Minimally invasive treatments of uterine fibroids

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Minimally invasive treatments of uterine fibroids

Minimaal invasieve behandelingen van uterus myomen

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Contents

Chapter 1

General introduction

Based on: MRI-guided HIFU ablation of benign and malignant lesions

M.J. Voogt, M.A.A.J. van den Bosch

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Uterine fibroids are benign tumors in women of childbearing age. These tumors originate in smooth-muscle cells of the uterus and are clinically apparent in about 25% of women[1]. The true clinical prevalence may be even higher, since pathological examination of surgical specimens suggests a prevalence as high as 77%[2]. Uterine fibroids are categorized according to their location: Intramural (within the myometrium), submucous (protruding into the uterine cavity), subserous (located beneath the serosa), pedunculated (attached to the serosa with a stalk) and intracavitary (*Figure 1*). Although benign and usually asymptomatic, fibroids can cause significant morbidity. Symptoms can include excessive menstrual bleeding, pain, bulk or pressure related symptoms, and reproductive dysfunction[1]. Moreover, women with uterine leiomyomas experience a significantly lower health related quality of life[3]. Spontaneous regression occurs following menopause, probably due to the decrease in the steroid hormones estrogen and progesterone. When treatment is considered necessary, general practitioners and gynecologists are the primary treating physicians. A broad spectrum of treatments is available. The first step is conservative treatments such as medical (hormonal) therapies and intra-uterine devices. When this fails to relief symptoms, invasive surgical treatments (myomectomy and hysterectomy) are an option. Myomectomy (surgical removal of the fibroid with conservation of the uterus) is mainly performed in women who want to preserve their fertility. Although successful in relieving symptoms, the risk of recurrence of fibroids is about 50% five years after surgery[4]. In The Netherlands, 13.000 hysterectomies are performed per year, including those for uterine fibroids. Although hysterectomy results in a decrease of symptoms and an improvement in quality of life[5-7], it is an invasive treatment associated with a risk of major complications and loss of the uterus[8, 9].

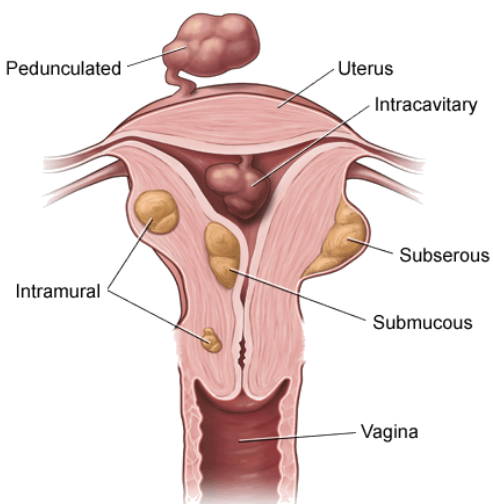

Figure 1. Types of uterine fibroids and their location in the uterus[33]

Since recent years, many women suffering from symptomatic fibroids are seeking uterus preserving minimally invasive treatments. Important reasons for this trend are the short hospital stay, fast recovery, and lower complication rates associated with minimally invasive therapy. Additional reasons are that there is no need for general anesthesia, and the wish to preserve the uterus for psychological or childbearing reasons[10]. Therefore, patients and physicians are increasingly interested in less invasive treatment modalities for uterine fibroids such as uterine artery embolization (UAE) and magnetic resonance-guided high intensity focused ultrasound (MR-HIFU). In randomized controlled trials, UAE has already proven to be a uterus-preserving alternative for hysterectomy with similar clinical results[11-13]. Recently, MR-HIFU, a completely non-invasive treatment method for uterine fibroids, was added to the available treatment spectrum.

Uterine Artery Embolization (UAE)

UAE was introduced in 1994 as an alternative to surgery for women with symptomatic fibroids[14]. Initially developed as a pre-surgical treatment to prevent peri-procedural hemorrhage during fibroid surgery, UAE alone often already resulted in a significant decrease in fibroid related symptoms, rendering the planned surgery unnecessary[15].
UAE is performed by an interventional radiologist, while the patient is consciously sedated. The procedure is performed under x-ray fluoroscopic guidance. After uni- or bilateral percutaneous introduction of a catheter in the femoral artery, the uterine arteries are selectively catheterized (*Figure 2*). The embolization material consists of particles (e.g. polyvinyl alcohol- or gelfoam particles) or microspheres (e.g. tris-acryl gelatine-, acrylamido PVA- or PMMA coated Polyzene-F microspheres). This is injected into both uterine arteries reducing or completely occluding the blood

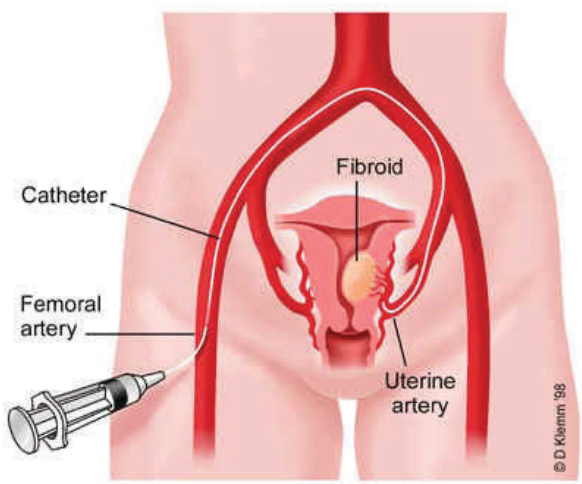

Figure 2. Technique of uterine artery embolization[34]

flow to the fibroids, and causing ischemic injury to the fibroids avoiding damage to healthy uterine tissue. After disruption of the arterial blood supply, fibroids will shrink resulting in a decrease of fibroid related symptoms.
The employment of this treatment has increased rapidly and UAE is currently considered a well-acknowledged and proven alternative to surgical treatment[16]. The EMMY and REST trial, both a randomized controlled trial comparing UAE with surgical fibroid treatment (hysterectomy or myomectomy), have shown satisfactory clinical results for UAE and surgery up to 24 months post-treatment[11-13, 17-19]. However, fibroid related symptoms may recur or new fibroids may develop. Although UAE is minimally invasive, peri- and post-procedural pain experience can be severe requiring rehospitalization, and there is a risk of infectious complications. The average recovery time to normal daily functioning is about two weeks after UAE, which is shorter than following hysterectomy, but substantial nevertheless.

Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU)

MR-HIFU is an image-guided, non-invasive treatment modality for thermal ablation of benign and malignant tumors[20]. MR-HIFU combines magnetic resonance imaging (MRI) and therapeutic ultrasound, using an ultrasound transducer integrated into the table top of an MR scanner (*Figure* 3). An array of piezoelectric ultrasound transducers generates a converging beam of ultrasound that propagates through tissue as a pressure wave.

Figure 3. MR-HIFU system (Sonalleve, Philips). Patient positioned on MRI tabletop with integrated focused ultrasound transducer, prepared to undergo fibroid treatment.

Focusing of the ultrasound beam leads to high levels of acoustic energy in a focal spot at a certain distance from the transducer. Primarily in the focus area, the acoustic energy is converted to heat, resulting in a sharply circumscribed lesion caused by thermal coagulation (*Figure 4*). Since the focus is very exact, skin and other tissues in the near and far fields of the ultrasound beam outside the focal spot (where acoustic intensities are much lower) are generally not affected by the generated heat. MRI is very well suited for treatment guidance, since MR images have a high spatial resolution and excellent soft tissue contrasts, resulting in adequate depiction of lesions and surrounding anatomy. This is important for pre-treatment patient selection and for treatment planning. Furthermore, MR technology provides the ability to perform real-time temperature mapping, most often using the temperature dependence of the chemical shift of the water proton resonance[21]. The temperature maps are used for steering of the focal spot during therapy for precise delivery of a lethal thermal dose to target volumes inside the tissue (*Figure 4*).

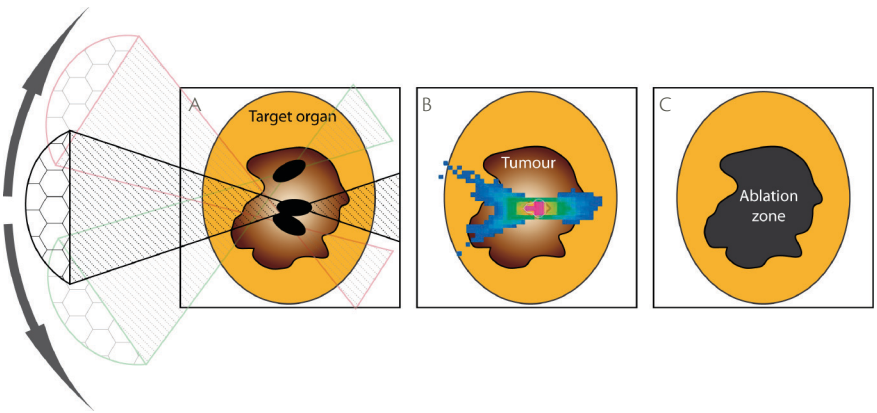

Figure 4. Schematic drawing of tumor ablation using MR-HIFU: **A)** Therapy planning using angulation of the ultrasound beam (3 target areas are shown); **B)** Real-time temperature map during sonication (highest temperature in central pink area); **C)** Treatment result after multiple sonications, visualized as a non enhancing area after administration of intravenous contrast.

Most clinical experience with MR-HIFU has been obtained with treatment of uterine fibroids. In 2004, the first commercially available MR-HIFU system (ExAblate 2000, InSightec, Haifa, Israel) received approval of the Food and Drug Administration (FDA) for clinical uterine fibroid treatment. Since then, several studies reporting the clinical effectiveness after MR-HIFU treatment have been published[22-28]. The traditional and most frequently used ablation approach is performed by iterative sonication of a single focal point (conventional point-by-point ablation technique)[26, 28]. This method results in relatively small ablation volumes per sonication applied. Between subsequent sonications a certain cooling period is required to prevent accumulation of heat in the

treated tissue. A drawback of MR-HIFU treatment is therefore its long treatment time. Therefore, research has been focused at technical developments to increase treatment efficacy and decrease treatment time.
Recently a new ablation strategy was developed, using a volumetric approach[29]. Hereby the transducer applies ultrasound energy in a continuous manner, while the focus is electronically steered in a series of concentric circular or spiraling trajectories of increasing size. In 2009, the first clinical MR-HIFU system using this volumetric technique became commercially available (Sonalleve, Philips Healthcare, Vantaa, Finland). The user can choose differently sized volumes to be ablated per sonication. The system also provides a thermal feedback method for automatic control of sonication using the temperature maps acquired by MR thermometry as an input[30]. The volumetric heating approach with temperature feedback could potentially lead to faster thermal ablation of larger volumes resulting in a shorter duration of the treatment procedure.

Outline of this thesis

The aim of this thesis was to assess clinical results and technical developments of two minimally invasive treatment modalities for symptomatic uterine fibroids: UAE and MR-HIFU. This thesis is structured as follows:

Part I

Uterine artery embolization for treatment of symptomatic uterine fibroids: European practice and clinical results

Since the early nineties, UAE has increasingly been used for uterine fibroid treatment. However, clinical practice may vary widely between different countries and hospitals. In **chapter 2** the results of a survey on clinical practice of UAE in European countries are described. Data on patient referral, embolization technique and material, and peri- and post-procedural care are presented.
Short-term treatment results for UAE were found to be satisfactory. However, it is important to evaluate long-term results to assess the endurance of the treatment. In **chapter 3** the clinical results of a study evaluating the efficacy of UAE treatment five years post-treatment are presented. Clinical outcome data, change in symptoms, menstrual status and subsequent therapies, and patient satisfaction are described. Factors associated with treatment failure are presented. Uterine fibroids have a negative effect on the quality of life (QoL) experienced by patients. Treatment of fibroid related symptoms may have a positive influence on QoL-related aspects of women's health. In **chapter 4** the effects of UAE on psychological and sexual well-being three months post-treatment are described. The influence on problems with sexual functioning is discussed.

Part II

Volumetric magnetic resonance-guided high intensity focused ultrasound for uterine fibroids: First clinical results and future technical developments

MR-HIFU using a point-by-point ablation technique has been used for uterine fibroid treatment in the past decade. In 2009 a new volumetric MR-HIFU technique was introduced. In **chapter 5** the results of the first clinical trial investigating safety and technical feasibility of the volumetric MR-HIFU approach for ablation of uterine fibroids are presented. Treatment capability and technical feasibility were assessed by comparison of the non-perfused volumes measured with MRI after ablation with treatment volumes predicted on the basis of thermal dose maps calculated from MR temperature maps acquired during ablation. Safety was determined by evaluation of complications, adverse events, and unintended lesions.
Treatment efficiency is an important issue during MR-HIFU treatment, since treatment times are relatively long and fibroids selected for treatment are usually large. Deliberate ablation of vessels supplying the fibroid may result in an increase in treatment efficiency. In **chapter 6** the first clinical experience with targeted vessel ablation during MR-HIFU treatment of uterine fibroids is presented. Clinical symptom improvement and fibroid shrinkage will be discussed.
Treatment result after MR-HIFU is generally visualized using contrast-enhanced MR imaging (CE-MRI), on which treated tissue is seen as a non-perfused and thereby non-enhanced volume (NPV). However, this technique cannot be used for peri-procedural treatment evaluation because potential hazardous effects of heating of contrast agents have so far not been studied in human beings. Also, the use of toxic contrast agents in individual patients should be minimized. Diffusion weighted imaging (DWI) can be used to show tissue characteristics based on the diffusion of water molecules within the intra- and extracellular space. It has been shown that thermal ablation with MR-HIFU leads to changes in the observed apparent diffusion coefficient (ADC)[31, 32]. The ADC is influenced by the choice of *b*-values used in DWI for calculation of the ADC. Depending on the choice of *b*-values, changes in ADC maps may primarily reflect changes in perfusion or diffusion. In **chapter 7** a study is presented in which it was investigated which *b*-value combinations for diffusion weighted MR imaging (DWI) and apparent diffusion coefficient (ADC) mapping can best be used to evaluate treatment results after MR-HIFU.

In **chapter 8** the results of our findings are summarized by subject. The relevance of our findings will be discussed in the context of the current literature.

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33. Figure 1: Source: www.jeffersonhospital.org
34. Figure 2: Source: www.fibroidworld.com

Part 1

Uterine artery embolization for treatment of symptomatic uterine fibroids:

European practice and clinical results

Chapter 2

Uterine fibroid embolization for uterine fibroids: A survey on clinical practice in Europe

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W.P.Th.M. Mali, L.E.H. Lampmann

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Abstract

Objective

To assess current uterine fibroid embolization (UFE) practice in European countries and determine the clinical environment for UFE in different hospitals.

Material and Methods

In May 2009, an invitation for an online survey was sent by e-mail to all members of the Cardiovascular and Interventional Radiologic Society of Europe, representing a total number of 1,250 different candidate European treatment centers. The survey covered 21 questions concerning local UFE practice.

Results

A total of 282 respondents completed the questionnaire. Fifteen questionnaires were excluded because they were doubles from centers that had already returned a questionnaire. The response rate was 267 of 1,250 centers (21.4%). Ninety-four respondents (33%) did not perform UFE and were excluded, and six centers were excluded because demographic data were missing. The remaining 167 respondents from different UFE centers were included in the study. Twenty-six percent of the respondents were from the United Kingdom (n = 43); 16% were from Germany (n = 27); 11% were from France (n = 18); and the remaining 47% (n = 79) were from other European countries. Most centers (48%, n = 80) had 5 to 10 years experience with UFE and performed 10 to 50 procedures annually (53% [n = 88] of respondents). Additional demographic data, as well as specific data on referral of patients, UFE techniques used, and peri-procedural and post-procedural care will be provided.

Conclusion

Although UFE as an alternative treatment for hysterectomy or myomectomy is widespread in Europe, its impact on the management of the patient with symptomatic fibroids seems, according to the overall numbers of UFE procedures, somewhat disappointing. Multiple factors might be responsible for this observation.

Introduction

Uterine fibroids are the most common benign tumors in women of childbearing age. Symptomatic fibroids can cause a diversity of symptoms, which can be divided into four categories: bleeding symptoms (irregular and/or heavy menstrual bleeding), pain (in the pelvic region and the back), bulk-related symptoms (pressure on bladder and bowel as well as increase in abdominal circumference), and subfertility[1]. These symptoms often lead to medical or surgical treatments.

During the last two decades, minimally invasive therapeutic options for uterine fibroids have increased considerably. Uterine fibroid embolization (UFE) was introduced in 1994 and is currently a well-acknowledged and proven alternative to surgical treatment[2, 3]. UFE is a percutaneous transcatheter embolization technique using embolization material to occlude the (end-)arteries supplying the fibroid. Devascularization causes infarction and consequently decreased fibroid size, which may result in effective alleviation of symptoms.

However, after the introduction of UFE as an alternative to more invasive approaches, a real widespread breakthrough, especially in general interventional radiology (IR), did not occur. Information on UFE still seems to be unavailable to a large number of women in Europe, and many gynecologists do not provide the option of UFE, or they inaccurately inform patients, using misleading facts. Specific data on the number of centers and interventionalists performing UFE in Europe and the number of UFE procedures per centre do not exist.

This publication reports the outcome of a survey among European interventional radiologists concerning UFE treatment. The purpose of this study was to determine actual data on the current clinical practice of UFE in European countries.

Materials and Methods

In May 2009, we designed a survey to assess current UFE practice in European countries. All professionally active European members of the Cardiovascular and Interventional Radiologic Society of Europe (CIRSE) were invited by e-mail to participate in this study. The total number of different candidate treatment facilities in Europe was 1,250. The questionnaire consisted of 21 questions concerning local clinical practice of UFE and related topics (see Appendix for complete questionnaire). The online button-driven questionnaire was designed for easy handling with a simple set-up to be sure that as many interventional radiologists as possible would participate in this study and could be able to complete all fields.

The first questions referred to demographic data concerning the treatment facility in which respondents were working. The next question was if the responding interventional radiologist performed UFE. In case the answer was "no," the questionnaire was excluded from the database. The remaining respondents were asked about the

interventional group in their facility (number of interventional radiologists and how many of them performed UFE). Respondents had to indicate the time period when their hospital staff started performing UFE as well as the number of UFE procedures performed per year. Respondents were asked to describe the referral pattern of patients (self-referral, e.g., directly to IR, referral by gynecologist, or referral by general practitioner) categorized as percentages adding up to 100%. The questionnaire also assessed who was responsible for pre-procedural and post-procedural patient care (radiologist, gynecologist, or both). The types of pain management, such as patient-controlled analgesia (PCA), epidural analgesia, or other—as well as the duration of hospitalization—were also inventoried. Specific procedure-related questions, such as preferred vascular access (unifemoral, bifemoral, or other), use of microcatheters, type of embolic agents (gelatin sponge, spherical or non-spherical embolic material) used, and the advocated embolization end point (complete stasis, sluggish flow, or pruned tree appearance), were asked. The use of magnetic resonance imaging (MRI) for pre-procedural and post-procedural evaluation was also discussed. The last items were aimed at the future expectations of the respondents concerning Magnetic Resonance-guided Focused Ultrasound (MRgFUS) as a new treatment alternative for uterine fibroids, and we asked if the treatment facility had a Web site to allow screening of the Web sites for dedicated information on UFE treatment. Participants were asked to complete the online questionnaire before the end of July 2009. To avoid bias, we decided to include only one survey per treatment centre. In case more than one questionnaire was returned from the same facility, we decided to include the first submitted survey in the study and exclude the duplicates.

Results

A total of 282 respondents returned the completed questionnaire (*Table 1*). Fifteen questionnaires were excluded because they were duplicates from treatment centers that had already returned a questionnaire. The response rate was therefore 267 of 1,250 candidate treatment centers (21.4%). Ninety-four respondents (33%) did not perform UFE and were consequently excluded from the study. Six questionnaires were excluded because essential demographic data were missing. Further contact efforts to obtain these missing data did not result in sufficient completion of the information, thus making rejection of these questionnaires inevitable. The remaining 167 respondents, all from different UFE centers, were included in the study. The geographic distribution of the respondents covered 24 countries in Europe, including Turkey. *Figure 1* shows the number of included treatment facilities per country.

Twenty-six percent (n = 43) of the respondents were from the United Kingdom; 16% (n = 27) were from Germany; 11% (n = 18) were from France; and the remainder (53%, n = 79) was from other European countries. Fifty-two percent (n = 86) of the respondents worked in an academic centre, and the remaining 48% (n = 81) worked

Table 1. Number of treatment centers per European country and response rate

Countries	Number of treatment centers	Number of respondents	Number of exclusions		Number of included centers (%)
			No UFE	Doubles	
Austria	54	14	5	0	9 (16.7)
Belgium	27	8	2	1	5 (18.5)
Bulgaria	7	2	1	0	1 (14.3)
Croatia	6	0	0	0	0 (0)
Cyprus	1	0	0	0	0 (0)
Czech Republic	35	2	2	0	0 (0)
Denmark	9	5	3	0	2 (22.2)
Finland	15	3	1	0	2 (13.3)
France	85	20	0	2	18 (21.2)
Germany	289	37	9	1	27 (9.3)
Greece	67	18	15	0	3 (4.5)
Hungary	19	2	0	0	2 (10.5)
Iceland	1	0	0	0	0 (0)
Ireland	14	9	2	1	6 (42.9)
Italy	50	12	6	0	6 (12.0)
Latvia	1	0	0	0	0 (0)
Luxembourg	6	1	1	0	0 (0)
Malta	1	0	0	0	0 (0)
Norway	23	9	3	0	6 (26.1)
Poland	27	3	0	2	1 (3.7)
Portugal	11	2	1	0	1 (9.1)
Romania	6	5	0	4	1 (16.7)
Russia	14	1	0	0	1 (7.1)
Serbia	7	1	1	0	0 (0)
Slovakia	4	1	0	0	1 (25.0)
Slovenia	6	1	0	0	1 (16.7)
Spain	52	12	1	1	10 (19.2)
Sweden	13	4	1	0	3 (23.1)
Switzerland	42	11	6	1	4 (9.5)
The Netherlands	109	30	16	1	13 (11.9)
Turkey	61	6	5	0	1 (1.6)
Ukraine	1	0	0	0	0 (0)
United Kingdom	189	57	13	1	43 (22.8)
Missing data		6			
Total	1250	282	94	15	167 (13.4)

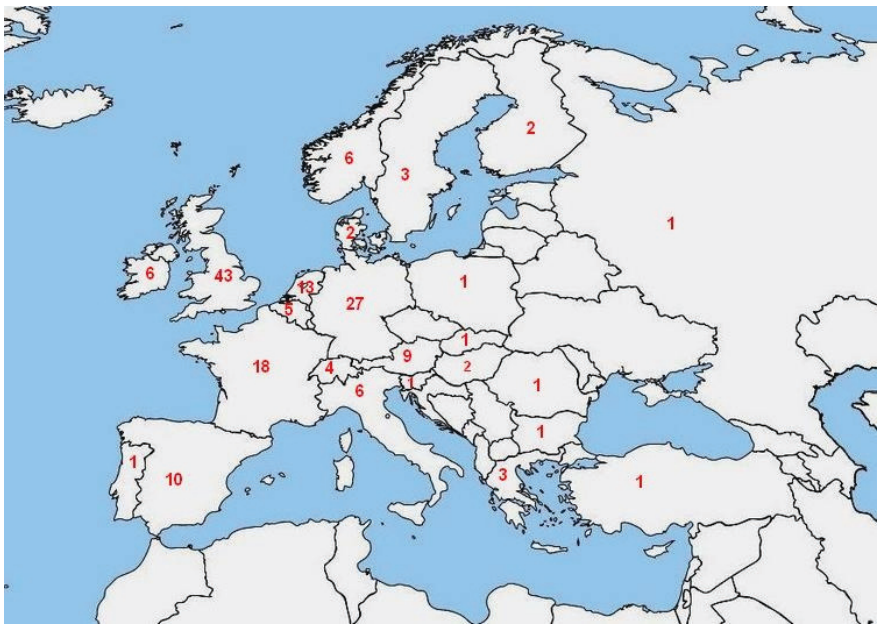

Figure 1. Number of included treatment facilities per European country

in a general hospital setting or private practice. The majority of the respondents (65%, n = 108) worked in a group with ≥1 interventional radiologist performing UFE. Only 1% (n = 2) of the respondents had >15 years of experience with UFE; 25% (n = 42) had 10–15 years of experience; the majority (48%, n=80) had 5–10 years of experience; and 26% (n = 43) had introduced UFE during the last 5 years.

