for post-HIFU imaging. The time between the first and the last sonication was in most patients about 1.5 hours. With increased experience, this time frame might be shortened, but this effort is limited by the need for cooling times between sonications.

Our study has several limitations. When planning the study, we estimated that we could include 10 patients within a 3 months period. Difficulties in finding suitable candidates, organizational obstacles due to restructuring of clinical services in our health region and finally periods of inactivity caused by technical problems with the HIFU unit, resulted in substantial delay. Okada et al. demonstrated the
importance of the learning curve on the results of HIFU treatment (2). Our incapability to perform faster ablation of larger volumes may at least partly be due to this effect. Even if our team may have maintained its routine in practical use of the HIFU unit during several animal studies, obviously only the regular use of the system in gynecological patients will reveal its true potential as an alternative treatment option of fibroids in our institution.

In conclusion, the Sonalleve HIFU system in a 3T scanner was able to induce non-perfused areas in all patients without major complications. Further studies are warranted to prove clinical benefit.
### Table 1. Main procedural data

<table>
<thead>
<tr>
<th>Patient nr.</th>
<th>Number of sonications</th>
<th>Size of treatment cell</th>
<th>Patient in the prone position (min.)</th>
<th>Time from first to last sonication (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8 mm</td>
<td>12 mm</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>20</td>
<td>3</td>
<td>159</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>19</td>
<td>1</td>
<td>164</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>9</td>
<td>9</td>
<td>161</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>21</td>
<td></td>
<td>156</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>8</td>
<td>12</td>
<td>153</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>12</td>
<td>15</td>
<td>139</td>
</tr>
<tr>
<td>Sum</td>
<td>130</td>
<td>91</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>20</td>
<td>12</td>
<td>10.5</td>
<td>156</td>
</tr>
</tbody>
</table>

### Table 2. Volume of uterus and fibroids before the procedure and at 30 days follow-up, treatment volume estimated by the HIFU system and the non-perfused volume (NPV) at contrast-enhanced MR examinations. All volumes in ml.

<table>
<thead>
<tr>
<th>Patient nr.</th>
<th>Fibroid volume</th>
<th>Uterine volume</th>
<th>Estimated treatment volume</th>
<th>Non-perfused volume (NPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>30 days</td>
<td>Before</td>
<td>30 days</td>
</tr>
<tr>
<td>1</td>
<td>546</td>
<td>454</td>
<td>763</td>
<td>630</td>
</tr>
<tr>
<td>2</td>
<td>195</td>
<td>n/a</td>
<td>440</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>78</td>
<td>280</td>
<td>280</td>
</tr>
<tr>
<td>4</td>
<td>180</td>
<td>210</td>
<td>410</td>
<td>380</td>
</tr>
<tr>
<td>5</td>
<td>305</td>
<td>260</td>
<td>580</td>
<td>440</td>
</tr>
<tr>
<td>6</td>
<td>510</td>
<td>560</td>
<td>930</td>
<td>1100</td>
</tr>
<tr>
<td>7</td>
<td>90</td>
<td>80</td>
<td>540</td>
<td>430</td>
</tr>
</tbody>
</table>

n/a = not available
Figure 1: T2-weighted images in the sagittal (1A) and coronal (1B) plane taken during treatment planning. Several planned treatment cells have been placed covering the fibroid. The cells have an ellipsoid shape in their longitudinal direction (A) and round in the transverse plane (1B). The focus of the treatment cell under planning is marked “A”, orange lines show the path of the ultrasound beam. The curved orange line in (1A) describes the margin of the far field. Electronic markers were placed in order to detect patient movement.

Figure 2: T1-weighted, contrast enhanced, sagittal image of the uterus acquired directly after the treatment. In (2A) a thermal map taken during heating of a 12 mm feedback cell is overlaid in order to facilitate comparison of the heated region and the resulting non-perfused volume. Orange and white lines shown in (2B) demark the border of the region that according to calculations of the system have undergone certain (white) or potential (orange) thermal damage. The area outlined in white is used to calculate the estimated treated volume.
References