Table 2 lists the number of UFE procedures, per year and per country, classified into five categories: ≤10, 10 to 50, 50 to 100, 100 to 200, and ≥200 UFE treatments annually. Most centers (53%, n = 88) performed between 10 and 50 treatments on an annual basis. Extreme numbers of UFE treatments were provided by two treatment facilities (one in France and one in Romania): They both performed approximately 500 procedures/year.

In *Table 3*, data on pre-procedural, peri-procedural, and post-procedural care management are listed. In the majority of cases (76%), patients were referred by a gynecologist for UFE, and only in a small minority (4%) were referred by a general practitioner. In the remaining cases (20%), patients referred themselves directly to the interventional radiologist. Pre-procedural care was generally performed by a combination of a gynecologist and radiologist (42%, n = 70). Pre-procedural MRI was considered a standard procedure by 56% (n = 90) of the responding radiologists. Pain management was preferably performed (76%, n = 122) using PCA. Some facilities (15%, n = 24) used epidural analgesia, and 9% (n = 14) employed other pain

Table 2. Annual number of UFE procedures (classified into five categories) performed in treatment facilities per country

Countries (n)	≤10	10 - <50	50 - <100	100 - <200	≥ 200
Austria (n = 9)	2	7	0	0	0
Belgium (n = 5)	1	4	0	0	0
Bulgaria (n = 1)	1	0	0	0	0
Denmark (n = 2)	0	2	0	0	0
Finland (n = 2)	1	1	0	0	0
France (n = 18)	5	10	1	1	1
Germany (n = 27)	11	14	1	1	0
Greece (n = 3)	2	1	0	0	0
Hungary (n = 2)	0	0	2	0	0
Ireland (n = 6)	1	3	1	1	0
Italy (n = 6)	6	0	0	0	0
Norway (n = 6)	3	3	0	0	0
Poland (n = 1)	0	0	1	0	0
Portugal (n = 1)	0	1	0	0	0
Romania (n = 1)	0	0	0	0	1
Russia (n = 1)	1	0	0	0	0
Slovakia (n = 1)	0	1	0	0	0
Slovenia (n = 1)	1	0	0	0	0
Spain (n = 10)	4	6	0	0	0
Sweden (n = 3)	2	1	0	0	0
Switzerland (n = 4)	3	1	0	0	0
The Netherlands (n = 13)	7	5	0	1	0
Turkey (n = 1)	1	0	0	0	0
United Kingdom (n = 43)	8	28	5	1	1
Total number of treatment facilities (n = 167)	60 (36%)	88 (53%)	11 (6%)	5 (3%)	3 (2%)

n = Number of treatment facilities

management protocols, such as intravenous medication (n = 8), oral medication (n = 1), a combination of PCA and epidural analgesia (n = 2), general anesthesia (n = 1), superior hypogastric plexus nerve block (n = 1), and neuroleptic medication (n = 1). Half of the respondents (50%, n = 81) admitted their patients for one overnight stay after UFE treatment. Only 1% (n = 1) performed UFE on an outpatient basis, and 3% (n = 5) admitted their patients for a total of four overnight stays. Post-procedural care was most frequently (55%, n = 91) provided by a combination of a gynecologist and radiologist. The majority of respondents (72%, n = 120) followed their patients up for 3 or 6 months, and 8% (n = 14) did so for >12 months.

Table 3. Pre-procedural, peri-procedural, and post-procedural care-related information

	%	N
Referral for UFE (n = 165)		
Self-referral	20	-
Gynecologist	76	-
General Practitioner	4	-
Pre-procedural care (n = 166)		
Radiologist	17	28
Gynecologist	41	68
Combination	42	70
Pain management (n = 160)		
Patient Controlled Analgesia (PCA)	76	122
Epidural analgesia	15	24
Other	9	14
Length of hospital stay (n = 163)		
Outpatient treatment	1	1
1 night	50	81
2 nights	33	54
3 nights	13	22
4 nights	3	5
Post-procedural care (n = 166)		
Radiologist	21	35
Gynecologist	24	40
Combination	55	91
Post-procedural follow-up schedule (n = 166)		
No follow-up	4	6
Follow-up for 3 months	41	69
Follow-up for 6 months	31	51
Follow-up for 12 months	16	26
Follow-up for > 12 months	8	14
Planned MRI-scan (n = 161)		
Pre-procedural	56	90
3 months post-procedural	18	29
6 months post-procedural	21	34
9 months post-procedural	0	0
12 months post-procedural	4	7
> 12 months post-procedural	1	1

n = Number of respondents who answered the specific question

In *Table 4*, UFE procedure-related details are listed. A large majority (81%, n = 134) of the respondents preferred unifemoral arterial access, whereas 17% (n = 28) chose bifemoral arterial puncture, and only 2% (n = 3) preferred brachial arterial access. Spherical embolic material was the favored embolic agent in 77% (n = 127) of the responding radiologists. The frequency of using microcatheters during UFE procedures

varied among the respondents. Only 3% (n = 5) indicated that they never use them; 36% (n = 60) use them only when considered necessary; and 34% (n = 56) always employ microcatheters during UFE. Fourteen percent (n = 24) used the so-called "pruned tree" appearance on fluoroscopic imaging as the UFE end point. The user frequency of the end points "complete stasis" and "sluggish flow" was quite similar (41%, n = 68 vs. 45%, n = 74).

Ninety percent (n = 151) of the treatment facilities had a Web site. We screened these Web pages for patient information on UFE. Nineteen percent (n = 31) contained dedicated passive or interactive treatment information for patients as well as physicians.

Table 4. UFE procedure-related information

	%	N
Preferred arterial access (n = 165)		
Uni-femoral	81 %	134
Bi-femoral	17 %	28
Brachial	2 %	3
Embolic agent (n =166)		
Gelatin sponge	1 %	2
Spherical embolic material	77 %	127
Non-spherical embolic material	22 %	37
Use of microcatheters (n =166)		
Never	3 %	5
Seldom	36 %	60
Regularly	27 %	45
Always	34 %	56
Used endpoint (n =166)		
Complete stasis	41 %	68
Sluggish flow	45 %	74
Pruned tree	14 %	24

n = Number of respondents who answered the specific question

Table 5 lists the annual number of treatments per centre in five categories for centers with and without a dedicated UFE Web site. This table illustrates that centers providing UFE information on a Web site have higher treatment numbers than facilities not operating an active Web site.

Future expectations for MR-HIFU as a thermoablative therapy for fibroids were indicated as "very promising" by 5% (n = 9) of the respondents; 30% (n = 50) thought it was "promising," and 28% (n = 47) did not see an important role for this treatment in the future. The remaining 36% (n = 60) had no opinion about this topic.

Table 5. Number of UFE treatments per category for centers with and without a dedicated UFE Web site

Number of UFE procedures per year:	UFE website?	
	No (n = 136)	Yes (n = 31)
≤10	41 % (n = 56)	13 % (n = 4)
10 - <50	51 % (n = 69)	61 % (n = 19)
50 - <100	6 % (n = 8)	10 % (n = 3)
100 - <200	1 % (n = 2)	10 % (n = 3)
≥ 200	1 % (n = 1)	6 % (n = 2)

Discussion

Since the publications of Ravina et al. in the early 1990s on pre-myomectomy transcatheter embolization to minimize blood loss during surgery, the surprising effects on decreased fibroid size and symptoms became evident and led to the first reports on UFE as a single treatment for symptomatic fibroids[2, 4]. After a worldwide introduction as a possible alternative to hysterectomy and many additional studies on this treatment, UFE now seems to fit into the treatment options available to women suffering from uterine fibroids.

The Cochrane review from 2006 cited that UFE resulted in the same patient satisfaction rate as surgery (myomectomy or hysterectomy)[5]. The length of hospital stay was decreased after UFE, and the return to daily activities was faster. Because UFE seemed to result in a higher minor complication rate and more unscheduled visits and readmission rates, the statement was made that additional focus on long-term follow-up was necessary to determine the real impact of UFE[6].

As a result, retrospective cohort studies examined and compared the results of UFE and hysterectomy, which lead to satisfying conclusions concerning safety, expectations, and cost-effectiveness over a longer follow-up period[7, 8]. Furthermore, randomized studies comparing UFE and surgery (hysterectomy or myomectomy) have been completed in the meantime, resulting in publications in major scientific journals[9–12]. However, in gynecological papers, the experimental character of UFE was only recently abandoned. Short, medium, and long-term follow- up data are currently available, leading to a more positive attitude from our gynecological colleagues[3, 13, 14].

Guidelines from different medical specialties currently consent that UFE is a valuable alternative to surgical management of symptomatic fibroids in carefully selected and informed patients[6, 15]. Bratby et al. quoted that level-1 evidence has established the role of UFE as a proper alternative treatment[16]. Last but not least, Bradley et al. stated that UFE is effective, safe, and durable and should be considered a true alternative to hysterectomy[3]. Apparently, the Cochrane review from 2006 is considerably outdated and must be revised as soon as possible.

This current European survey showed interesting findings on clinical UFE practice in a variety of treatment centers in different European countries. It was nevertheless interesting to discover the marked variation in current UFE practice across European centers in terms of distribution, approach, treatment care, and numbers. The top five of countries with the highest number of UFE centers were (starting with the highest) the United Kingdom, Germany, France, The Netherlands, and Spain. UFE facilities were not exclusively restricted to academic centers (52%), as probably could be expected, but were also present in general hospital and/or private settings. Our survey also illustrates that although in 2009 UFE was widespread throughout European countries, the majority of centers (53%) performed only between 10 and 50 UFE procedures/year. Only 5% performed >100 cases annually. Most respondents (65%) were active in a group of interventionalists performing UFE, providing potential 24-h/7-day coverage of patient care. The overall impression that UFE is not new in Europe was expressed by the fact that the majority of centers (74%) had >5 years of experience with UFE.

Participation with gynecologists was performed by the majority of interventionalists in both pre-procedural (42%) and post-procedural (55%) patient care. Pre-procedural and post-procedural care solely by IR was noted in only 17 and 21% of centers, respectively. Gynecologists were the main referrers for UFE treatment. The preferred pain management in the majority of centers (76%) was PCA, as expected, and most centers (50%) admitted the patients for one overnight stay after the procedure.

In terms of facility-related efficacy estimation, it was disappointing to note that only 24% of centers followed-up their patients for >12 months, 31% for only 6 months, and the majority (41%) for only 3 months. Although the use of pre-procedural and post-procedural MRI is advocated widely to properly map and follow-up a UFE candidate, only 56% of centers employed a pre-UFE MRI-planning protocol. Post-procedural MRI follow-up was even more disappointing, probably related to the poor follow-up intervals as stated previously. Contrast-enhanced MRI is by all means the only reliable imaging modality to obviate sufficient devascularization, e.g., a technically successful embolization.

The fact that most centers (81%) used a unifemoral arterial access for UFE minimizes the concern about potential adverse events occurring at the puncture sites, and using the Waltman loop maneuver might also be of great help in cases of steep aortic bifurcation issues. Although 66% of interventional radiologists do not use microcatheters, or use them only if necessary, coaxial use of microcatheters might be important to avoid vascular spasms, resulting in inadequate devascularization of fibroids, thus leading to inferior clinical results. The chosen embolization end point may depend on the type of embolization material used. In the minority of centers, the pruned-tree appearance on fluoroscopic images is still used as the end point indicator. Sluggish flow in the uterine artery, e.g., the Shlansky-Goldberg method (stasis during five heartbeats)[17], was employed in equal frequency as total stasis of contrast medium

in the uterine artery. Concerning embolization material, no solid conclusive data are available to date on superior clinical outcome after UFE with a certain type embolic agent, although studies are pointing in the direction of calibrated microspheres[18–21]. It was therefore interesting to notice that a large majority of centers (77%) favored the use of these microspheres. Gelatin sponge was still employed in 1% of the centers. Although the role of the industry in promoting spherical embolic agents cannot be underestimated, the advantages of calibrated microspheres during UFE procedures, especially when using microcatheters, are evident. Less clogging of microcatheters and better prediction of the level of devascularization might result in a smooth, swift, and successful UFE procedure.

Some treatment centers have dedicated fibroid clinics for pre-procedural consultation and post-embolization clinical and radiologic follow-up. These centers of excellence often employ well-designed and properly executed public relations focused on potential patients and referring physicians. Kroencke stated the importance of using the media to enhance patient awareness of treatment options[22]. We should not underestimate the inventiveness of modern patients in their search for alternative treatment options independent from their treating physician. Not only the Internet, but also magazines, radio, and television, can be used by treatment centers to reach potential patients. The creation of an interactive Web site is a unique opportunity to do so. This study indicated that treatment centers operating a Web site containing dedicated UFE information performed more procedures than centers that do not use Web site possibilities, thus emphasizing the efficacy of such strategies. However, the presence of such a Web site might not be the only explanation for this finding.

Another important point in building a UFE practice is that interventional radiologists must become accustomed to treating patients in a clinical environment. UFE treatments must be performed by a multidisciplinary team, including gynecologists and anesthesiologists. It is extremely important, as quoted by Keeling et al., that interventional radiologists see the patient in the first place instead of a uterine fibroid that must be embolized[23]. Although quality of care is becoming increasingly important, it is no longer acceptable to meet the patient in the angiographic suite for the first time, perform the embolization procedure, and never see her again.

Concerning new therapeutic developments, it was amazing to notice that Magnetic Resonance-guided Focused Ultrasound was categorized as a "very promising" respectively "promising" new treatment option by only 5% respectively 30% of the centers. Thirty-six percent did not see any role for MRgFUS in the future. However, recent papers show that MRgFUS can be a treatment option with satisfying results for a selection of patients[24–26]. The low levels of confidence we found might be partially biased by uneasy feelings toward a possible competitive treatment for UFE. Another reason could be that MRgFUS devices are expensive to acquire and therefore many of the respondents' facilities will never have the opportunity to obtain one. Moreover,

current focused ultrasound technology can treat only relatively small volumes of fibroid tissue at a time, and respondents might see this as an essential factor limiting the number of patients that can be treated with this technique.

A limitation of this study was the low response rate (21.4%). All CIRSE members received an invitation to participate in this online questionnaire; however, only a relatively small percentage responded. Therefore, we do not have the illusion of possessing a solid and complete data set on this subject because not all centers performing UFE completed the questionnaire. A low response rate is always a problem when conducting a survey, and it tends to be even lower when using an electronic survey instead of a survey sent by postal mail[27, 28]. Therefore, the results published here are not an absolute view on UFE practice in Europe. It is possible that the non-responding interventional centers do not perform UFE except, for instance, only nonvascular interventions. Another possibility is that some of the centers performing UFE are not members of CIRSE and therefore did not receive a survey invitation. Moreover, a key issue in survey research is non-response bias, which occurs when respondents differ in meaningful ways from non-respondents. It is possible that the responders are more actively involved in this subject than non-responders and are therefore more willing to participate in this survey.

We conclude with the statement that UFE as an alternative treatment for hysterectomy or myomectomy is widespread in Europe. However, the impact on the management of the patient with symptomatic fibroids seemed, according to the overall number of UFE procedures, disappointing. A more active attitude toward clinical IR, together with effective public relations, might establish a more solid fundament for UFE treatment in the future.

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Appendix

Uterine Fibroid Embolization Survey Europe

Demographic information

Name institution:
Name respondent:
In which country are you working:
In which city are you working:

Do you perform Uterine Fibroid Embolization (UFE)? ☐ Yes ☐ No

Interventional group

How many interventionalists are in your group?
- ☐ I am alone
- ☐ 1 physician
- ☐ 2 physicians
- ☐ 3 physicians
- ☐ 4 physicians

How many interventionalists in your group perform UFE:

When did your group start performing UFE (year):

How many procedures does your group perform annually:

Patient care

Could you indicate the percentages of referrals (Adding up to 100%):
Self (patient): %
Gynecology: %
General Practitioner: %

Who provides the pre-treatment care?
- ☐ Self (radiologist)
- ☐ Gynecologist
- ☐ Combination

Who provides after care?
- ☐ Self (radiologist)
- ☐ Gynecologist
- ☐ Combination

Procedure

Pain management:
- ☐ PCA (patient controlled analgesia)
- ☐ Epidural
- ☐ Other:

Which vascular access site do you prefer?	☐ Unifemoral ☐ Bifemoral ☐ Other:
Do you use microcatheters?	☐ Never ☐ Seldom ☐ Regularly ☐ Always
Which embolic agent do you use?	☐ Gelfoam ☐ Spherical ☐ Non-spherical
What do you use as endpoint during your procedures?	☐ Complete stasis ☐ Sluggish flow ☐ Pruned tree
How long is the hospital stay?	☐ Outpatient basis ☐ 1 night stay ☐ 2 nights stay ☐ 3 nights stay ☐ 4 nights stay ☐ 5 nights stay
What is your follow-up schedule?	☐ No follow-up ☐ 3 months ☐ 6 months ☐ 12 months ☐ > 12 months
When do you perform an MRI scan?	☐ Pre-procedural ☐ 3 months post-procedural ☐ 6 months post-procedural ☐ 9 months post-procedural ☐ 12 months post-procedural ☐ > 12 months post-procedural
General	
Does your institution have a website?	☐ No ☐ Yes:
How many UFE procedures do you expect for 2009:	
What do you expect of MRI-guided focused ultrasound?	☐ Very promising ☐ Promising ☐ Nothing ☐ Do not know

Chapter 3

Long-term outcome of uterine artery embolization for symptomatic uterine leiomyomas

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Abstract

Objective

To evaluate long-term outcome and factors associated with treatment failure after uterine artery embolization (UAE) in women with symptomatic uterine leiomyomas.

Material and Methods

One hundred consecutive women treated with UAE for symptomatic uterine leiomyomas participated. Clinical outcome data (i.e., changes in symptoms, menstrual status, subsequent therapies) and satisfaction data were collected. Treatment failure was defined by subsequent major surgery (i.e., hysterectomy or myomectomy), a second embolization, or a lack of symptom improvement at the patient's final follow-up interval. Possible predictors of failure were age, clinical baseline characteristics (i.e., bleeding, pain, and bulk), and imaging results (e.g., percent volume reduction of the dominant tumor). Cox proportional-hazards analysis was used to determine factors associated with failure.

Results

Follow-up was available in 93 women (median follow-up, 54 months; range, 45– 87 y). Continued symptom relief was observed in 72% of patients (n = 67). Among the 26 women with treatment failure (28%), 11 (42%) underwent hysterectomy, four (15%) myomectomy, and eight (31%) repeat embolization. Three (12%) reported no improvement. In women without any additional surgery (n = 70), heavy menstrual bleeding, pain, and bulk-related symptoms improved in 97%, 93%, and 92%. Ninety percent of all women (n = 93) were satisfied or very satisfied at final follow-up. Predictors of failure were a lack of improvement in bleeding (hazard ratio [HR], 9.0; 95% CI, 3.1–26.3; $P < .001$) or pain (HR, 7.4; 95% CI, 2.2–24.4; $P < .001$) at 1 year after UAE and the percent reduction in dominant tumor volume (HR, 0.97; 95% CI, 0.95–0.99; P .007).

Conclusion

UAE in women with symptomatic leiomyomas leads to long-term symptom improvement. Predictors of failure were a lack of improvement in bleeding or pain at 1 year and the percent reduction in dominant tumor volume.

Introduction

Uterine leiomyomas are common benign tumors in women of childbearing age. Symptomatic uterine leiomyomas can be treated by medical treatment or surgery [1]. For several reasons[2], an increasing number of women want to preserve their uterus, leading to the development of uterus-sparing therapies such as uterine artery embolization (UAE), myomectomy, and high-intensity focused ultrasound treatment. UAE was introduced as an alternative treatment to surgery for women with symptomatic leiomyomas[3]. The employment of this treatment has increased rapidly. UAE has been recognized as an effective alternative to hysterectomy and myomectomy[4]. Several published studies showed favorable clinical outcomes and satisfaction at as long as 1 year after embolization[5–10]. However, these results do not guarantee similar results later on, and little has been reported regarding long-term outcomes after UAE[11–13].
The aim of the present study was to investigate long-term clinical results (mean follow-up, 54 months; median, 54 months; range, 42– 87 months), the incidence of additional therapies, and long-term patient satisfaction. An additional aim was to assess factors influencing the clinical outcome and patient satisfaction after UAE.

Materials and Methods

Women participating in this study were the first 100 consecutive patients treated between August 1998 and July 2002 with UAE for symptomatic leiomyomas at a single institution. This study was approved by the local medical ethical committee as required by law. Informed consent was obtained from all participants.

Inclusion and Exclusion Criteria

The study included women with symptomatic uterine leiomyomas, an indication for hysterectomy, and a minimum follow-up period of 3.5 years. This included women who, for personal reasons such as a possible desire to conceive in the future, did not want to undergo hysterectomy. The symptoms were divided into three groups: bleeding problems (ie, menorrhagia with or without anemia or metrorrhagia), pain (ie, dysmenorrhea, dyspareunia, and pelvic pain), and bulk-related problems (ie, subjective size of an enlarged abdomen, pressure on bladder or rectum with symptoms of urinary frequency and constipation). All women underwent one or more of the following treatments without sufficient clinical results: iron supplementation, various hormonal treatments (54%), gonadotropin-releasing hormone analogue treatment, levonorgestrel-containing intrauterine device use, use of hemostatic agent (ie, tranexamic acid), analgesic agent use, myomectomy, or myolysis (ie, coagulation of blood supply to the uterine tumor).
Postmenopausal or pregnant women were excluded, as were women with suspected

or confirmed gynecologic malignancy, avascular calcified leiomyomas, any gynecologic infection, pure adenomyosis (without any leiomyomas), or thin-stemmed pedunculated leiomyomas with a stalk diameter smaller than one third of the tumor diameter. Tumor or uterus size (or volume) was not a factor in any exclusion criterion. Before UAE, standard gynecologic assessment (including diagnostic hysteroscopy to exclude intracavitary pathologic processes) was performed. In addition, pelvic magnetic resonance (MR) imaging was done at baseline and at 3-, 6-, and 12-month follow-up. MR imaging was performed to confirm the diagnosis of uterine leiomyomas, measure the size of the uterus, and determine the size and location of the dominant leiomyoma. Adenomyosis was identified if present. The number of leiomyomas was estimated and divided into four categories: one, two, three, or at least four tumors. Tumor and uterine volumes were calculated according to the formula for a prolate ellipse (length x width x diameter x 0.5233) as described by Orsini et al[14].

In December 2005, all women were asked to complete the same questionnaire as in previous stages of the study. Patients were asked to indicate whether they were experiencing bleeding, pain, or bulk-related symptoms. In comparing answers to the questionnaire between time points, we noted whether symptoms changed, and this was scored as improved or not improved. Adverse events such as vaginal infections and/or dryness, leiomyoma expulsion, and menopausal symptoms were recorded. At each time point, patient satisfaction results were classified as very satisfied, satisfied, or not satisfied. Women with a potential desire to conceive in the future were asked if they had become pregnant or tried to become pregnant after UAE. An inventory was made of all subsequent gynecologic therapies after UAE—any medical therapies, surgical interventions (ie, hysterectomy, myomectomy, hysteroscopic resection of leiomyomas, or diagnostic hysteroscopy and curettage), or additional UAE procedure—and the exact moment of their occurrence. Major interventions were defined as hysterectomy, myomectomy, or repeat embolization according to the classification by Spies et al[11]. Cases were considered failures when an additional major intervention was needed or no improvement was seen at final follow-up.

Embolization Procedure

Embolization was started after selective catheterization of the left uterine artery, guiding of the catheter into the right uterine artery by means of the Waltman loop maneuver[15], and embolization of the right side. The intention was to carry out bilateral embolization in all women. When spasm in the uterine artery occurred, it was treated medically with tolazoline or nitroglycerin. In women who wanted to become pregnant, both femoral arteries were punctured and embolization was performed by two radiologists simultaneously to limit radiation exposure of the ovaries.

The embolization material consisted of non-spherical polyvinyl alcohol (PVA) particles (Contour; Boston Scientific/Target Therapeutics, Fremont, California) 355–710 µm in

size or calibrated tris-acryl gelatin microspheres (CTGMs; Embosphere and Embogold, Biosphere Medical, Roissy, France) 500 –900 μm in size. We switched completely from PVA particles to CTGMs after the first 45 treatments because CTGMs were easier to use in targeted embolization of the peritumoral plexus with no intracatheter aggregation and blockage. With PVA particles, the aim was to achieve a proper angiographic embolization endpoint, i.e., proximal total occlusion of both uterine arteries. When using CTGMs, the angiographic embolization endpoint was defined as complete occlusion of branches to the peritumoral plexus and sluggish flow in the ascending segment of the uterine artery, leaving the main uterine artery, cervicovaginal branches, and utero-ovarian anastomoses patent. The choice of embolic agent used was influenced by factors such as operator preference of a new technique selected at the time and was independent of patient or tumor characteristics.

Women stayed hospitalized for one night for clinical observation. Before the procedure, antibiotics (2 g cefazolin) were administered intravenously. Pain was controlled by administering 10 mg morphine intramuscularly and a 100 mg suppository of a nonsteroidal anti-inflammatory drug or a patient-controlled analgesia pump. Nausea was treated with 4 mg ondansetron.

Statistical Methods

Univariate analyses were used to determine the distribution of each baseline and outcome measure. Patients were stratified into clusters according to all possible combinations of symptoms (i.e., bleeding, pain, and bulk). Subsequently, analyses of variance were performed to examine the relationship between (i) these clusters and the number of additional therapies and (ii) the clusters and clinical improvement. We considered patients to have shown clinical improvement when all leiomyoma-related symptoms within the cluster had improved after UAE. To determine the relationship between major interventions (i.e., hysterectomy, myomectomy, or repeat embolization) and baseline characteristics, clinical results, and imaging results during the first year after UAE, Cox proportional-hazards regression analysis was used. The variables included were age, indication for UAE (i.e., bleeding symptoms, pain, or bulk related symptoms), therapies before UAE, number and localization of leiomyomas, presence of apparent adenomyosis, embolization material used (i.e., non-spherical or spherical particles), uni- or bilateral procedure, baseline volumes of the uterus and dominant leiomyoma, percent reduction in volume at 3 and 6 months after UAE, symptoms at 3- and 6-month follow-up, and hormonal therapies started after UAE. Survival time was defined in months from UAE until censorship. Cox proportional-hazards regression analysis was also employed to determine the relationship between long-term failure (i.e., major intervention or no improvement at final follow-up) and baseline characteristics and imaging results. In addition to the variables mentioned earlier, percentage volume reduction and symptoms at 12 months after UAE were

included. Women who had a major intervention in the first 12 months after UAE were excluded from this analysis. Cox proportional-hazards regression was performed for all cases of treatment failure (i.e., major intervention or no improvement at final follow-up) during the whole follow-up period. The same covariates as mentioned earlier were used in this analysis. In addition, Cox proportional-hazards regression was used to examine the association between dissatisfaction with UAE over the whole follow-up period and covariates. Covariates were baseline characteristics; clinical and imaging results at 3, 6, and 12 months; and any subsequent interventions. Data are presented as medians with ranges, or means with SDs, and Cox proportional-hazards regression results are presented as hazard ratios (HRs), 95% CIs, and *P* values. *P* values less than .05 were considered statistically significant. Data were analyzed with SPSS software (version 12.0; SPSS, Chicago, IL).

Results

Of the 100 women enrolled in the study, follow-up data were obtained at 3 and 6 months in 92 women, at 12 months in 88 women, and at final follow-up in 93 women. The median final follow-up time after UAE was 54 months (range, 42– 87 months). Two patients died during follow-up: one of pulmonary carcinoma and one of pre-existing chronic obstructive pulmonary disease. Five women could not be traced.

The mean age of the women at the time of UAE was 43 years (range, 25–53 y). Forty percent of women (n = 40) did not have children and 19% had never been pregnant. Ninety-four women were white, five were black, and one was Asian. Additional general characteristics are listed in *Table 1*. The mean baseline uterine volume obtained by MR imaging was 510 mL (median, 403 mL; range, 54 –1,750 mL). The mean dominant leiomyoma volume was 170 mL (median, 130 mL; range, 2–1,123 mL). Five women had apparent adenomyosis accompanying the leiomyomas. With regard to unsuccessful types of treatment before UAE, hormones were the most frequent form of treatment (54%), of which 42% constituted oral contraceptives, 5% hormone replacement therapy, 13% progestativa, and 1% danazol. In addition, gonadotropin-releasing hormone analogues were used by 14% of women and a levonorgestrel-containing intrauterine device was used by 4%. Iron supplements were used by 44% of the women, analgesics by 6%, and haemostatic agents by 18%. In addition, laparoscopic myomectomy, hysteroscopic myomectomy, and myolysis were performed in 3%, 8%, and 1% of women, respectively.

UAE was performed bilaterally in 97 women and unilaterally in three women as a result of spasm (n = 2) or aplasia (n = 1) of one uterine artery. After the first year, 11 percent of women (10 of 89) needed a major intervention and data from 11 women were missing (*Table 2*). Of the remaining 79 women, bleeding improved in 85% (62 of 73), pain in 89% (40 of 45), and bulk-related symptoms in 84% (38 of 45). Regarding satisfaction, 91% of women (72 of 79) were very satisfied or satisfied. At the final

Table 1. General patient characteristics (N = 100)

Characteristic	%
Indication for UAE	
Menorrhagia /anemia	94
Pain	57
Bulk-related symptoms	54
Number of leiomyomas	
1	33
2	12
3	5
≥4	50
Location of dominant leiomyoma	
Intramural	78
Submucosal	22
Subserosal	10
Pedunculated	4

follow-up, the incidence of major interventions increased to 25% (23 of 93) and data from seven women were missing. Of these remaining 70 women, bleeding improved in 97% (64 of 66), pain in 93% (38 of 41), and bulk-related symptoms in 92% (35 of 38). Three women reported no improvement at all. The satisfaction score was 99% (69 of 70; very satisfied or satisfied). With all women included (n = 93), the satisfaction was 90% (84 of 93) after a median of 54 months of follow-up.

Subsequently, women were stratified into all possible combinations of the three symptoms before UAE. This resulted in seven clusters, of which three were very small. No woman reported pain only, one woman had pain and bulk-related symptoms, and five women had only bulk-related symptoms (*Table 3*). There were no differences among symptom clusters with regard to the number of additional therapies or improvement of symptoms after UAE (P = .71; *Table 3*).

Of the 23 women with a major intervention, 11 underwent hysterectomy, four myomectomy, and eight repeat UAE. Of these 23 women, 19 exhibited insufficient tumor infarction on contrast agent– enhanced MR imaging at 3 months. Insufficient infarction was a result of unilateral embolization in one woman, spasm in five women, and insufficient embolization (i.e., no proper angiographic embolization endpoint) in the remaining 13 women. Of the eight women who underwent a second embolization, none exhibited vasospasm during the first UAE procedure. In addition, two cases of necrotic leiomyoma (with fever) and new symptoms resulting from new leiomyomas in two women necessitated major intervention. The median time between UAE and major intervention was 18 months (range, 2– 49 months). Eight women underwent repeat UAE: seven had complete symptom relief after the second procedure and one had complete symptom relief after the third. To determine a UAE learning curve,

Table 2. Clinical results and major interventions

	3m	6m	12m	Median 54m
Missing data	8	8	11(1†)	7(2†)
Major intervention*	3/92 (3)	7/92 (8)	10/89 (11)	23/93 (25)
Hysterectomy	3/92 (3)	3/92 (3)	4/89 (4)	11/93 (12)
Myomectomy	0/92 (0)	2/92 (2)	3/89 (3)	4/93 (4)
Repeat UAE	0/92 (0)	2/92 (2)	3/89 (3)	8/93 (9)
Bleeding‡				
Improved	72/83 (87)	72/80 (90)	62/73 (85)	64/66 (97)
Not improved	11/83 (13)	8/80 (10)	11/73 (15)	2/66 (3)
Pain‡				
Improved	46/50 (92)	46/48 (96)	40/45 (89)	38/41 (93)
Not improved	4/50 (8)	2/48 (4)	5/45 (11)	3/41 (7)
Bulk‡				
Improved	46/50 (92)	46/51 (90)	38/45 (84)	35/38 (92)
Not improved	4/50 (8)	5/51 (10)	7/45 (16)	3/38 (8)
Satisfaction‡				
Very satisfied	24/89 (27)	39/86 (45)	45/79 (57)	51/70 (73)
Satisfied	55/89 (62)	36/86 (42)	27/79 (34)	18/70 (26)
Not satisfied	10/89 (11)	11/86 (13)	7/79 (9)	1/70 (1)

Note. Values in parentheses are percentages unless otherwise specified.

* Cumulative major interventions comprising the three rows below

† Number of patients who died before the follow-up interval

‡ Changes in symptoms and satisfaction are displayed for women who were not missing at that interval and did not undergo a major intervention until then.

outcomes in the first 50 women were compared with the second 50 women. No difference was found between the groups.

Thirty-four of 93 women (37%) started using hormonal therapy. Indications were contraception (n = 14), menopausal or postmenopausal symptoms (n = 7), endometriosis (n = 3), and menstrual discomfort (n = 3). In seven women, recurrent symptoms were the reason to start hormonal therapy. Five needed subsequent major intervention.

The median uterine and dominant leiomyoma volumes measured at 3-, 6-, and 12-month follow-up are displayed in *Figure 1*. Median volume reductions of the dominant leiomyomas were 44%, 53%, and 61%, whereas uterine volume reductions were 31%, 40%, and 44%, respectively, at 3, 6, and 12 months.

Transient amenorrhea after UAE was observed in 17% of women (16 of 93). Leiomyoma expulsion was reported in 12% (n = 11). Twenty-nine women (33%) had become postmenopausal. The mean ages of this group of women were 48 years (SD, 3.0 y) at the time of embolization and 50 years (SD, 3.3 y) at their first report of permanent amenorrhea. The mean interval from UAE until permanent amenorrhea was 23 months (median, 24 months; range, 0 – 46 months). Transient vaginal discharge

Table 3. Symptom clusters before UAE and clinical improvement

Symptom	No of pts.	Lost to Follow-up	Pts. with clinical improvement*	Hysterectomy	Myomectomy	Repeat UAE	Median (range) Follow-up (months)
Bleeding	35	3	24/26 (92)	1	1	4	48.3 (41.8-80.0)
Pain	0	-	-	-	-	-	-
Bulk	5	0	3/3 (100)	2	0	0	56.1 (42.7-87.1)
Bleeding and pain	21	1	13/14 (93)	1	1	2	58.1 (42.5-80.0)
Pain and bulk	1	0	1/1 (100)	0	0	0	52.0 (52.0-52.0)
Bleeding and bulk	13	2	6/8 (75)	1	1	1	56.5 (44.4-66.5)
Bleeding, pain and bulk	35	3	24/26 (92)	1	1	4	48.3 (41.8-80.0)

* A patient is improved when all symptoms in a particular cluster have improved. Values in parentheses are percentages

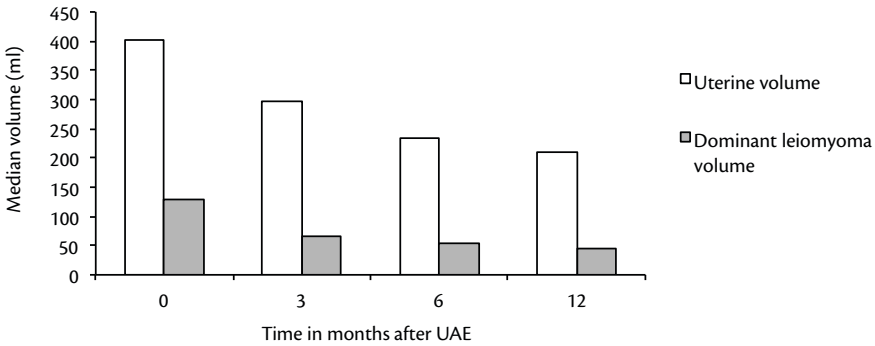

Figure 1. Median volumes measured 0, 3, 6 and 12 months after UAE

Table 4. Symptoms after UAE as predictors for future failure

	Early failure (0 –12 months after UAE)	Late failure (12 months after UAE through final Follow-up)	Overall failure (UAE through final Follow-up)
After 3 months			
Bleeding	8.2 (2.0-33.6) *P* = .003	5.5 (1.2-25.5) *P* = .030	7.6 (2.8-20.5) *P* < .001
Pain	NS	NS	3.5 (1.2-10.6) *P* = .025
Bulk	NS	7.5 (1.6-35.1) *P* = .010	NS
After 6 months			
Bleeding	25.6 (4.9-133) *P* < .001	NS	7.2 (2.7-19.3) *P* < .001
Pain	NS	7.3 (1.6-34.1) *P* = .010	5.6 (1.6-19.5) *P* = .007
Bulk	NS	NS	NS
After 12 months			
Bleeding		11.4 (3.5-37.4) *P* < .001	9.0 (3.1-26.3) *P* < .001
Pain		12.6 (3.5-45.7) *P* < .001	7.4 (2.2-24.4) *P* < .001
Bulk		4.2 (1.2-15.3) *P* = .029	NS

Note. - Values are HRs (95% CI) and P value. NS = not significant.

was reported in 17% of women (n = 16). Eight percent of women reported vaginal infections, mainly during the first months after UAE. Vaginal dryness was noted in 15% (n = 14). However, this started mostly after the onset of permanent amenorrhea and not directly after UAE.

Before embolization, 16% of women (n = 16; mean age, 37.6 years) had a possible desire to conceive after UAE and 10% (n = 10) were actively seeking to become pregnant (mean age, 36.5 years). However, only four women actually attempted to become pregnant. One woman became pregnant twice and delivered two full-term children. No peripartum complications were noted. One woman was 9 weeks pregnant at the last follow-up. The other two women did not become pregnant.

A lack of improvement in bleeding symptoms at 3- and 6-month follow-up was a significant predictor of a major intervention during the first year (*Table 4*). None of the other covariates assessed was of significant influence on early failure.

Sixteen of 89 women (18%) had late failure, i.e., a major intervention after the first year after UAE or a lack of improvement at final follow-up. Bleeding symptoms and bulk-related symptoms that not improved at 3 months were significant predictors of failure in the future, as was a lack of improvement of pain at 6 months (*Table 4*). A lack of improvement in bleeding, pain, or bulk-related symptoms at 12-month follow-up were all predictors of future failure. The percent reduction of dominant leiomyoma volume at 12 months was related to long-term failure. For each percent increase in volume reduction, the chance for future failure decreased by a factor of 0.97 (i.e., HR of 0.97; 95%, CI, 0.95– 0.99; P = .007). In addition, the percent reduction of uterine volume was significantly associated with failure (HR, 0.98; 95% CI, 0.96 –1.0; P = .049), but after adjusting for percent reduction of dominant leiomyoma volume, this association was no longer significant (P = .54). All other covariates assessed were of no significant influence.

Subsequently, predictors of overall failure (i.e., major interventions or lack of improvement at final follow-up) over the total follow-up period were examined. Twenty-six cases met the criteria for treatment failure. No improvement in bleeding symptoms and pain were significant predictors of future failure at 3, 6, and 12 months after UAE (*Table 4*). The percentage volume reduction of the dominant leiomyoma at 12 months was significantly associated with future failure (HR, 0.97; 95% CI, 0.95– 0.99; P = .008). Less volume reduction of the leiomyoma was associated with an increased chance of failure. We did not find age at the time of UAE to be related to future failure (P = .56). No significant relation was found between the baseline volumes of the uterus and dominant tumor and future failure (P = .70 and P = .86, respectively). All other covariates assessed were not of significant influence.

All women were included in the analysis of satisfaction with UAE. At the final follow-up, nine of 93 women (10%) were not satisfied. The association between dissatisfaction and baseline characteristics, clinical outcome, and imaging results were determined. A subserosal localization of the dominant leiomyoma was significantly associated with dissatisfaction at final follow-up (HR, 5.5; 95% CI, 1.4 –21.5; P = .013). A lack of improvement of bulk-related symptoms at 3 and 12 months after UAE was also significantly associated with dissatisfaction (HR, 12.0; 95% CI, 1.2–118.1; P = .033; respectively; HR, 14.4; 95% CI, 2.0 – 103.5; P = .008) at the final follow-up. Women who had a major intervention were almost 21 times more likely to be dissatisfied at final follow-up than women who did not have a major intervention (HR, 20.6; 95% CI, 2.6 –165; P = .004). Regarding major interventions, hysterectomy was significantly associated with dissatisfaction at the final follow-up (HR, 41.8; 95% CI, 5.2– 338.4; P = .001). For myomectomy and repeat UAE, no significant relationship was found. When

a case was defined as a failure at the final follow-up, this was also associated with patient dissatisfaction with treatment (HR, 15.6; 95% CI, 1.9 –126.1; P = .010). No other characteristics predicted dissatisfaction at final follow-up.

Discussion

The aim of the present study was to investigate long-term clinical results, rate of additional therapies, and long-term patient satisfaction, and to assess factors influencing clinical outcomes and patient satisfaction after UAE. We found continued symptom relief in 72% of the women treated with UAE, and 90% reported to be satisfied or very satisfied after a median follow-up of 54 months. Although 25% of the women underwent a major intervention, only 12% needed a hysterectomy. Our findings are comparable to the results of Spies et al[11], who found continued symptom relief in 73%, a major intervention rate of 20%, and a hysterectomy rate of 14%. Katsumori et al[13] reported a symptom control rate of 89.5% at 5 years after UAE with gelatin sponge particles. Walker and Barton-Smith[12] reported high symptom control rates and a 16% incidence of subsequent interventions after UAE.

In contrast to existing studies, we looked at seven symptom clusters, i.e., possible combinations of symptoms presented by the women before UAE. We showed that three symptom clusters are uncommon: pain only, bulk only, and the combination of the two. The majority of patients reported more than one symptom, mostly in combination with bleeding. With regard to long-term outcomes in the different clusters, we found no significant difference in improvement. Moreover, in our study, the symptom clusters did not result in differences concerning additional therapies.

In our study, the number of women who started to use hormonal therapy (for various reasons) after UAE was high. The literature about the effects of hormonal therapy in women with leiomyomas is not conclusive[16,17]. In our analysis, no significant relation was found between the use of hormones after UAE and the risk of subsequent major interventions.

Several factors associated with major intervention or failure after UAE were identified in this study, i.e., menorrhagia or pain after 12 months. After a mean observation period of 13 months after UAE, Huang et al[18] found persistent menorrhagia and persistent abdominal pain to be present in 59% and 23% of women who required additional surgery, respectively. Spies et al[11] showed that long-term failure was more likely in women who had not experienced an improvement at 1-year follow-up; however, they did not stratify this for different symptomatologies.

The percentage volume reduction of the dominant leiomyoma at 12 months after UAE was a predictor for long-term failure and failure in the total follow-up period. Spies et al[11] reported also that decrease in volume reduction of the dominant tumor was associated with failure.

Investigators have been concerned about the effect of uterine volumes on clinical outcome. Some reports failed to show any correlation[19,20], whereas others demonstrated favorable outcomes after UAE in large uterine volumes[21,22]. Kido et al[21] reported remarkable symptom improvement in women with large uterine volumes of diffuse leiomyomatosis. Prollius et al[22] described that large uterine volumes did not decrease the efficacy of UAE, but concluded that, in women with a very large uterus and predominant bulk-related symptoms, alternative treatment options should be explored because, after UAE, these women are still left with a large mass. Marret et al [23] defined two predictive factors for leiomyoma recurrence after UAE at a median of 30 months of follow-up: the number of tumors and the size of the dominant tumor. Spies et al[11] also reported long-term failure to be more likely in those with baseline dominant tumor volumes greater than the median measurement.

In our study, we did not find any baseline characteristic of significant influence. Size and number of leiomyomas are of lesser importance to clinical outcome. Because no baseline predictors or conditions associated with failure were found in this study, it remains difficult to select women with the best chances for a successful outcome beforehand. However, we did find more dissatisfaction in women with a subserosal localization of the dominant tumor. Although not statistically significant, women with bleeding and bulk-related symptoms had less improvement after UAE compared with the other clusters in our study. It might be that, when the group of women in this symptom cluster increases, the difference will be statistically significant. Therefore, gynecologists have an important role in pre- and post-procedural counseling and instituting additional treatment when necessary. Interventional radiologists are necessary in counseling about and performing this specialized procedure. It is of paramount importance to provide women information about the limitations of UAE to avoid unrealistic expectations.

We hypothesize that the infarction percentage of the leiomyoma is the most important factor for a successful clinical outcome of UAE. Pelage et al[24] investigated the clinical differences between women with and without complete infarction of the dominant leiomyoma. Incomplete tumor infarction did not affect outcome immediately, but the recurrent growth of uninfarcted tissue could lead to symptom recurrence. In our study, the type of embolic agent (non-spherical or spherical particles) did not affect the long-term results, which implies that infarction, rather than the embolic agent used, is of importance. This is in accordance with the results demonstrated by Spies et al[24], who, in a randomized comparative study, reported no substantive differences between outcomes of embolization with PVA particles and CTGMs[25].

Comparable with other studies, the patient satisfaction after UAE was high at final follow-up[9,12,26]. However, among women who scored their satisfaction as satisfied or very satisfied, some had undergone a major intervention. This was also found by Smith et al[9]. An explanation for this contradictory finding could be that women who

underwent UAE are a selected population[2,12]. Partially as a result of the extensive counseling of the gynecologist and the radiologist in our institution, these women are very motivated to undergo the procedure and are often reluctant to undergo surgery. A second reason for the high satisfaction rate might be the extra attention during clinical (and scientific) follow-up given to these women who participated in this study.
Our current study has some limitations. First, the population of women treated with UAE changed over time. Initially, only small numbers of women were treated with UAE. When more information became available, we started offering UAE to younger women, those who wished to conceive in the future, and those with very large leiomyomas. With regard to UAE in women with symptomatic leiomyomas who wish to conceive, physicians should proceed with caution. Although uncomplicated pregnancies and normal deliveries have been reported after UAE, there is insufficient evidence regarding the safety of the procedure in women seeking to give birth. To date, pregnancy-related outcomes remain understudied[27,28]. The current consensus opinion is that myomectomy is the preferred therapy in this subgroup of women with symptomatic uterine leiomyomas who wish to conceive. These women may be offered UAE after failed myomectomy, in cases in which myomectomy may be difficult, or when a surgical option is rejected by the patient[12]. The second limitation of our study is that the embolization procedure and its post-procedural management were changed. We switched from non-spherical PVA to spherical CTGMs with a different angiographic embolization endpoint because spherical CTGMs were considered easier to work with, i.e., no occlusion of microcatheters and a more targeted embolization of the uterine leiomyomas. Post-procedural pain management was changed to the primary use of a patient-controlled analgesia pump. Also, the attitude of the gynecologist toward post-procedural complications became different. Nowadays, we have more knowledge to distinguish symptoms of uterine infection from the more common post-embolization syndrome[29]. Before performing a hysterectomy, these two conditions need to be carefully distinguished because, in the latter, it is justified to remain expectative. These changes of attitude might have had an impact on the clinical outcomes and satisfaction in our study.
In the present study, we evaluated the results of 100 women. For some analyses, these women were divided into different groups, with some being small. This leads to very large confidence intervals, as can be seen in the data for predictors of dissatisfaction. Studies with larger numbers of patients are required to allow more definitive conclusions to be drawn.
In conclusion, our data show that UAE as treatment for symptomatic uterine leiomyomas leads to long-term improvement of symptoms in the majority of women. Women's satisfaction is high, even when an additional major intervention is needed. We found no baseline predictors or conditions associated with treatment failure.

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Chapter 4

Sexual functioning and psychological well-being after uterine artery embolization in women with symptomatic uterine leiomyomas

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Abstract

Objective

To assess the effects of uterine artery embolization (UAE) on psychological and sexual well-being three months after treatment.

Materials and methods

A prospective study in 141 premenopausal women with symptomatic uterine fibroids who underwent UAE. Main outcome measures were changes in scores on a questionnaire concerning sexual well-being (ranging from 0 to 32, a higher score indicating better functioning) and a questionnaire concerning psychological well-being (SCL-90, ranging from 0 to 360, a higher score indicating more emotional and somatic concerns).

Results

The total score for sexual functioning showed a statistically significant increase from 20.3 to 22.7 three months after UAE, indicating that sexual functioning improved. Thirty-four percent and 37% of women reported an increase in sexual activity and desire. The percentage of women reporting sexual problems of lubrication, orgasm, or pain decreased 7%, 36%, and 14%, respectively. The total SCL-90 score showed a statistically significant decrease from 133 to 116 three months after UAE, indicating a decrease in emotional and somatic concerns.

Conclusions

Sexual and psychological well-being improved significantly three months after UAE in women with symptomatic uterine fibroids. Sixty-eight percent had an increase in the total score for sexual functioning. Problems with sexual functioning were statistically significantly decreased.

Introduction

Uterine fibroids are common benign tumors in women of childbearing age. When fibroids were symptomatic, women used to ask for medical or surgical therapies such as hysterectomy[1]. More recently, women are seeking minimally invasive, uterus-sparing therapies such as uterine artery embolization (UAE) and magnetic resonance guided focused ultrasound (MRgFUS) to treat symptomatic uterine fibroids[2, 3]. One of the reasons why women want to preserve their uterus is because hysterectomy might have negative effects on sexual well-being[4], although the literature on this issue is not conclusive[5–9]. Little is known about sexual functioning after UAE[10–13]. Furthermore, the effect of UAE on patients' psychological well-being and the relation to clinical symptoms is unknown.

Our study determined the effects of UAE on sexual and psychological well-being. Sexual functioning, psychological well-being, and clinical symptoms were assessed before and three months after UAE. In addition, possible associations between baseline characteristics, psychological well-being, sexual well-being, and clinical symptoms were assessed.

Materials and Methods

Consecutive women awaiting UAE (n = 195) were asked to participate in this prospective study. A total of 165 (85%) women agreed to participate. The treatments were completed between June 2002 and January 2005 at the St. Elisabeth Hospital in Tilburg, the Netherlands. The study was approved by the medical ethics committee of the St. Elisabeth Hospital, Tilburg, as required by Dutch law. We obtained informed consent from all women.

Included were women with symptomatic uterine fibroids and an indication for hysterectomy that had been treated extensively (medically or surgically) without sufficient clinical result. This also included women with a (latent) wish to conceive who therefore did not want hysterectomy. The symptoms were divided into three groups: bleeding problems (menorrhagia, with or without anemia), pain (dysmenorrhea, dyspareunia, abdominal pain, back pain, and leg pain), and bulk-related problems (pelvic pressure, urinary frequency, and constipation).

Excluded were postmenopausal or pregnant women, women with already infarcted and/or calcified uterine fibroids (visualized with contrast-enhanced magnetic resonance imaging [MRI] as avascular fibroids), any gynecologic infection, pure adenomyosis (without any fibroid), or thin-stemmed pedunculated fibroids with a stalk diameter less than one third of the fibroid diameter (detected using MR imaging in three orthogonal planes). The latter were excluded because of the possibility of detachment of the fibroid into the abdominal or uterine cavity, and the risk of infection after UAE. Moreover, thin-stemmed pedunculated fibroids can be treated more easily with myomectomy, and thus this is the preferred treatment.

Twenty-two women were excluded because they did not meet the inclusion criteria (pedunculated fibroid [n = 9], endometrial carcinoma [n = 1], pure adenomyosis [n = 3], endometritis [n = 1]) or because they had refrained from the embolization treatment (n = 8). Another two women were excluded because they needed additional surgical treatment (both myomectomy) in the follow-up period (three months after the first embolization). Thus, a total of 141 women were included in the analysis.
All women were examined by a gynecologist, and pelvic MRI was performed at baseline and at three months after UAE to confirm the diagnosis of uterine fibroids and to measure the size of the uterus and the dominant fibroid. The formula for a prolate ellipse (L x W x D x 0,5233) was used, as described by Orsini et al.[14].

Questionnaires

The women were asked to fill in three questionnaires: a questionnaire concerning sexual dysfunction, the Symptom Checklist 90 (SCL-90), and a symptom-related questionnaire. The questionnaires were sent to the patient and were completed before the embolization treatment and three months after treatment.
The questions concerning sexual dysfunctions (*Table 1*) were selected from the Questionnaire for Screening Sexual Dysfunctions (QSD)[15,16], a self-report questionnaire used to detect sexual dysfunctions that has been used in several studies[9,17]. Research on the validity of this instrument is available[18]. There are questionnaires for different kinds of sexual relationships available: for men and women with a female partner, a male partner, and without a partner. We used the questionnaire for women with a male partner. The QSD consists of 36 questions determining the presence, frequency, and experienced discomfort of sexual dysfunctions. The first 16 questions concern the general perception of the patient's own sexuality and frequency of sexual activity. The next 18 questions concern different types of problems during sexual activity.

Table 1. Questions concerning sexual dysfunction

How often did you experience a sexual desire?
How often were you sexually active?
Problems with vaginal lubricationa:
How often was your vaginal lubrication less than desired?
How often was your vaginal lubrication shorter than desired?
Problems with orgasma:
How often did you reach an orgasm during sexual activity?
Problems with genital paina:
How often, before, during or after sexual activity, did you experience pain or an unpleasant sensation in your genital area?

[a] A problem was regarded as present when at least one of the questions concerning the problem was scored with 'several times', 'often' or 'every time', with the exception of the question concerning the frequency of orgasm for which a problem was regarded as present when 'several times', 'sometimes' or 'hardly ever' was scored.

From the first part, we selected two questions to measure the frequency of desire for sexual contact and the frequency of sexual activity measured on a 7-point Likert scale ranging from 0 (hardly ever) to 6 (several times a day), and from the latter part we selected four questions concerning the presence of sexual dysfunctions.

Two questions about vaginal lubrication and one about genital pain were scored on a 5-point Likert scale ranging from 0 (always) to 4 (hardly ever); one question about reaching an orgasm was scored on a 5-point Likert scale ranging from 0 (hardly ever) to 4 (always). These questions were used to identify patients having problems with lubrication, orgasm, or genital pain. These items were selected as they were considered to be influenced most by UAE. We considered a problem to be present when a patient scored at least one of the questions concerning the specific problem with "several times," "often," or "every time," except for the question concerning the frequency of orgasm. In this instance, a problem was considered to be present when "several times," "sometimes," or "hardly ever" was scored.

The last question concerned the patient's degree of satisfaction with her present sexual life (measured on a 5-point Likert scale ranging from 0 (very dissatisfied) to 4 (very satisfied). These questions were all related to the sexual functioning in the past month.

The seven questions together have a Cronbach's alpha coefficient of 0.68. We also calculated a total score by adding up all scores for each question. The possible score range is 0 to 32. A lower score indicates more problems in sexual functioning. Three months after UAE, women were asked to indicate for each question whether the frequency of experiencing the particular issue had increased, remained equal, or decreased compared with baseline.

The SCL-90 is a multidimensional self-report inventory designed to evaluate emotional and somatic concerns[19]. The questionnaire consists of 90 items with a 5-point response scale ranging from "symptom absent" to "symptom very often present." The patient has to indicate to what extent she suffered from a particular concern in the past week. The questionnaire consists of eight subscales: agoraphobia, fear, depression, somatic concerns, insufficiency of thought and action, distrust and interpersonal sensitivity, hostility, and sleep disturbances. Every subscale can be scored separately. The scores of all subscales can also be summed to obtain a total score. The total SCL-90 score ranges from 0 to 360. A higher score indicates more emotional and somatic concerns. The questionnaire has a good validity and reliability[20, 21].

The third questionnaire was a homemade inventory of symptoms leading to UAE. Women were asked if they suffered from menorrhagia, dysmenorrhea, abdominal pain (apart from during menstruation period), pelvic pressure, dyspareunia, constipation, urinary frequency, back pain, or leg pain. These symptoms were selected as being the most reported symptoms by women with symptomatic uterine fibroids. For each of nine items, women could indicate whether the symptom was present or not. This

questionnaire has a good internal consistency with a Cronbach's alpha coefficient of 0.72. Three months after UAE, women had to indicate whether their symptoms had worsened, had improved, or were unchanged. We calculated the percentage of symptoms that improved for each woman.

Embolization Procedure

UAE was performed after selective catheterization of the left uterine artery and guiding the catheter into the right uterine artery by means of the Waltman loop maneuver[22]. Bilateral embolization was intended in all women. Spasms were treated with tolazoline or nitroglycerin. In women who desired future pregnancy, embolization was performed on two sides at the same time to limit radiation exposure to the ovaries. We used calibrated trisacryl gelatin microspheres (CTGM) (Embosphere and Embogold; Biosphere Medical, Roissy, France), size 500–900 microns. The angiographic embolization endpoint was a complete occlusion of branches to the perifibroid plexus, with sluggish flow in the ascending segment of the uterine artery, and leaving the main uterine artery, cervicovaginal branches, and utero-ovarian anastomoses patent.
Women were hospitalized for one night for clinical observation. Before the procedure, antibiotics (2 g cefazolin) were administered intravenously. Pain was controlled by administering 10 mg of morphine intramuscularly and a 100-mg suppository of a nonsteroidal anti-inflammatory drug (NSAID) or a patient-controlled analgesia pump. We used 4 mg of ondansetron to treat nausea. Women were advised to refrain from sexual intercourse for a period of 6 weeks after UAE.

Statistical Analysis

Univariate analyses were used to determine the distribution of each baseline and outcome measure. Paired-samples t-test was used to calculate the changes in continuous variables between baseline and three months after UAE. When there was a skewed distribution, the nonparametric Wilcoxon signed rank test was used. Multiple regression was used to investigate associations between baseline and imaging factors and outcome measures three months after UAE. The variables included were age, number of fibroids, volume of the uterus and the dominant fibroid, total SCL-90 score, total score on the sexual dysfunctions questionnaire, and the total number of symptoms at baseline. $P<.05$ was considered statistically significant. Data were analyzed using SPSS 12.0 software (SPSS Inc., Chicago, IL).

Results

Of the 141 women who agreed to participate, all of the questionnaires were completed by 118 (83.7%) women at baseline, and by 107 (75.9%) women after three months. The mean age of the participating women was 42.7 years (range: 24 to 54 years). Ninety

percent of the women were white, 6% black, and 4% Asian. All women received medical treatment before UAE (oral contraceptives, progestatives, gonadotropin-releasing hormone analogs, levonorgestrel-containing intrauterine device, iron supplements, analgesics, or haemostatic agents); (hysteroscopic) myomectomy was performed in 11%, and endometrial ablation in 1.4%.

At baseline, the volumes of the uterus and the dominant fibroid were 559 mL (± 461 standard deviation [SD]) and 261 mL (± 314 SD), respectively. The number of fibroids was one fibroid in 41% of women, two fibroids in 12%, three fibroids in 9%, and four or more fibroids in 38%. The procedure was performed bilateral in 138 (97.9%) of the women. Three months after UAE, the volume of the dominant fibroid and the uterus were statistically significantly reduced compared with baseline to 167 mL (± 234 SD) (P<.0005) and to 377 mL (± 338 SD) (P<.0005), respectively.

Fifty percent of the women were nulliparous, and the majority of women had no wish to become pregnant in the future (68%). Sixteen percent were actively trying to become pregnant, and another 16% had a possible desire for future pregnancy.

Sexual Dysfunctions Questionnaire

At baseline, the mean total score on the sexual dysfunctions questionnaire was 20.3 (± 4.8 SD). This was statistically significantly increased three months after UAE to 22.7 (± 4.1 SD, P < .0005), indicating that sexual functioning had improved. Sixty-eight percent of the women scored higher three months after UAE compared with baseline. All scores on the seven items about sexual functioning showed a statistically significant increase, except for the question about whether vaginal lubrication was less than desired (was unchanged) (see the first three columns of *Table* 2). The frequency of sexual activity and satisfaction with sexual functioning increased the most.

At baseline, 19% of the women reported a problem with lubrication, 47% with orgasm, and 28% with pain. *Figure 1* shows the change in the percentage of women reporting sexual problems. There was a statistically significant decrease in the percentage of women reporting a problem with lubrication, orgasm, or pain (P=.007, P=.002, and P=.024, respectively) three months after UAE. As shown in the last three columns of *Table 2*, women indicated for each question if the frequency of the particular issue increased, remained equal, or decreased three months after UAE in comparison with baseline. The frequency of sexual desire, sexual activity, and satisfaction all increased after UAE. For the other issues, the results were less obvious, and most women did not report a change compared with baseline. When we considered only the women reporting an increased frequency of sexual activity (n = 33) compared with baseline, the results are clearer. Lubrication increased in 31%, the duration of lubrication increased in 29%, the frequency of reaching an orgasm increased in 44%, pain was reduced in 42%, and satisfaction increased in 74%.

Table 2. Sexual functioning at baseline and at the 3-month follow-up

	Baseline	3 months FU	P value	Compared with baseline (%)		
				Increased	Unchanged	Decreased
Frequency of sexual desire[a]	2.8 (1.4)	3.2 (1.2)	0.01	34	62	4
Frequency of sexual activity[b]	2.1 (1.3)	2.7 (1.4)	<0.0005	37	57	6
Lubrication less than desired[b]	3.4 (1.0)	3.6 (0.8)	0.14	16	75	9
Duration of lubrication shorter than desired[b]	3.4 (1.0)	3.7 (0.8)	0.03	13	80	7
Frequency of orgasm[c]	2.6 (1.3)	3.0 (1.1)	0.001	19	76	5
Pain in genital area[b]	3.0 (1.2)	3.4 (1.0)	0.005	6	70	24
Satisfaction[d]	2.1 (1.4)	2.7 (1.1)	<0.0005	34	58	8

[a]Measured on a seven point Likert scale ranging from 0 ('hardly ever') to 6 ('several times a day')
[b]Measured on a five point Likert scale ranging from 0 ('always') to 4 ('hardly ever')
[c]Measured on a five point Liker scale ranging from 0 ('hardly ever') to 4 ('always')
[d]Measured on a five point Likert scale ranging from 0 ('very dissatisfied') to 4 ('very satisfied')

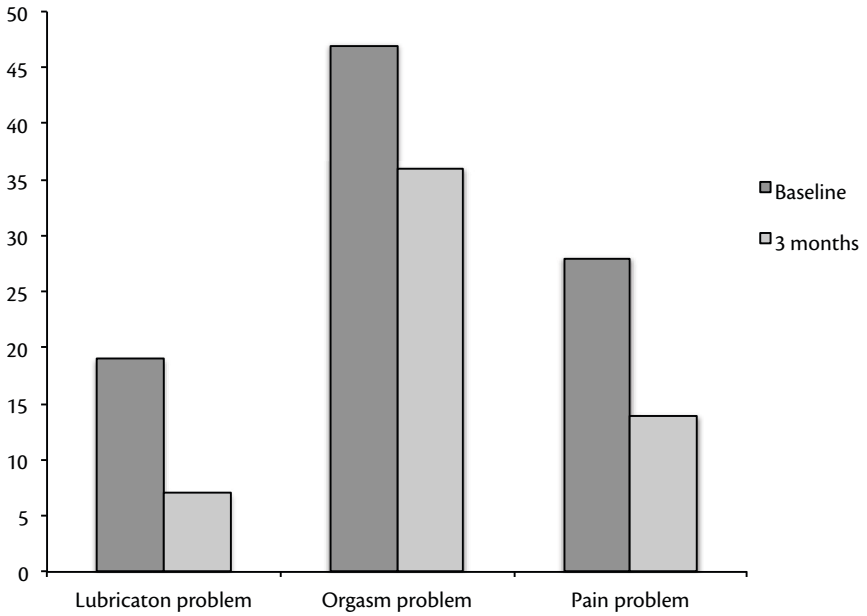

Figure 1. Percentage of women with sexual problems

Symptom Checklist 90

At baseline, the total SCL-90 score was 133 ± 41 SD. Three months after UAE, this score showed a statistically significant decrease to 116 ± 31 SD (P<.0005). Concerning the subscale scores, there was a statistically significant reduction in the scores for agoraphobia, fear, somatic concerns, insufficiency of thought and action, distrust and interpersonal sensitivity, hostility, and for sleep disturbances (P<.005 for all of these subscales). Only the subscale depression did not statistically significantly change after UAE.

Symptom List

The symptoms reported by women at baseline were menorrhagia in 86%, urinary frequency in 67%, dysmenorrhea in 58%, back pain in 53%, abdominal pain in 45%, pelvic pressure in 42%, leg pain in 35%, constipation in 33%, and dyspareunia in 32%. The median number of symptoms women reported was five. At three months after UAE, the total number of symptoms had decreased in all women. Menorrhagia was improved in 91%, urinary frequency in 76%, dysmenorrhea in 77%, back pain in 75%, abdominal pain in 86%, pelvic pressure in 97%, leg pain in 73%, constipation in 75%, and dyspareunia in 79%.

Regression Analysis

Multiple regression was used to examine the relationship between the total sexual dysfunction score, total SCL-90 score and subscales, and clinical symptoms. We corrected for age, volume of the uterus and the dominant fibroid, and the total number of fibroids. At baseline, we found a statistically significant association (P=.001) between the total SCL-90 score and the total score on the sexual dysfunctions questionnaire. Women who scored higher on the SCL-90 (indicating a higher level of physical and emotional concerns) reported lower sexual well-being. Three months after UAE, the association between the two questionnaires was still statistically significant (P=.006). The total SCL-90 score at baseline was not related to the total sexual dysfunctions score after three months, indicating that the baseline level of emotional and somatic concerns does not predict the outcome in sexual functioning three months after UAE. When we divided the total SCL-90 score in subscales, we found no relation with sexual functioning between any of the subscales at baseline or three months after UAE.
The total number of symptoms at baseline and the symptom improvement percentages after three months were not associated with sexual functioning at baseline or at three months after UAE. The total SCL-90 score at baseline was statistically significantly (P<.0005) associated with the number of symptoms reported at baseline. The more symptoms women reported, the higher the total SCL-90 score, indicating a higher level of physical and emotional concerns. Three months after UAE, we found no association between the total number of symptoms at baseline or the percentage improvement of symptoms at three months and the total SCL-90 score. Age, the number of fibroids, and the volume of the dominant fibroid and the uterus were not found to predict scores on SCL-90 or the sexual dysfunction questionnaire at baseline or at three months after UAE.

Discussion

We determined the effects of UAE on sexual and psychological well-being and on clinical symptoms before and three months after UAE. We found a statistically significant improvement in sexual functioning, psychological well-being, and physical symptoms three months after UAE in women with symptomatic fibroids. We found a relation between sexual and psychological well-being. Better sexual well-being was associated with better psychological well-being.
Our findings concerning sexual functioning are comparable with the scarce literature available on this subject. Hehenkamp et al.[10] compared changes in sexuality between women undergoing hysterectomy or UAE in a randomized trial. After six months, they found a significant reduction in sexual discomfort in the UAE group as well as a significant improvement in sexual pleasure. The frequency of sexual activity also increased. Sexual well-being six months after UAE was reported as improved or the

same compared with baseline in most women. Smith et al.[11] also found a significant improvement in sexual functioning after UAE.

The improvement in sexual functioning we found in our study was small but statistically significant. We do not have an explanation for this minor improvement, but we do know that sexual well-being is influenced by many factors. The improvement might be due to a decrease in physical symptoms (i.e., menorrhagia, fatigue caused by anemia, and pain), but improvement in psychological factors (i.e., body-image, depression) is likely to be influential as well. There were also women who scored lower on the questionnaire concerning sexual dysfunctions, indicating more problems. Factors that also may influence sexual functioning in a negative way are life stress in general, stress in relation to the partner, bad general health, and financial worries. However, these factors are complex and unknown, so we chose not to correct for them. Therefore, it is difficult to determine whether a change in sexual functioning (either positive or negative) can completely be assigned to UAE. The change in sexual functioning might be more pronounced when corrections are made for these items.

One of the reasons why women opt for UAE instead of hysterectomy is because they are worried that hysterectomy might have a negative impact on their sexual well-being. Masters and Johnson[23] suggested that the uterus plays a role in the physiology of the vaginal orgasm, and thus hysterectomy might have a negative effect on orgasm by eliminating the uterine contribution. Also, after hysterectomy the local nerve supply and anatomical relations of the pelvic organs are considered disrupted. During UAE, there is a risk of unintended nontargeted embolization of cervicovaginal branches. This may lead to ischemia or local infarction of cervical and vaginal tissue. Innervation of this area is carried out by the uterovaginal plexus. Theoretically, as suggested in a case report by Lai et al.[24], embolization of the cervicovaginal branches could lead to an alteration of perceived sensations from the pelvic organs, causing impairment in achieving orgasm, pain, and less lubrication. However, there is no evidence to support this theory.

Although there were significant reductions in problems with lubrication, orgasm, and pain, even after UAE the percentages were still quite high, with 7% of women having a problem with lubrication, 36% with orgasm, and 14% with pain. This is in contrast with the percentages that Roovers et al.[9] reported about sexual well-being after hysterectomy. They used the same questionnaire, but they did ask women whether the issue was considered as bothersome. At baseline, we found a much higher (50%) percentage of women with an orgasm problem compared with the Roovers study (30%). We chose to objectively assess the percentage of women with a problem by asking how often they experienced it; Roovers et al.[9] assessed it subjectively by asking to what extent a woman suffered from it.

Compared with baseline, there was an increase in frequency of sexual desire and sexual activity and satisfaction. Most of the other issues remained equal to baseline.

When we selected only patients who reported an increased frequency of sexual desire, the change in results was more obvious. Thus, women with an increase in sexual activity showed better results on the different issues. This might be due to the fact that for women who have a higher frequency of sexual activity it is easier to determine whether each issue improved.

We used the SCL-90 to determine emotional and physical well-being. Three months after UAE, there was a statistically significant improvement compared with baseline. The SCL-90 is a reliable questionnaire to determine psychological well being, but its length (90 items) is a disadvantage. Although the symptom list we used was a homemade questionnaire, it had good internal consistency.

A limitation of this study is that we did not include a control group. This might have been useful, especially to investigate the changes in sexual and psychological well-being in a healthy population and to compare them with a symptomatic population. Another limitation was the lack of some general characteristics among our study population, such as social status, marital status, general health, and financial worries, as these might influence psychological and sexual well-being.

We conclude that sexual and psychological well-being and clinical symptoms all statistically significantly improved three months after UAE in women with symptomatic uterine fibroids. Furthermore, there was a statistically significant relation between sexual and psychological well-being. Although in theory UAE might have a detrimental effect on sexual well-being, we did not find it in this study.

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Part 2

Volumetric magnetic resonance-guided high intensity focused ultrasound for uterine fibroids:

First clinical results and future technical developments

Chapter 5

Volumetric feedback ablation of uterine fibroids using magnetic resonance-guided high intensity focused ultrasound therapy

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Abstract

Objective

The purpose of this prospective multicenter study was to assess the safety and technical feasibility of volumetric Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU) ablation for treatment of patients with symptomatic uterine fibroids.

Materials and methods

Thirty-three patients with 36 fibroids were treated with volumetric MR-HIFU ablation. Treatment capability and technical feasibility were assessed by comparison of the Non-Perfused Volumes (NPVs) with MR thermal dose predicted treatment volumes. Safety was determined by evaluation of complications or adverse events and unintended lesions. Secondary endpoints were pain and discomfort scores, recovery time and length of hospital stay.

Results

The mean NPV calculated as a percentage of the total fibroid volume was 21.7%. Correlation between the predicted treatment volumes and NPVs was found to be very strong, with a correlation coefficient *r* of 0.87. All patients tolerated the treatment well and were treated on an outpatient basis. No serious adverse events were reported and recovery time to normal activities was 2.3 ± 1.8 days.

Conclusion

This prospective multicenter study proved that volumetric MR-HIFU is safe and technically feasible for the treatment of symptomatic uterine fibroids.

Introduction

Uterine fibroids are common benign tumors in women, with a prevalence ranging from 25% to 77%[1, 2]. Fibroids can cause menorrhagia, pelvic pain, bulk-related symptoms and infertility, resulting in a reduced quality of life. There are a variety of therapies available to achieve symptom relief, including hysterectomy, myomectomy, uterine artery embolization and medical therapy[1–5].

Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU) is a new, non-invasive treatment technique for uterine fibroids, where tissue is thermally ablated by absorption of acoustic energy delivered into the target tissue using high intensity focused ultrasound[6]. Magnetic Resonance Imaging (MRI) is used for planning and real-time monitoring of the treatment. A number of studies have shown the clinical effectiveness of MR-HIFU for fibroid treatment[7–13].

The traditional approach for MR-HIFU is performed by iterative sonication of a single focal point, with each sonication followed by a cooling period (point-by-point ablation technique)[6, 14]. However, with this approach a relatively large portion of the delivered energy is lost via diffusion of heat out of the small-targeted region, and long treatment times are required. Based on recent animal studies, a novel volumetric ablation technique of temporally switching the position of a single focal spot along outward-moving concentric circles, has been proposed to provide a significant improvement in both treatment efficacy and ablation homogeneity[15]. Volumetric heating allows ablation of larger volumes, with diameter of treatment cells up to 16 mm, and potentially reduces the treatment time. The purpose of this clinical trial was to assess the safety and technical feasibility of volumetric MR-HIFU ablation for treatment of patients with symptomatic uterine fibroids.

Materials and Methods

This multi-centre prospective study was conducted at four sites located in France, Korea, Germany, and The Netherlands. The trial (NCT00897897) was approved by the hospitals' ethical committees and country-specific regulatory bodies before trial initiation. All patients gave written informed consent for inclusion.

Included were pre- or peri-menopausal women with symptomatic uterine fibroids, 18–59 years of age, uterine size smaller than 24 weeks of pregnancy, dominant fibroid size of ≥3 cm and ≤12 cm, transformed Symptom Severity Score (SSS) of ≥40 points on the Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QoL), and a normal cervical smear. Exclusion criteria were (desire for future) pregnancy, general MR imaging contraindications, other pelvic diseases, and extensive scarring of the lower abdominal wall because of the increased risk of pain or skin burns caused by such scars. Screening MR images of the pelvis were acquired in prone position (1.5 Tesla Achieva, Philips Healthcare, Best, The Netherlands) using a receive-only torso XL

coil. This included T2-weighted imaging in three orthogonal planes, and T1-weighted imaging before and after intravenous administration of a gadolinium-based contrast agent, Gadopentetate Dimeglumine (Magnevist; Schering AG, Berlin, Germany, 0.1 mmol per kg body weight). MR images were used to determine the number of fibroids, location, size, treatment accessibility, contrast enhancement and presence of other pelvic diseases.

The day before treatment patients had to complete the UFS-QoL questionnaire assessing symptoms and quality of life[16] and depilated the skin of the lower abdomen. Patients arrived in the clinic in a fasting state. A Foley catheter was inserted to control bladder volume, and an intravenous catheter was used to allow administering of contrast agent and intravenous sedation with fentanyl citrate. Rectal body temperature was recorded and added to the temperature variation maps inherent to PRF thermometry to obtain absolute temperatures as is necessary for treatment. Pain and discomfort scores were recorded before start of treatment. Pain was assessed on a scale from 0 to 10 according to the Visual Analogue Scale, where 0 stands for 'no pain' and 10 for 'worst pain imaginable'[19]. Discomfort was scored on a scale from 0 to 3: "none" (0), "mild" (1), "moderate" (2), and "severe" (3).

The patient was positioned on the HIFU tabletop in prone position, with the fibroid placed above the transducer. A gel pad and a mixture of degassed water and ultrasound gel were used to optimize acoustic coupling between the system and the patient. The patient was given a stop button to allow her to abort sonication if experiencing pain or discomfort. Treatment planning was performed based on 3D T2-weighted images of which the system automatically performed Multiplanar Reconstructions (MPRs) displaying three orthogonal views (sagittal, transversal and coronal) simultaneously to facilitate planning. Treatments were performed with the Sonalleve MR-HIFU system (Philips Healthcare, Vantaa, Finland), integrated into a 1.5 Tesla MR imaging system (*Figure 1*). Ablation was performed with a volumetric technique using nominal frequencies of 1.2 or 1.45 MHz[15]. During sonication, the transducer applied ultrasound energy in a continuous manner in a series of concentric circular trajectories of increasing size. The differently sized volumes that the user may choose to be ablated per sonication, which is also shown as a graphical object by the system, are called treatment cells. These treatment cells with nominal diameters of 4, 8, 12 or 16 mm (and resulting treatment volumes of 0.1, 0.6, 2.3, and 5.4 mL, respectively) were planned within the target treatment area (*Figure 2*).

The heating produced by these volumetric sonications was measured simultaneously with sonication using Proton Resonance Frequency (PRF) shift- based MR thermometry[17]. Temperature imaging was performed in 6 slices (3 target region coronal slices perpendicular to the beam path; 1 sagittal slice capturing the heating within the beam path; 1 near-field slice monitoring for excessive heating of the skin and fat-layer; 1 far-field slice monitoring for excessive heating at the posterior wall of

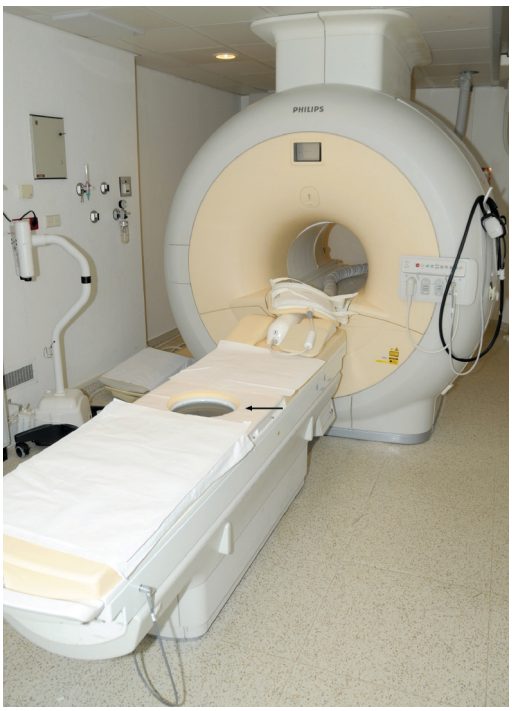

Figure 1. The Sonalleve MR-HIFU system consists of a 1.5 T clinical MRI scanner and a 256-element focused ultrasound transducer integrated in the treatment tabletop.

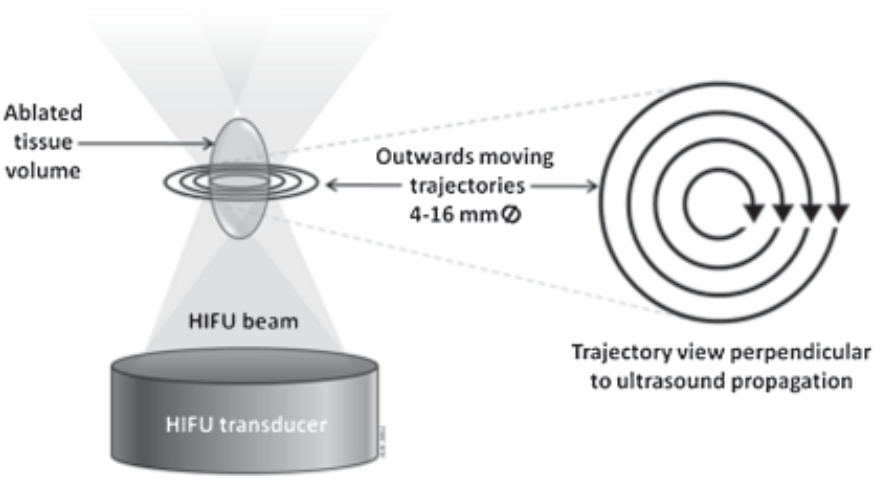

Figure 2. Schematic presentation of the volumetric ablation trajectory. The electrically steered acoustic focus is moved along concentric circular sub-trajectories on a plane perpendicular to the HIFU beam producing an ellipsoidal thermal volume (diameter = 4, 8, 12 or 16 mm).

the fibroid) updated every 3 s using gradient-echo multi-shot echo planar imaging. The system provided the option of using the online acquired temperature information for automatically controlling the sonication using a thermal feedback method[18], which stops the sonication when the measured thermal ablation and temperature profile match with that intended for the chosen treatment cell.

Immediately post-treatment, T1-weighted MR images were acquired before and after contrast administration to visualize the treatment result, i.e. the Non-Perfused Volume (NPV). Following this, the patients were taken to the recovery room and monitored before being discharged. Data on pain, discomfort, and adverse events were collected. Phone interviews addressing pain and recovery were performed 24, 48, and 72 h after treatment, and also at one and two weeks post-treatment. MR imaging was scheduled 1 month after treatment. Quality of life was assessed 1 month post-treatment using the UFS-QoL[16]. Adverse Events (AEs) were recorded and classified according to the Society of Interventional Radiology (SIR) classification[20].

Technical feasibility was assessed by comparison of the NPVs with MR thermal dose predicted treatment volumes. Volume measurements of fibroids and NPVs were performed based on voxel summation. The volume of interest was manually segmented with contours on each relevant image slice. The number of voxels within each contour was calculated and the sum of voxels multiplied by the voxel volume to compute the total volume. The NPV was also calculated as a percentage of the fibroid volume (NPV ratio)[21]. Safety was determined by evaluation of complications or AEs and unintended lesions. Pain and discomfort scores, length of hospital stay, symptom improvement and quality of life, were assessed as well.

Statistical analysis was performed using the SAS® statistical package (SAS; SAS Institute, Cary, NC, USA). Descriptive statistics were used to determine the distribution of baseline data and outcome measures. Paired t-tests were used for statistical comparison between baseline and 30 days follow-up for mean pain and quality of life scores; p-values <0.05 were considered statistically significant.

Results

Thirty-three patients were enrolled in this study, with 38 treatable fibroids. Patient demographics are presented in *Table 1*. Three women had more than one fibroid treated. Two patients were excluded from analyses: one patient underwent uterine artery embolization one week after MR-HIFU treatment, because of unsatisfactory treatment results due to insufficient heating of the fibroid, and the other patient underwent surgical fibroid removal in another hospital for unknown reasons. *Figure 3* provides an overview of the fibroid symptoms in the 31 patients that were finally included, the most commonly reported symptoms being excessive menstrual bleeding and pain.

Technical feasibility was assessed by comparison of the actual MR-measured NPVs with predicted treatment volumes based on MR thermal dose maps. The mean NPV

calculated as a percentage of the total fibroid volume was 21.7% (range 0–66%), whereas the mean predicted treatment volume was 34.5 mL ± 30.1. *Figure 4a* displays the predicted treatment volume as a function of the NPV for each fibroid. The correlation coefficient *r* was 0.87, representing a very strong correlation. *Figure 4b* displays the corresponding Bland-Altman plot of thermal dose predicted treatment volume and NPV showing the absolute difference with mean ± 1.96 SD acceptance limits.

No serious adverse events occurred. A total of 85 AEs were reported in 31 patients, with a mean of 2.6 AEs per patient (*Table 2*). None of the AEs were major according to the SIR classification[20]. AEs typically resolved within 3 days post-treatment, however two patients reported ongoing AEs at 30 days follow-up (one patient with sciatic

Table 1. Patients (n=33) baseline characteristics

Age (years)[a]	44.8 ± 5.2
Weight (kg)[a]	61.5 ± 10.1
Height (cm)[a]	163.8 ± 6.2
Race (%)[b]	
Caucasian	51.5 (17/33)
Asian	30.3 (10/33)
African American	3.0 (1/33)
South American	6.1 (2/33)
Other	9.1 (3/33)
Inclusions per centre (%)[b]	
France	48.5 (16/33)
Korea	30.3 (10/33)
Germany	12.1 (4/33)
The Netherlands	9.1 (3/33)

[a] Data are means ± standard deviations

[b] Numbers used to calculate percentages are in parentheses

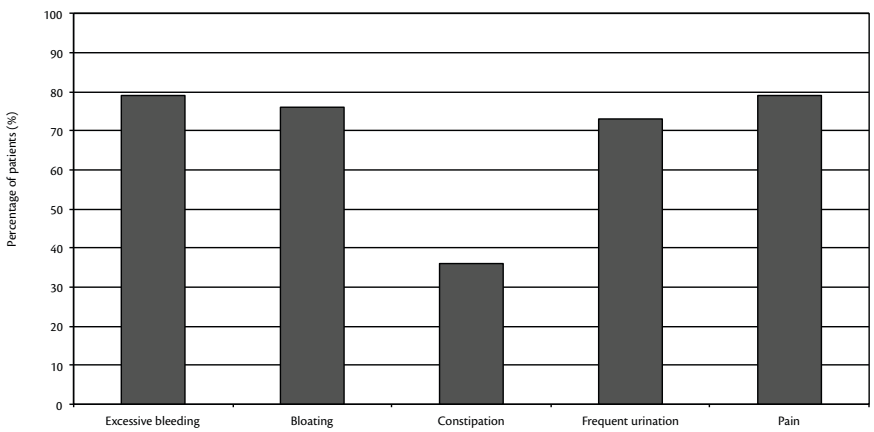

Figure 3. Distribution of fibroid symptoms. The average number of symptoms per patient was 3.2 out of 5.

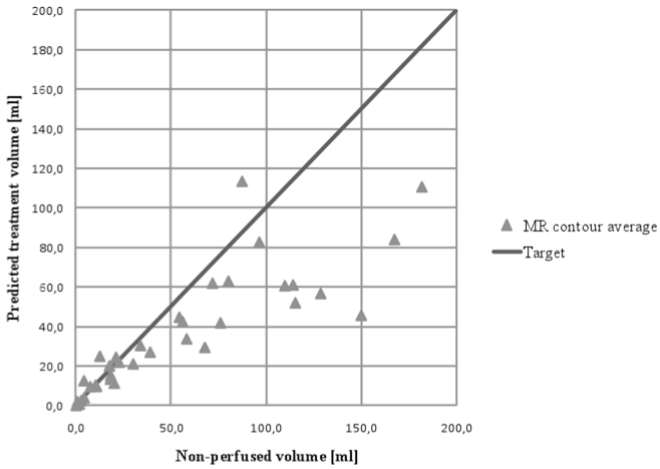

Figure 4a. Thermal dose predicted treatment volume as a function of non-perfused volume. The diagonal line shows the target performance.

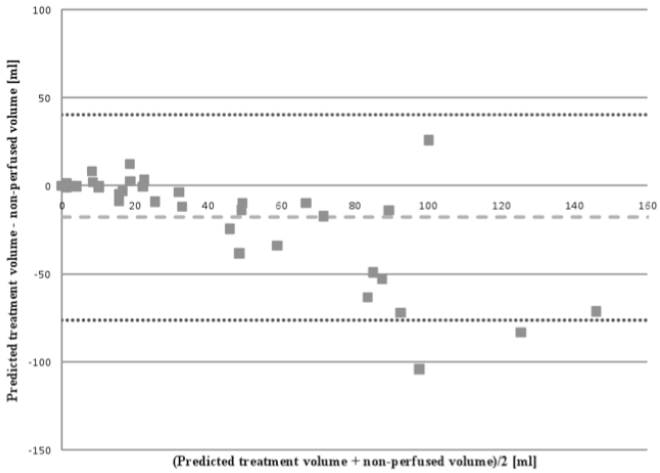

Figure 4b. Bland Altman plot of thermal dose predicted treatment volume and non-perfused volume showing absolute difference with mean ± 1.96 SD acceptance limits.

nerve pain, spontaneously resolved after 139 days, and one patient with leg pain, resolved after 93 days post-treatment). *Figure 5* shows pain and discomfort scores during follow-up. Mean baseline reported pain score was 1.8 ± 2.6, with an increase in pain score to 2.4 ± 2.6, 24 h post-treatment, however this increase was not significant ($p = 0.343$). At the end of follow-up, the mean pain score was significantly reduced to 0.1 ± 0.5 ($p = 0.002$). Mean baseline discomfort was 0.8 ± 0.8, decreasing to 0.18 ± 0.50 at hospital discharge. Mean length of hospital stay was 9.3 h ± 3.3, with a maximum of 17.0 h. Time needed to return to work and normal activities ranged from 1–19 days (mean 4.4 ± 4.4) and 1–7 days (mean 2.3 ± 1.8) respectively.

Table 2. Adverse events reported in patients treated with MR-HIFU

Adverse events (AEs)	N = 31
Pain	
Abdominal pain	17 (55%)
Positional related pain	10 (32%)
Sonication related pain	7 (23%)
Sciatic nerve pain	1 (3%)
Gynecologic	
Abdominal discomfort	13 (42%)
Urinary pain or difficulty	7 (23%)
Vaginal bleeding post-treatment	3 (10%)
Hematuria	1 (3%)
Vaginal irritation	1 (3%)
General	
Fatigue	6 (19%)
Headache	4 (13%)
Fever > 38° Celsius	3 (10%)
Nausea	3 (10%)
Skin irritation	3 (10%)
Other	6 (19%)
Total	85

Data are number of patients, with percentages in parentheses.
One patient may have experienced more than one AE.

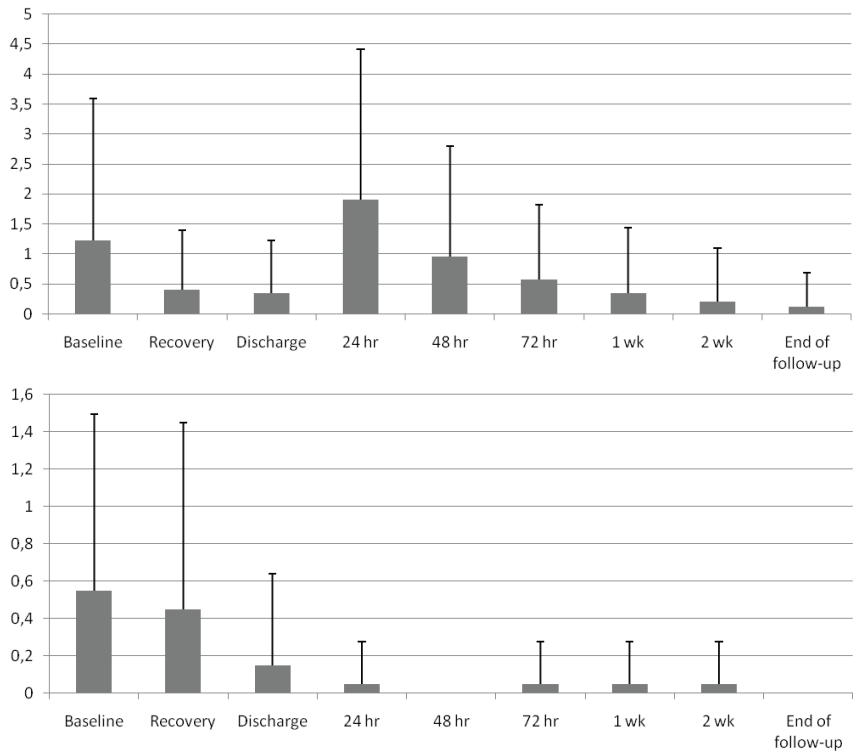

Figure 5. Mean pain (**a**, range 0-10) and discomfort (**b**, range 0-3) scores (including error bars) at consecutive follow-up points.

Discussion

Our results showed that volumetric ablation of uterine fibroids with the Sonalleve MR-HIFU system is both safe and technically feasible. No serious adverse events occurred, and concordance between the predicted treatment volume and the NPV was found in 33 out of 36 treated fibroids (concordance rate of 92%).

In this study we used the volumetric MR-HIFU Sonalleve system for treatment of patients with symptomatic fibroids. Previous studies used the ExAblate 2000 (InSightec, Haifa, Israel) HIFU system, which uses a different ablation strategy[6]. The main advantage of the volumetric ablation technique is that it allows for a controlled heating of a larger volume per sonication by rapid spiral wise movement of the focal spot. Additionally thermal ablation is controlled utilizing feedback control[15]. This could potentially reduce treatment time for a given treatment volume in future studies. The aim of this feasibility study was to assess safety and technical feasibility. The technical performance rate we found for the Sonalleve system is at least equal to those reported in the literature for the ExAblate 2000. In our study, the ratio between NPV and the predicted treatment volume is 1.4 ±0.6, while McDannold reported a ratio of 1.9 for the ExAblate 2000 system between the non-perfused area and the predicted treatment area in the central coronal plane of the treatment[21]. The match between treated volumes (NPVs) and predicted treatment volumes in our study was very good with a 92% concordance rate that may in part be attributed to the homogeneous ablation with sharp thermal dose borders produced by the utilized volumetric ablation technique. The findings of McDannold are also supported by two earlier feasibility studies from Stewart et al. and Tempany et al. that showed similar results[6, 14, 21, 23].

Also the safety profile of the Sonalleve system is similar to what has been reported in the literature for the ExAblate 2000. Minor adverse events were reported such as abdominal tenderness, nausea, or first-degree skin burns. Treatments were performed on an outpatient basis[6, 14, 22]. Since this feasibility study focused on safety of a novel MR-HIFU system for treatment of patients with uterine fibroids, a potential limitation is its small population included in the study and the relatively short reported patient follow-up of one month. Longer follow-up will be needed to report the clinical efficacy of the treatment as quantified by improvement of symptoms and an increased quality of life already of patients treated. These outcomes will be reported in a separate article. Another limitation of this study was that only a maximum of 50% ablation of the fibroid volume was allowed. Recent studies have shown that treatment success is largely dependent on the ablation volume and the percentage of ablated fibroid tissue, with increased fibroid shrinkage, improved symptom relief, and fewer additional treatments being obtained when larger volumes of the fibroid are ablated[7, 8, 24, 25]. Fibroid shrinkage is especially relevant for women suffering from bulk-related symptoms. MR-HIFU treatment should therefore be focused on treating as much fibroid tissue as possible.

Reducing safety margins to sensitive structures such as the bowel and the uterine serosa is inevitable to achieve this, and has already proven to be safe[26, 27].

In conclusion, this study proved that volumetric MR-HIFU with the Sonalleve system is safe and technically feasible for the treatment of symptomatic uterine fibroids. Future studies will be aimed at treatment of more patients with larger ablation volumes. Longer follow-up periods will be required to provide information about clinical outcome.

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Chapter 6

Targeted vessel ablation for more efficient magnetic resonance-guided high intensity focused ultrasound ablation of uterine fibroids

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Abstract

Objective

To report the first clinical experience with targeted vessel ablation during magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) treatment of symptomatic uterine fibroids.

Materials and methods

Pretreatment T1-weighted contrast-enhanced magnetic resonance angiography was used to create a detailed map of the uterine arteries and feeding branches to the fibroids. A three-dimensional (3D) overlay of the magnetic resonance angiography images was registered on 3D T2-weighted pretreatment imaging data. Treatment was focused primarily on locations where supplying vessels entered the fibroid. Patients were followed six months after treatment with a questionnaire to assess symptoms and quality of life (Uterine Fibroid Symptom and Quality of Life) and magnetic resonance imaging to quantify shrinkage of fibroid volumes.

Results

In two patients, three fibroids were treated with targeted vessel ablation during MR-HIFU. The treatments resulted in almost total fibroid devascularization with nonperfused volume to total fibroid volume ratios of 84, 68, and 86%, respectively, of treated fibroids. The predicted ablated volumes during MR-HIFU in patients 1 and 2 were 45, 40, and 82 ml, respectively, while the nonperfused volumes determined immediately after treatment were 195, 92, and 190 ml respectively, which is 4.3 (patient 1) and 2.3 (patient 2) times higher than expected based on the thermal dose distribution. Fibroid-related symptoms reduced after treatment, and quality of life improved. Fibroid volume reduction ranged 31–59% at six months after treatment.

Conclusion

Targeted vessel ablation during MR-HIFU allowed nearly complete fibroid ablation in both patients. This technique may enhance the use of MR-HIFU for fibroid treatment in clinical practice.

Introduction

Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) is a noninvasive outpatient treatment option for symptomatic uterine fibroids[1–3]. A limitation of MR-HIFU in clinical practice is its long treatment time. Fibroids are generally large tumors, and a single sonication yields a treatment volume of only a few milliliters. Cooling time between subsequent sonications also extends treatment duration[4]. Another limitation is that, in most patients, only part of the fibroid volume can be treated with MR-HIFU as a result of treatment safety margins. In clinical studies, ablated tissue, defined as nonperfused volume (NPV)—that is, the non-enhancing area on contrast-enhanced T1-weighted magnetic resonance images (MRI) acquired immediately after treatment—ranged from 2–100% of the fibroid volume, with a mean of 43%[4–16].

However, because the ablated volume correlates linearly with relief of clinical symptoms, treatment should be aimed at ablating as much fibroid tissue as possible within acceptable treatment times[7, 8, 12].

We present a novel method of MR-HIFU ablation in two patients with uterine fibroids, which allowed ablation of larger volumes. The method is called targeted vessel ablation because MR-HIFU is intentionally aimed at the uterine artery supplying the fibroid.

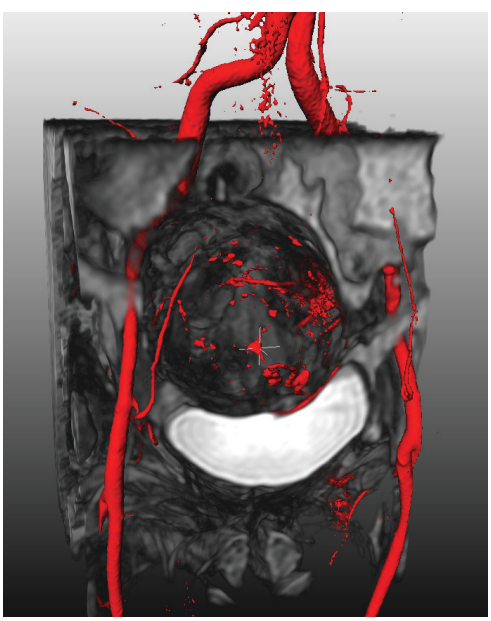

Figure 1. Reconstruction of T2-weighted MR image fused with MR angiography images, showing the blood vessels in red

Materials and Methods

We treated two patients who both participated in a prospective clinical study investigating the efficacy of volumetric MR-HIFU treatment for uterine fibroids in our hospital. The ethics committee approved this study, and informed consent was obtained. Postmenopausal status and desire for pregnancy were exclusion criteria, as were extensive scarring of the lower abdomen, MRI contraindications, and major comorbidities. Diagnostic contrast-enhanced MRI with a 1.5 T magnetic resonance (MR) scanner (Achieva; Philips Healthcare, Best, The Netherlands) was performed with the patient in prone position to evaluate patient suitability for MR-HIFU. Interposition of bowel between fibroid and abdominal wall, hyper intense signal of the fibroid on T2-weighted MRI, total number of fibroids ≥10, and a fibroid size of >10 cm in diameter were other exclusion criteria[4]. MRI included T2-weighted imaging in three orthogonal planes, and T1-weighted imaging before and after intravenous administration of a gadolinium-based contrast agent (Gadovist, Bayer Schering Pharma, Berlin, Germany; 0.1 mmol/kg). Additionally, MR angiography (MRA) with double-dose contrast agent was performed (TR 4.7 ms; TE 1.2 ms; flip angle 40°; matrix 256 x 128; FOV 430 x 430; slice thickness 15.0 mm; NSA 1) to assess blood supply toward the fibroid.

MRA resulted in a detailed map of the uterine arteries and feeding segmental branches of the fibroid. A three-dimensional reconstruction of the MRA images was made and projected on T2-weighted screening images in three orthogonal planes. Vessels were projected in color to facilitate visualization (*Figure 1*). Location of the supplying blood vessels and possibilities for safe, targeted vessel ablation were evaluated. Imaging processing was performed by MeVisLab software (MeVis Medical Solutions, Bremen, DE).

Treatment was performed with the Sonalleve MR-HIFU system (Philips Healthcare, Helsinki, Finland) integrated with a 1.5 T MRI scanner. The Sonalleve MR-HIFU system uses volumetric ablation with automated feedback for real-time tissue temperature mapping in multiple planes, steering of the focal point via real-time feedback, and temperature control delivering an optimal dose to the target location[17]. Patients were consciously sedated during treatment. Treatment was focused primarily on the area where vessels entered the fibroid. Treatment cells with a diameter of 8 or 12 mm were centrally placed overlapping in and around this area. The initial power level was 120 W, adjusted to a higher level when insufficient buildup of heat was visualized on the temperature map. Apart from the targeted vessel ablation, we also performed MR-HIFU ablation of the fibroid tissue with respect for the treatment safety margins.

Directly after treatment, contrast-enhanced (CE) MRI was performed to visualize the treatment result. We used these images to calculate the fibroid volume, NPV, and the applied predicted thermal dose volume. The NPV is defined as the non-enhancing area within the fibroid on CE T1-weighted images, corresponding to the devascularized area. Fibroid volumes and NPVs were calculated by a sum-of-slice method. Regions

of interest were outlined in each sequential slice with a MR workstation (ViewForum R5.1V1L2 SP3, Philips Medical Systems, The Netherlands), and the volume of each segment was calculated and summed for all slices. The NPV was also calculated as a percentage of the fibroid volume to indicate the ablated fibroid percentage. The predicted thermal dose volume (PTV) applied was calculated by the MR-HIFU system and defined as the volume receiving a thermal dose of 240 equivalent minutes at 43°C (threshold value for thermal ablation)[18]. This is the actual treated volume as planned during the MR-HIFU treatment. Dividing of the NPV by the PTV resulted in the ratio between these two values.

Patients were followed for six months. One, three and six months after treatment, patients received questionnaires. Follow-up CE MRI was performed three and six months after treatment.

Treatment effect was quantified by fibroid shrinkage 3 and 6 months after treatment and improvement in symptoms and quality of life. Symptom and quality-of-life scores were assessed at baseline, and one, three, and six months after treatment with the Uterine Fibroid Symptom and Quality of Life questionnaire[19].

Results

Two patients were treated, aged 37 and 48 years. Presenting symptoms included menorrhagia, bloating, pelvic pain, and frequent urination. *Table 1* lists baseline symptom and health-related quality-of-life scores. Treatment in patient 1 was aimed on the dominant fibroid (*Figures 2A, B*) with a volume of 232 ml (7.8 x 8.1 x 6.6 cm). Patient 2 had two large intramural fibroids (designated A and B) with volumes of 135 ml (6.4 x 6.0 x 6.4 cm) and 222 ml (5.8 x 7.1 x 8.3 cm).

Table 1. Baseline symptom and health related quality-of-life scores

	Patient 1 (Age 37 years)	**Patient 2 (Age 48 years)**	
Fibroid volume (ml)		Fibroid A	Fibroid B
Baseline	232 ml	135 ml	222 ml
3 months post-treatment (volume change)	173 ml (-25%)	85 ml (-37%)	132 ml (-41%)
6 months post-treatment (volume change)	161 ml (-31%)	56 ml (-59%)	115 ml (-48%)
Transformed Symptom Severity Score[a]			
Baseline	31.3	53.1	
3 months after treatment	9.4	34.4	
6 months after treatment	9.4	12.5	
Health related quality of life score[b]			
Baseline	88.8	58.6	
3 months after treatment	93.1	84.5	
6 months after treatment	100.0	98.3	

[a] Transformed Symptom Severity Score: range 0-100 points, higher score indicating more symptoms

[b] Health Related Quality of Life score: range 0-100 points, higher score indicating better quality of life

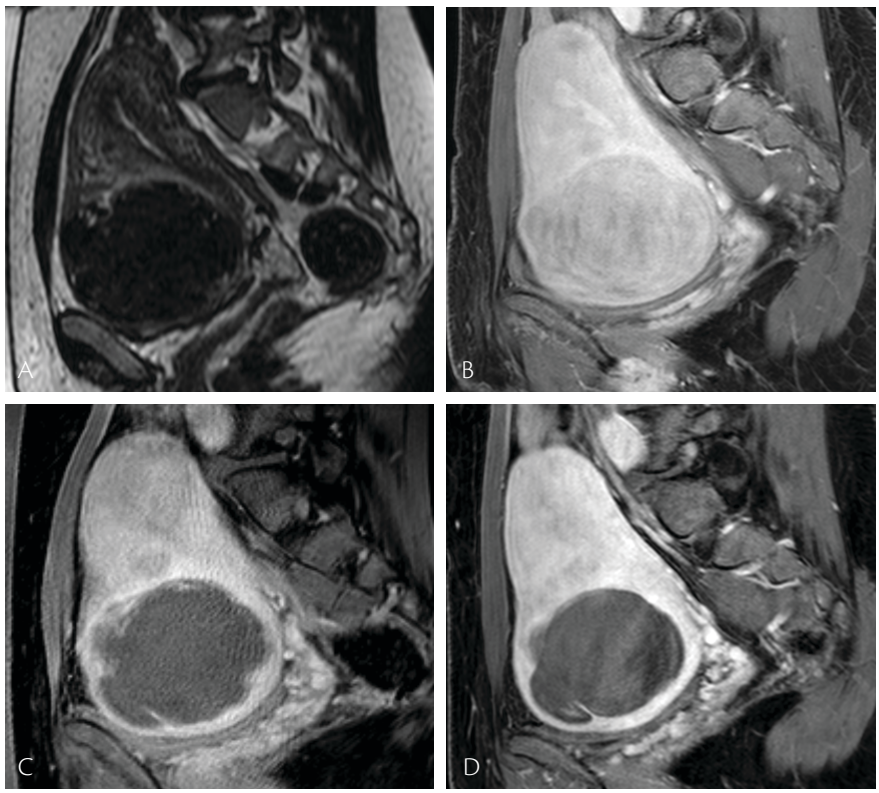

Figure 2. Patient 1. **A** Pretreatment sagittal T2-weighted image showing the fibroid selected for treatment. **B** Pretreatment CE T1-weighted image showing vascularization of all fibroids. **C** Post-treatment CE T1-weighted image showing almost complete devascularization of the large fibroid. **D** CE T1-weighted image acquired 6 months after treatment

In patient 1, targeted vessel ablation was performed using three 12-mm (dimensions 12 x 30 x 30 mm) and two 8-mm (dimensions 8 x 20 x 20 mm) treatment cells (*Figure 3*). The required ultrasound power to achieve sufficient heating in this area was higher than in other areas of the fibroid (150–180 W instead of 120 W). The PTV calculated by the MR-HIFU system was 45 ml; however, the NPV in the target fibroid was 195 ml (*Figure 2C*)—4.3 times larger than expected based on the PTV. The NPV as a percentage of the fibroid volume was 84% (195/232 ml). Additionally, four small fibroids, which were also present, were also completely devascularized, although they were not sonicated.

In patient 2, targeted vessel ablation was performed with two 8-mm treatment cells (power 100–120 W). The PTVs were 40 ml (fibroid A) and 82 ml (fibroid B). The NPVs in the targeted fibroids were 92 ml (fibroid A) and 190 ml (fibroid B); 2.3 (92/40 ml),

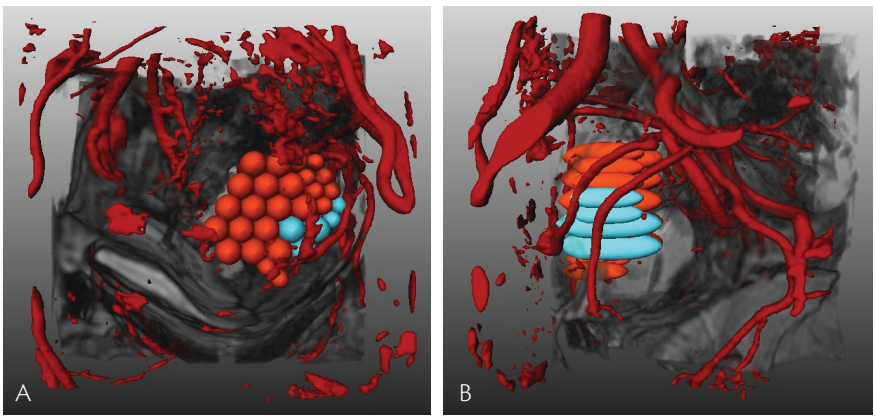

Figure 3. Patient 2. Post-treatment sagittal (**A**) and coronal (**B**) reconstruction of sonicated treatment cells on T2-weighted images fused with MR angiography. Orange cells were easy to heat; blue cells did not heat very well. The blue cells were located on a large supplying vessel

respectively, which was 2.3 (190/82 ml) larger than expected. The NPVs as percentage of fibroid volume were 68% (92/135 ml) and 86% (190/222 ml).

Total treatment time (from first to last sonication) for these patients was 132 and 213 min. Total time in the MR room was approximately 60 min longer. Sonication time (actual time that sonications were executed) was 22 and 37 min.

Both patients experienced mild to severe abdominal pain the first days after treatment, which resolved with over-the-counter pain medication. No skin burns or serious adverse events occurred. Three and six months after treatment, follow- up MRI was performed (*Figure 2D*). The volume of the treated fibroids did shrink during follow-up, and both patients experienced a reduction in symptoms and an increase in quality of life over the six-month follow-up period (*Table 1*).

Discussion

We presented a novel method for targeted vessel ablation during MR-HIFU treatment of uterine fibroids, resulting in nearly complete fibroid necrosis in two patients. The percentage of devascularized tissue was, respectively, 4.3, 2.3, and 2.3 times larger than expected based on predicted thermal dose volumes. Post-processing of the sonicated treatment cells with MRA images confirmed ablation of segmental branches of the uterine arteries. Both women reported a clinically relevant improvement in symptoms three and six months after treatment.

The hypothesis of targeted vessel ablation was developed after observations that the NPV on post-treatment CE T1-weighted MR images was larger than expected based on the actual ablated volume[20, 21]. For the MR-HIFU system used in this study, we found a

ratio of 1.4 ± 0.6 during conventional fibroid treatments[4]. De Melo et al. [22] demonstrated a similar case of complete fibroid necrosis after limited MR-HIFU treatment, resulting in 98% volume decrease twelve months after treatment.

The exact pathophysiologic mechanism that occurs during vessel ablation is still unclear. Several theories have been proposed. Hynynen et al.[23] proved that noninvasive vessel occlusion could be achieved using MR-HIFU. Wu et al.[24] showed that MR-HIFU can induce tumor vessel necrosis in solid malignancies, which may be a promising strategy for future treatments. The possible mechanism is that the thermal stimulus causes vessel constriction, resulting in decreased cooling by blood and thus increased temperature, inducing thermal coagulation of the vessel wall. Detailed visualization of fibroid-supplying blood vessels is necessary to perform targeted vessel ablation. We used contrast-enhanced MR angiography; however, this requires the usage of a contrast agent. Contrast cannot be administered immediately before MR-HIFU treatment because the possible side effects of heating of gadolinium-based contrast are unclear. Therefore, we planned targeted vessel ablation on screening contrast-enhanced MR angiography images acquired several weeks before treatment. A limitation of this approach is that patient position on the treatment day is not equal with screening. A solution would be to use a non-contrast-based method to visualize the supplying blood vessels so it can be used before treatment. Integration of image processing for treatment planning of targeted vessel ablation in the workflow is essential to plan vessel ablation on the treatment day, instead of using screening images. The next step for research is investigating how to do this and implementing it into the workflow. Unfortunately, targeted vessel ablation is not possible in all candidates. Treatment must be safe, and generally used safety margins to sensitive structures have to be taken into account. Moreover, areas containing vessels might be difficult to heat because of the heat sink effect, and thus do not receive a sufficient dose for necrosis[25].

Ablated fibroid volume correlates linearly with relief of clinical symptoms after MR-HIFU[7,8,12]. For uterine fibroid embolization, which is another minimal invasive treatment option for uterine fibroids, these results are quite similar. Kroencke et al. [26] studied the effect of partial versus complete infarction after uterine artery embolization on fibroid-related symptoms and the rate of additional interventions. They found that women with >90% fibroid infarction showed significantly better symptom control and fewer additional treatments than women with a lower infarction rate. This study emphasizes the relevance of focusing on treating as much fibroid tissue as possible with MR-HIFU.

We conclude that targeted vessel ablation is a promising new method to enhance treatment results, and MR-HIFU ablation of uterine fibroids is efficacious in clinical practice.

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Chapter 7

Diffusion weighted MR imaging using different *b*-value combinations after volumetric MR-guided High Intensity Focused Ultrasound of uterine fibroids

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Abstract

Objective

The purpose of this study was to assess the value of diffusion weighted MR imaging (DWI) and apparent diffusion coefficient (ADC) mapping using different *b*-value combinations for the evaluation of treatment results after magnetic resonance imaging-guided high intensity focused ultrasound (MR-HIFU) ablation of uterine fibroids.

Materials and methods

Imaging data from fourteen patients from two different treatment centers with a total of seventeen symptomatic uterine fibroids treated with MR-HIFU ablation was analyzed. Pre-treatment and directly post-treatment images were obtained using T1-weighted contrast-enhanced (CE) imaging and DWI using *b*-values of 0, 200, 400, 600 and 800 s/mm^2, on a 1.5-T MR-HIFU system. ADC maps were constructed for quantitative analysis of ablation results. Regions of interest localized to non-perfused areas on post-treatment CE images and normal myometrium were drawn to identify treated regions inside the fibroids. ADC values were obtained from treated and non-treated uterine fibroid tissue. Four different combinations of *b*-values were used to calculate ADC maps: 1) using all *b*-values; 2) using the lowest two *b*-values emphasizing perfusion effects (0, 200 s/mm^2); 3) using the highest *b*-values emphasizing mainly diffusion effects (400, 600 and 800 s/mm^2); and 4) using lowest and highest *b*-values which is the most commonly used method in literature (0, 800 s/mm^2).

Results

The mean ADC in treated fibroid tissue decreased immediately post-treatment compared with pre-treatment values. Calculating the ADC using only the lowest two *b*-values (0 and 200 s/mm^2) was found to show significantly reduced ADC values in treated fibroid tissue compared with non-treated tissue. When higher *b*-values were used (400, 600 and 800 s/mm^2), an increase in ADC was found. Normal myometrium showed no change in ADC value after treatment.

Conclusion

We conclude that DWI and ADC mapping can be used for evaluation of treatment results after volumetric MR-HIFU of uterine fibroids. The significant decrease in the ADC of treated tissue seen with the lowest two *b*-values probably reflects the decreased perfusion in the treated region, whereas the significant increase in diffusivity observed with higher *b*-values can possibly be related to the direct thermal damage done to the tissue, resulting in damaged cell membranes. Low *b*-values result in the best agreement of lesion detection on ADC maps with the visualization of treated fibroid tissue in CE MRI scans.

Introduction

Uterine fibroids are common benign tumors affecting women of childbearing age, causing symptoms of heavy menstrual bleeding, pain, pressure, and subfertility[1]. Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU) is a completely non-invasive thermo-ablative treatment for uterine fibroids[2]. Focused ultrasound energy is used to induce tissue heating, resulting in coagulative necrosis and cell death. Magnetic resonance imaging (MRI) offers excellent anatomical resolution for treatment planning and monitoring, and has the possibility for real-time temperature mapping[3].

Immediately post-treatment, contrast-enhanced T1-weighted MR-imaging is used to assess the treatment result. Ablated tissue will appear as a non-enhancing region, referred to as non-perfused volume (NPV). In general, the NPV is larger than expected considering the truly ablated volume, likely due to destruction of blood vessels within the fibroid during treatment resulting in down-stream tissue necrosis[4, 5]. Therefore, peri-procedural visualization of the NPV would be relevant since this devascularized tissue does not require further ablation, resulting in an increase in treatment efficacy. Contrast-enhanced imaging peri-procedurally should be limited, given the possible side effects, the unknown safety profile of the agent after heating, and the fact that the acceptable dose of contrast agent is limited. A repeatable, non contrast-agent dependent method would therefore be preferred.

An imaging method that can possibly provide the required information during the treatment procedure without the use for a contrast agent is diffusion-weighted MR imaging (DWI). This technique can be used to show contrasts based on differences in the diffusivity of water molecules within the intra- and extracellular space, using strong additional gradient lobes in the MRI pulse sequence. The strength, duration and timing of the additional gradient lobes (expressed in the *b*-value in seconds/mm^2) determine the amount of diffusion weighting. It has been suggested that after thermal ablation with MR-HIFU, cytotoxic edema occurs resulting in decreased diffusive motion of water molecules in that area due to cell swelling[6]. DWI shows high signal intensity in such regions corresponding to a lower diffusion coefficient (D [mm^2/s]). However, other mechanisms causing motion of molecules also lead to contrast on DWI, for instance perfusion effects due to capillary flow. Therefore, it is preferred to refer to the measured diffusion coefficient (D) as the apparent diffusion coefficient (ADC) of water, which is an indicator of the average mobility of water molecules in each voxel of a certain tissue. By fitting a model for signal loss as a function of the diffusion coefficient to DWI signal intensities acquired at different *b*-values, ADC values can be calculated. At least two *b*-values are required to calculate the ADC. When low *b*-values are used, perfusion effects can be more strongly reflected in the ADC value, while diffusion effects without perfusion influences would mainly be visible on ADC maps calculated from DWI acquired at higher *b*-values[7].

DWI has already proven to be valuable in the differentiation of benign and malignant uterine tumors[8-11], and to assess different types of uterine fibroids[12, 13]. It was also used for the response assessment of uterine fibroids and myometrium after uterine artery embolization[14]. Jacobs et al. and Pilatou et al.[6, 15, 16] earlier demonstrated the effectiveness of DWI/ADC mapping for treatment monitoring after MR-HIFU treatment. However, both groups only used two different *b*-values to calculate the ADC: 0 and 1000 s/mm^2. The aim of our study was to assess the performance of DWI and ADC mapping using different *b*-value combinations for the evaluation of treatment results after volumetric MR-HIFU ablation of uterine fibroids. In particular, our aim was to investigate what combination of *b*-values allows the best differentiation of ablated fibroid tissue from untreated tissue.

Materials and Methods

Patients

Fourteen patients with a total number of seventeen treatable uterine fibroids who underwent volumetric MR-HIFU ablation were included in this prospective study. Patients were extracted from a clinical trial investigating safety and efficacy of a volumetric MR-HIFU system (Sonalleve, Philips Healthcare, Helsinki, Finland)[17], approved by the investigational review board of our institution. Written informed consent was obtained from all patients. In- and exclusion criteria for this study have been published earlier[17]. Patients underwent screening MRI on a 1.5 Tesla MR imaging system (Achieva; Philips Healthcare, Best, The Netherlands) to identify number, size, location, and accessibility for MR-HIFU of the fibroids. Screening MR imaging consisted of T2-weighted turbo spin echo (TSE) and T1-weighted contrast-enhanced (CE) imaging of the pelvis using intravenous gadoteric acid (Dotarem, Guerbet, Roissy, France, 0.1 mmol/kg). The most important scan parameters for the MRI sequences are listed in *Table 1*.

MR-HIFU treatment

Patients were prepared for MR-HIFU treatment and treated according to the study protocol published earlier[17]. Treatments were performed with an MR-HIFU system (Sonalleve, Philips Healthcare, Helsinki, Finland) allowing volumetric heating using a 256-element HIFU transducer, integrated into a clinical 1.5-Tesla MR imaging system (Achieva, Philips Healthcare, Best, The Netherlands)[18]. Patients were treated in prone position. Ablation was performed with a volumetric technique using frequencies of 1.2 or 1.45 MHz[17, 18], depending on required penetration depth.

The DWI series was a multi-slice spin echo-echo planar imaging (SE-EPI) sequence with five *b*-values: 0, 200, 400, 600, and 800 seconds/mm^2. DWI was acquired pre-treatment and immediately post-treatment before the intravenous administration of

contrast agent. T1-weighted CE-imaging was acquired 30 seconds after contrast agent injection. These images were used to assess the non-perfused volume (NPV). Scan parameters for the MRI sequences are shown in *Table 1*.

Table 1. Most important scan parameters for screening and treatment MRI

	T2w	**Post-contrast T1w**	**DWI**
Type of scan	TSE Turbo factor 31	3D TFE TFE factor 22	Multi-slice Single shot Spin Echo-EPI
TE/TR (ms)	100 / 3224	3.2 / 6.6	64 / 3049
Flip angle (deg)	90	10	90
Fat suppression	No	SPAIR	SPAIR
FOV (mm^3)	250 x 250 x 117	350 x 300 x 150	250 x 188 x 105
Acquired voxel (mm^3)	0.60x0.77x4.00	0.99x1.00x3.00	2.23x2.26x7.00
Reconstructed voxel (mm^3)	0.49x0.49x4.00	0.66x0.66x1.50	2.23x2.23x7.00
Scan duration (min:sec)	4:44	2:58	5:51

Image analysis

The DW images at different *b*-values were used for measurements of signal intensities within the fibroid. A circular region of interest (ROI) was placed in normal myometrium, treated and non-treated fibroid tissue on a slice of the $b = 0$ s/mm^2 diffusion weighted image (i.e. an image without actual diffusion weighting). Post-treatment T1-weighted CE-images were used to identify devascularized areas. Corresponding areas on DW images and ADC maps were determined and ROIs were placed inside these areas. ROIs were drawn to include most of the treated fibroid, while care was taken to stay away from the edges of the fibroid and the devascularized areas to reduce partial volume effects. ROI size depended on the size of the fibroid and of the non-perfused volume, so that a homogeneous part in the center of the fibroid was embedded (range ROI size fibroid 19-1112 pixels; range ROI size myometrium 14-54 pixels). The signal intensity was averaged over the ROI for each *b*-value to calculate the signal intensity S(*b*). ADC color maps were calculated by voxel-wise fitting of the following function to the data points: $S(b) = S_0 \cdot e^{-b \cdot ADC}$, in which S_0 is the signal without diffusion weighting obtained for $b = 0$ s/mm^2. Four different combinations of *b*-values were used to calculate the ADC: 1) using all *b*-values (0, 200, 400, 600, and 800 s/mm^2); 2) using the lowest two *b*-values to emphasize perfusion effects (0, 200 s/mm^2); 3) using the highest *b*-values to emphasize diffusion effects (400, 600 and 800 s/mm^2); and 4) using lowest and highest *b*-values (0, 800 s/mm^2)[6]. By using these different approaches for calculating the ADC, we wanted to evaluate the variation in ADCs for treated and untreated tissue with the choice of *b*-values.

Statistical Analysis

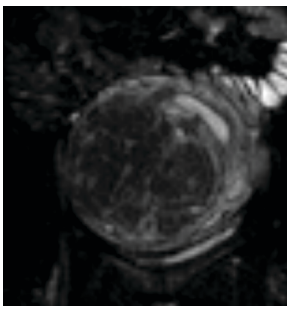
Paired samples t-test was used to calculate the statistical significance of any differences between pre- and post-treatment ADC values of treated and untreated fibroid tissue, and pre- and post-treatment ADC values of normal myometrium. Results are presented as mean value ± standard deviation (SD). P-values ≤0.05 are considered statistically significant. Data analysis was performed using SPSS software (SPSS Inc., Chicago, IL).

Results

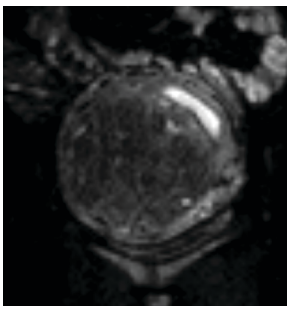
Seventeen fibroids in fourteen patients were treated and analyzed. DWI and ADC maps obtained before MR-HIFU treatment showed no regions of increased or decreased signal intensity indicating necrotic or degenerated areas in the fibroids that were selected for treatment (*Figure 1*).

On post-treatment T1-weighted CE-images, non-perfused volumes (NPVs) indicating devascularized tissue were detected in all patients. Post-treatment DWI showed increased signal intensity in these areas, indicating restricted diffusion. These hyperintense regions demonstrated good agreement visually with the NPVs on T1-weighted CE-images. *Figure 2a and 2b* show an example of a T1-weighted CE-image and DWI using different *b*-values acquired directly post-treatment.

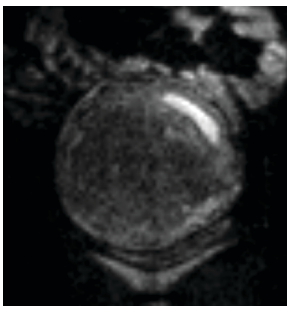
Mean ADC values calculated using different *b*-value combinations at baseline and immediately post-treatment are shown in *Table 2*. There was a significant ($p=1.6 \times 10^{-6}$) decrease in the mean ADC of treated fibroid tissue post-treatment (1.447×10^{-3} mm^2/s) compared with baseline (2.106×10^{-3} mm^2/s) when low *b*-values (0 and 200 s/mm^2) were used for ADC mapping. For this *b*-value combination, we found a uniform decrease in the ADC for all individual fibroids. When high *b*-values were used (400, 600 and 800 s/mm^2) the mean ADC increased significantly post-treatment (p=0.001). When we looked at the individual fibroids, 15 showed an increase in ADC, one no change, and one a decrease. Other *b*-values combinations did not result in significant ADC changes. The ADC of normal myometrium did not change after treatment. *Figure 3* shows the ADC values for fibroid tissue and myometrium pre- and post-treatment. Post-treatment ADC color maps were constructed using the four different *b*-value combinations (*Figure 2c*). The low *b*-value combination (0 and 200 s/mm^2) resulted in the highest contrast between treated and non-treated fibroid and uterine tissue. The region with decreased ADC for this *b*-value combination visually agreed best with the NPV on post-treatment T1-weighed CE-images.



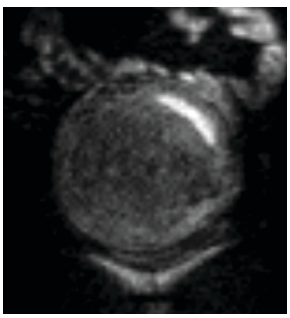
b = 0 s/mm^2



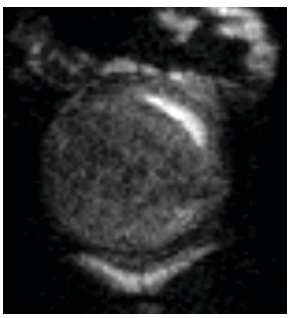
b = 200 s/mm^2



b = 400 s/mm^2

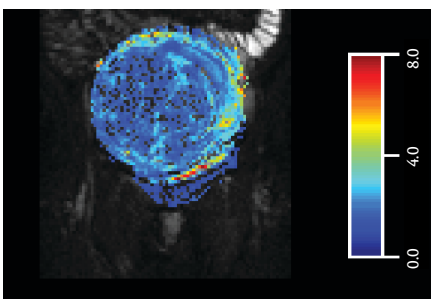


b = 600 s/mm^2

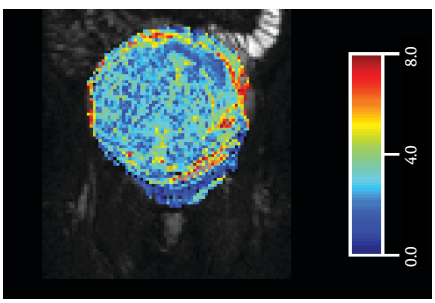


b = 800 s/mm^2

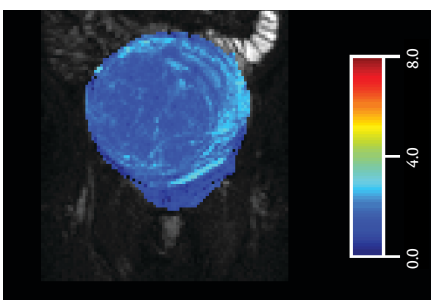
Figure 1a. Pre-treatment coronal DWI acquired using different *b*-values (images scaled per *b*-value)



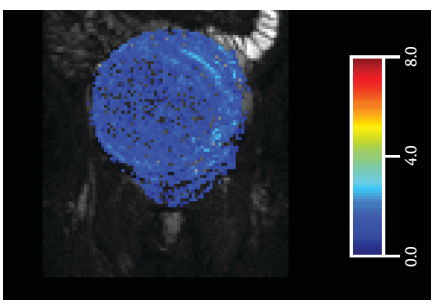
All *b*-values



b = 0 and 200 s/mm^2

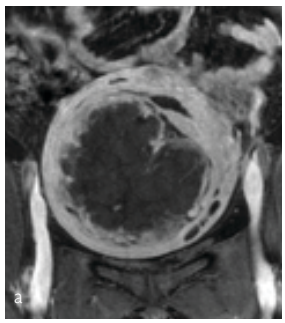


b = 400, 600 and 800 s/mm^2

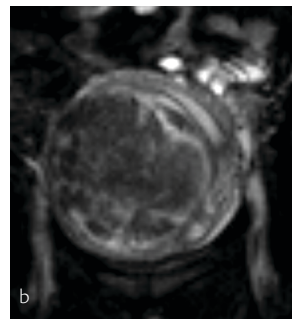


b = 0 and 800 s/mm^2

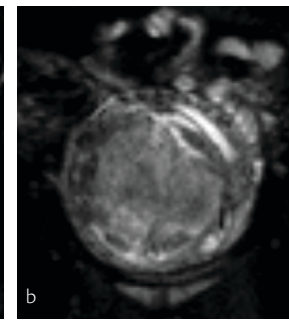
Figure 1b. ADC color maps reconstructed using different *b*-value combinations showing no areas of in- or decreased signal intensity inside the fibroid selected for treatment.



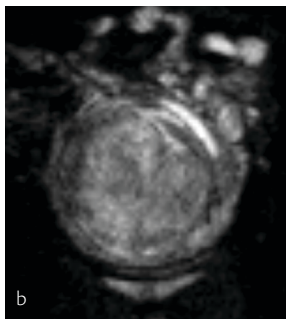
T1-weighted CE image



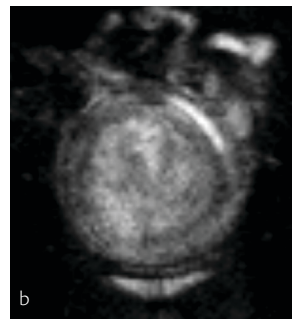
b = 0 s/mm



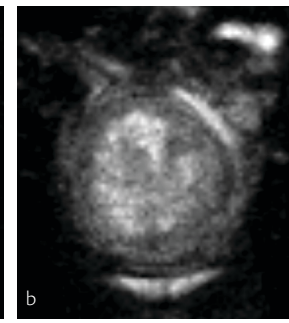
b = 200 s/mm^2



b = 400 s/mm^2

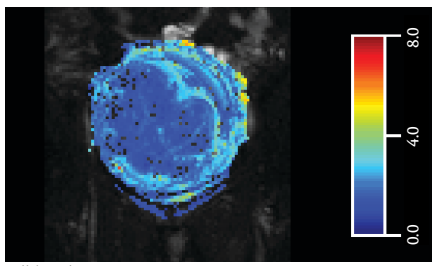


b = 600 s/mm^2

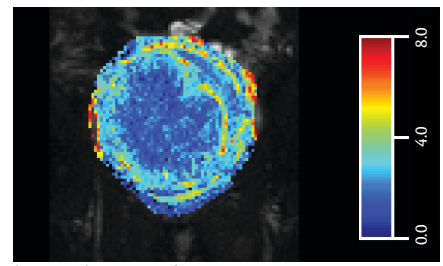


b = 800 s/mm^2

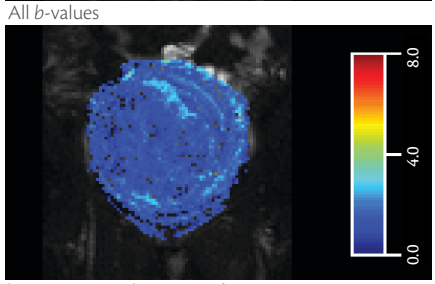
Figure 2 a. Post-treatment T1-weighted CE-image showing the non-perfused volume. **b.** Post-treatment DWI acquired using different *b*-values, showing areas of increased signal intensity inside the treated fibroid (images scaled per *b*-value).



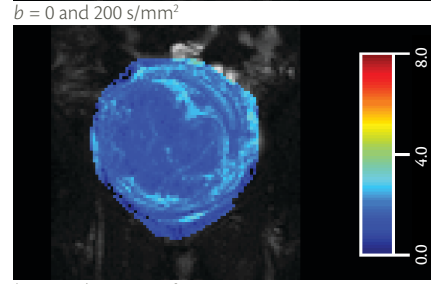
All *b*-values



b = 0 and 200 s/mm^2



b = 400, 600 and 800 s/mm^2



b = 0 and 800 s/mm^2

Figure 2c. Post-treatment ADC color maps reconstructed using different *b*-value combinations

Table 2a. ADC values calculated with different ***b***-value combinations at baseline and post-treatment

***b*-values used for ADC calculation**	**ADC VALUE (10^{-3} mm²/s) ***		
	Treated fibroid tissue		P-value
	Pre-treatment	Post-treatment	
0, 200, 400, 600, and 800 s/mm²	1.141 ± 0.3	1.106 ± 0.3	0.643
0 and 200 s/mm²	2.106 ± 0.2	1.447 ± 0.3	0.000
400, 600, and 800 s/mm²	0.553 ± 0.3	0.824 ± 0.3	0.001
0 and 800 s/mm²	1.024 ± 0.3	1.041 ± 0.2	0.794

* Mean ADC value ± standard deviation

Table 2b.

***b*-values used for ADC calculation**	**ADC VALUE (10^{-3} mm²/s) ***		
	Normal myometrium		P-value
	Pre-treatment	Post-treatment	
0, 200, 400, 600, and 800 s/mm²	2.291 ± 0.4	2.377 ± 0.5	0.447
0 and 200 s/mm²	3.706 ± 0.8	3.627 ± 0.9	0.720
400, 600, and 800 s/mm²	0.974 ± 0.4	1.064 ± 0.3	0.282
0 and 800 s/mm²	1.773 ± 0.2	1.842 ± 0.2	0.225

* Mean ADC value ± standard deviation

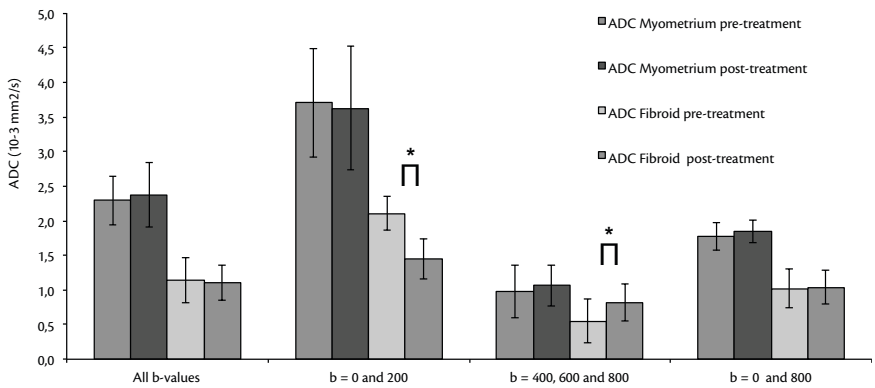


Figure 3. ADC values for fibroid and myometrium tissue pre- and post-treatment

Discussion

We used DWI and ADC mapping for the evaluation of treatment results immediately after MR-HIFU treatment of uterine fibroids. Our results show that the measured ADC value in fibroid tissue is influenced by the choice of *b*-values used for ADC calculation. When the ADC was calculated using low *b*-values (0 and 200 s/mm²), there was a significant decrease in the ADC value in the treated region in all fibroids. The area with a decreased apparent diffusion coefficient on ADC color maps acquired using the low

b-value combination (0 and 200 s/mm^2) resulted in the best visual agreement with the non-perfused volume on T1-weighted CE-images. We found a significant increase in ADC value after MR-HIFU treatment with use of higher *b*-values (400, 600 and 800 s/mm^2) for ADC calculation, but for this combination of *b*-values the tissue response was not uniform for all individual fibroids. Other *b*-value combinations showed no significant change in ADC values pre- and post-MR-HIFU treatment. Also, we found no significant change in the ADC value of normal uterine myometrium pre- and post-treatment, indicating that MR-HIFU treatment does not influence the cellular environment of myometrium.

Our results suggest that it is possible to separate diffusion effects from perfusion effects using different *b*-value combinations for calculation of the ADC. When low *b*-values are used for DWI, perfusion effects play a prominent role in the ADC, as was described by Le Bihan et al.[7]. Since uterine fibroids are highly vascular tumors, they are well perfused[19, 20]. Therefore, we believe that the apparently restricted diffusion in the non-perfused volume we observed immediately post-treatment mainly reflects a reduced perfusion effect and can be explained by destruction of small blood vessels during treatment and compression of blood vessels by edema[21]. The observed change in ADC when three higher *b*-values were used suggests that the reduced perfusion is actually accompanied by an increase in diffusivity directly after ablation, which may be due to direct thermal damage done to the cell membranes. Cell edema as a reaction on tissue damage may also have affected the observed diffusion coefficient.

Jacobs et al studied the use of DWI and ADC mapping for treatment monitoring after MR-HIFU[6]. They found a decrease in ADC value of treated fibroid tissue after MR-HIFU using *b*-values 0 and 1000 s/mm^2, demonstrating that DWI and ADC mapping were feasible for identification of ablated tissue after MR-HIFU. Pilatou et al. in their study investigated tissue changes observed in DWI after MR-HIFU treatment of uterine fibroids and studied the relationship with contrast imaging, thermal dosimetry, and change in ADC[16]. They found that the hyperintense area found on DWI underestimated the non-perfused volume on T1-weighted CE-imaging with increasing non-perfused volume. They used two *b*-values (0 and 1000 s/mm^2) in their study to calculate the ADC. The change in signal intensity on ADC maps was unpredictable, some fibroids showing an increase while others showed a decrease in ADC value immediately post-treatment compared with pre-treatment values. The results we found when we used *b*-values of 0 and 800 s/mm^2 for ADC calculation are comparable to the results of Pilatou et al. For this combination, we did not find a significant change in the ADC value after MR-HIFU treatment. The visual comparison of the ADC color maps with *b*-values 0 and 800 s/mm^2 and non-perfused volume on T1-weighted CE-images was less precise than for other *b*-value combinations, resulting in an underestimation of the NPV.

Overall, our results suggest that there is predominantly a change in perfusion after MR-HIFU treatment due to vessel destruction, and that low *b*-values might be the best choice for ADC calculation.

The results we found are promising for MR-HIFU treatment, indicating that it is possible to determine the extent of effectively treated tissue in a non-invasive way. This can become a helpful tool especially for peri-procedural treatment monitoring, since this is a non-invasive technique without the use of an intravenous contrast agent. In addition to previous studies published by Jacobs et al. and Pilatou et al.[6, 15, 16], we demonstrated that the choice of *b*-values used for ADC mapping influences the absolute ADC values and contrasts in the ADC maps. For immediate post-treatment imaging, low *b*-values (0 and 200 s/mm^2) give the best contrast between non-perfused and perfused tissue, which leads to our conclusion that perfusion effects mainly cause the observed reduction in the apparent diffusion coefficient immediately post-treatment.

We conclude that DWI and ADC mapping are feasible for non-invasive evaluation of the treatment result after MR-HIFU. Using only low *b*-values (0 and 200 s/mm^2) for ADC mapping highlights changes in perfusion and resulted in the best contrast between treated and non-treated fibroid tissue, showing a significant decrease in the ADC value.

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Chapter 8

General Discussion

General Discussion

Uterine artery embolization (UAE) is a minimally invasive treatment for uterine fibroids. This thesis describes the 5-year follow-up results of UAE and the impact of UAE on sexual and psychological well-being in patients with symptomatic uterine fibroids. Also, the variations seen in clinical practice of UAE, regarding patient recruitment and selection, treatment protocol and post-treatment patient care in European countries is discussed.

Magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) offers a promising novel non-invasive treatment option for uterine fibroids. In this thesis we describe the first clinical experience with a new volumetric MR-HIFU ablation technique. Methods to increase treatment efficacy are presented, as well as MR imaging techniques that can be used for post-treatment evaluation.

In this chapter we will discuss the relevance of our findings in the context of the current literature on UAE and MR-HIFU in clinical fibroid treatment. Additionally, based upon the research described in this thesis, we provide recommendations for future studies and patient care.

Part I

Uterine artery embolization for treatment of symptomatic uterine fibroids: European practice and clinical results

Since its introduction in the early nineties, UAE as a minimally invasive treatment modality for symptomatic uterine fibroids has evolved rapidly. Currently, UAE is considered a well-acknowledged alternative to surgical treatment[1].

Data from several randomized controlled trials comparing UAE with surgical treatment (hysterectomy or myomectomy) are available to support this statement[2-12]. Recently, a systematic review and meta-analysis summarizing the evidence on short-, mid-, and long-term results of these studies has been published[13]. Intra-procedural treatment results showed that UAE resulted in a significantly shorter treatment duration (79 vs. 95 minutes for hysterectomy and 59 vs. 109 minutes for myomectomy[6, 7], and in less blood loss (31 ml vs. 436 ml)[6]. No significant differences were found regarding intra-procedural complications between UAE and surgery[6, 7, 9].

Short-term treatment results (up to six months follow-up) showed that hospital stay was shorter after UAE (mean difference of 3.2 days for pooled data)[6, 9, 13], and resumption of work was sooner (mean 28 vs. 63 days and median 20 vs. 62 days)[2, 14]. The rate of intra-procedural complications was not significantly different between the UAE and hysterectomy group[6, 9] and between the UAE and myomectomy group [7]. Early post-procedural, febrile morbidity was significantly lower following UAE compared with hysterectomy (4.9 vs. 20 %)[6]. The need for blood transfusion was also significantly lower after UAE. However, late post-procedural results showed a six times higher

readmission rate after UAE, mostly for pain and fever[6, 9, 13]. The rate of post-procedural complications was significantly higher after UAE compared with hysterectomy (61.7 vs. 41.3 %)[6], although complications following UAE were less severe than after hysterectomy. Mid-term outcome (six months – two years follow-up) showed a significantly higher rate of additional interventions (*i.e.* hysterectomy, repeat UAE, myomectomy, curettage, or endometrial ablation) in the UAE group one year post-treatment (odds ratio of 5.8 for pooled study data)[2, 12, 13], and after two years (28 vs. 8%)[12]. Ovarian function, health related quality of life, and treatment satisfaction did not differ between the UAE and surgery group[2, 4, 5, 10].

Two years after treatment, almost 90% of the women who underwent UAE reported to be symptom free or to experience considerable symptom improvement[4, 12]. Recently, the results 5 years post-treatment of two randomized controlled trials (EMMY and REST trial) have been published[8, 11]. Quality of life and patient satisfaction were excellent and did not differ between the UAE and surgery group. Both studies found a significantly higher rate of re-interventions in the UAE group than in the surgery group (odds ratio of 5.4 for pooled study data)[13]. The EMMY trial reported a re-intervention rate of 35% five years after an initial UAE treatment, compared with 11% re-interventions in the hysterectomy group. The hysterectomy rate after UAE was 28%. Of the women who underwent UAE, symptoms of menorrhagia were improved or completely resolved in 83% of patients. The REST trial reported a re-intervention rate of 32% after UAE, versus 4% after surgery. The hysterectomy rate after UAE was 19% in this study. Despite the risk of additional interventions after UAE, a major advantage of UAE over hysterectomy is preservation of the uterus, which is extremely important for women desiring future pregnancies.

In chapter 3 we present a study assessing treatment outcome five years after UAE. At the time we performed this study (in 2005) no long-term follow-up data from randomized controlled trials was available. However, the results we found are quite similar to those of the EMMY and REST trial[8, 11, 15]. We found continued symptom relief in 72% of patients five years after UAE, and 90% was satisfied or very satisfied with the treatment result. We reported a re-intervention rate of 25%, with a hysterectomy rate of 12%. These re-intervention percentages are lower than in the EMMY and REST trial. However our study was a prospective, uncontrolled, single arm, single center study, in contrast to the EMMY and REST trial that were both large multicenter randomized controlled studies. Selection of patients for our study was different than for the EMMY and REST trial. Most of our patients chose the option of UAE treatment to avoid a hysterectomy, being extremely motivated to undergo a uterus preserving treatment. Our treatment facility (Sint Elisabeth hospital, Tilburg, The Netherlands) is a center of excellence for UAE treatment, performing over 150 procedures per year, resulting in considerable treatment experience. Patients included in both the EMMY and REST trial were randomized for either UAE or surgery, and therefore consented in the possibility

of undergoing hysterectomy. Moreover, the EMMY trial only included patients who suffered from menorraghia as the predominant complaint, while we included also women with predominant pain or bulk-related symptoms. This resulted in different patient populations. All these factors together might explain the differences in outcome we found.

Results of the EMMY trial concerning sexual functioning are comparable to the results of our study evaluating sexual and psychological well being after UAE (presented in chapter 4), although different questionnaires were used[3, 16]. Hehenkamp et al. evaluated sexual functioning up to two years after UAE and hysterectomy using the Sexual Activity Questionnaire, consisting of the subscales 'pleasure', 'discomfort', and 'habit' (frequency of sexual activity). Both the UAE and hysterectomy group showed an improvement in sexual functioning; no differences between both groups were found. Six months after treatment, they found a significant increase for the UAE group in the subscales 'pleasure' and 'habit', while patients reported a decrease in the 'discomfort' subscale. Twenty-five percent judged the quality of their sex life the same as at baseline (before treatment), and 32% reported an improvement.[3] In our study, we evaluated sexual functioning three months after UAE. We found a significant increase of the total score for sexual functioning indicating improvement, measured with a subset of questionnaires derived from the Sexual Dysfunctions Questionnaire. Moreover, 34% reported an increase in sexual activity, and 37% an increase in desire. The percentage of women reporting sexual problems of lubrication, orgasm, or pain decreased by respectively 7, 36 and 14%. We also found that psychological health was positively related to sexual well-being.[16]

Two studies have shown the clinical relevance of complete fibroid infarction after UAE for sustaining symptom relief up to five years post-treatment[17, 18]. Fibroid infarction was defined on contrast-enhanced T1-weighted MR-imaging using a visual scoring system or 'eye balling' and was classified as 'complete' (100% infarction), 'almost complete' (90-99% infarction), or 'partial' (<90% infarction). Women with complete fibroid infarction showed significantly better symptom control than patients who had almost complete fibroid infarction or partial fibroid infarction (respectively 90-93%, 71-84%, and 60-72%). The need for additional interventions was also lower for women with complete fibroid infarction (respectively 0-3%, 15-20% and 20-50% re-intervention rate). Median uterine fibroid volume decrease was found to be slightly lower after partial and almost complete fibroid infarction than after complete infarction (respectively 53%, 59%, and 55%)[17]. In our study we found a relation between the percentage volume reduction of the dominant fibroid and the risk of treatment failure, where a lower percentage reduction resulted in a higher chance of failure[15]. Therefore, UAE treatment should be aimed at acquiring complete fibroid infarction.

Although UAE as a treatment modality for uterine fibroids is widespread in European countries as shown in our results of a European survey presented in chapter 2, the number of procedures performed per center is still relatively low[19]. Most centers perform between 10 and 50 procedures per year, while only a minority (5% of respondents) perform >100 procedures per year. However, since UAE requires a specialized technique with a learning curve, it is likely that the success rate is largely dependent on expertise of the interventional radiologist performing the procedure. The treatment facility where the UAE treatments in our studies were done is a center of excellence for UAE performing over 150 procedures per year, which can explain the relatively better results compared with both the REST and EMMY trial regarding the re-intervention rate 5-years post-treatment. Therefore, we would advice to perform UAE procedures in high throughput centers. This way, women have the best chances of symptom relief without the need for future intervention.
Even though UAE has proven to be a safe and effective treatment method for uterine fibroids that can compete with surgical treatment, there are still some drawbacks for this treatment that should be taken into account when counseling a patient for UAE. The experience of pelvic pain after UAE, most likely caused by ischemia of the fibroid and usually lasting <24 hours, is the most commonly reported side effect and can be severe. In a study of Pron et al. assessing 555 patients, 55% reported pain that was very uncomfortable or intolerable[20], indicating the need for adequate pain management protocols[21]. Another frequent morbidity, occurring in up to 50% of treated patients, is post-embolization syndrome, including fever, pain, malaise and/or nausea, lasting from a few hours to a few days. The cause is probably an immune-mediated response after embolization of the fibroid and the uterus[22]. As for all treatments, patients should be carefully informed about possible adverse events and treatment expectations.

Part II

Volumetric Magnetic Resonance-guided High Intensity Focused Ultrasound for uterine fibroids: First clinical results and future technical developments

Magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) was introduced in 2004 as a non-invasive treatment modality for uterine fibroids. To date, most clinical experience has been obtained with an MR-HIFU system using the conventional point-by-point ablation technique (ExAblate 2000, InSightec, Haifa, Israel). This approach consists of iterative sonication of a single focal point[23, 24]. Several studies have shown promising clinical results up to three years post-treatment using the ExAblate 2000 MR-HIFU system[25-35]. An increase on the Symptom Severity Score (part of Uterine Fibroid Symptom and Quality of Life [UFS-QoL] questionnaire) of 10 points is considered to be a clinically significant improvement[36], reported in 71-83% of patients six months after MR-HIFU and in 51-89% twelve months after treatment[25, 29, 31, 34]. The

ablated tissue can be visualized post-treatment as a non-enhancing area (referred to as non-perfused volume or NPV) on contrast-enhanced T1-weighted MR images. Non-perfused volume percentages of treated fibroids ranged from 2-100% with a mean of approximately 36%[25-30, 33]. Reported fibroid shrinkage percentages ranged from 13-37% six months post-treatment[26-31, 34, 35], 9-37% at twelve months follow-up[29, 31, 35], 28-40% two years after treatment[27, 35], and was found to be 32% after three years[35]. The point-by-point ablation method results in relatively small ablation volumes of several milliliters per sonication applied. Moreover, between subsequent sonication a certain cooling period of several minutes is needed to prevent accumulation of heat inside treated fibroid tissue. This resulted in relatively long treatment times ranging from 27 minutes to 6.5 hours with a mean of approximately 3.5 hours[27, 29-32].
Recently a new ablation strategy has been developed by Philips Healthcare, based upon a volumetric approach[37, 38]. The transducer applies ultrasound energy in a continuous manner in a series of concentric circular trajectories of increasing size. The first commercially available clinical MR-HIFU system using this volumetric technique was launched in 2009 (Sonalleve, Philips Healthcare, Vantaa, Finland). The user can choose differently sized treatment volumes per sonication (called treatment cells), with in plane diameters of 4-16 mm corresponding to cigar-shaped volumes of 0.1-5.4 milliliters. Furthermore, the system allows the use of time-resolved temperature mapping during ablation for automatic feedback control of sonications[38]. These technical developments can potentially lead to faster and more accurate thermal ablation resulting in a shorter treatment time. In chapter 5, a study was described in which we have shown the safety and technical feasibility of the Sonalleve MR-HIFU system for treatment of uterine fibroids[39]. The safety profile we found regarding complications and adverse events and the occurrence of unintended lesions is similar to that reported in the literature for the ExAblate 2000[23, 24].

Appropriate patient selection is critical for ensuring the success of MR-HIFU in patients. Unfortunately, a significant percentage of patients, ranging from to 26 to 84% according to the available literature, is currently not eligible for treatment[40-43]. First, women with general contraindications for MR imaging (*i.e.* severe claustrophobia, pacemaker implant, allergy for gadolinium-based contrast agents) cannot be treated with MR-HIFU. Next, MR imaging is used to screen patients for treatment suitability. Excluded are women who have very large fibroids (>10 cm diameter), multiple small fibroids (usually >10), or fibroids located deep inside the body (>8 cm, due to the limited ultrasound penetration depth the MR-HIFU system). Other exclusion criteria are interposition of bowel loops between the fibroid and the abdominal wall and extensive scarring of the lower abdominal skin, since the exact focus of the ultrasound beam is negatively influenced by propagation through air filled structures or tissue irregularities. Fibroids with high signal intensity on T2-weighted MR images (higher

than that of surrounding myometrium) are considered highly vascular and therefore difficult to heat because of the heat sink effect. Devascularized (identified on contrast-enhanced MR imaging as non-enhancing tissue) or calcified fibroids are also not suitable for treatment[26, 40-43]. Women desiring future fertility are currently excluded from treatment because of unknown effects on fertility. However, several case reports have been published showing positive pregnancy outcomes after MR-HIFU treatment[44-47]. Patient anatomy manipulation and techniques for expanding patient selection for MR-HIFU treatment are currently under investigation. These techniques include a) displacement of bowel loops with gel pads or filling of the bladder to lift the bowel loops anterior from the uterus en provide an acoustic window for the ultrasound beam; and b) use of acoustic reflectors between the transducer and the skin to protect scar tissue, and better visualization of scars using a paramagnetic contrast fluid[48-50]. Eventually, these technical developments will increase the percentage of patients eligible for MR-HIFU treatment.

As for UAE, the ablated fibroid volume after MR-HIFU treatment was found to correlate linearly with relief of clinical symptoms[28, 29, 33]. Therefore, treatment should be aimed at ablating as much fibroid tissue as possible. The first clinical trials used very stringent treatment protocols, making it almost impossible to ablate a large fibroid volume since rigorous safety margins had to be taken into account during treatment. These safety margins included: A minimal margin of 1.5 cm from the focal spot to the uterine serosa, and at least 4 cm distance between the focal spot and sensitive structures such as bowel loops and bone had to be maintained to prevent unintentional heating of these tissues. Also, cooling times between subsequent sonications was long (several minutes) to prevent build-up of heat in treated fibroid tissue[24, 34]. This resulted initially in small ablation volumes (<10% of the fibroid volume). After the initial safety studies less restrictive treatment protocols were used for treatment in clinical practice[25, 51].
Another key issue for MR-HIFU treatment is the long treatment time needed for fibroid ablation. Since uterine fibroids are in general large tumors and a single sonication results in only a small ablation volume, treatment may take several hours or even multiple sessions to be completed. Therefore, research should be aimed at technical innovations that can reduce treatment time. In chapter 6 we presented targeted vessel ablation as a possible method[52]. The concept of targeted vessel ablation is that by selective ablation of supplying vessels to the fibroid, down-stream necrosis can be established resulting in a large devascularized area. To achieve targeted vessel ablation, 3D magnetic resonance angiography (MRA) images resulting in a detailed map of the uterine arteries and feeding segmental braches were overlaid onto anatomical T2-weighted images of the fibroids. MR-HIFU treatment was specifically aimed at sonication of supplying vessels to the fibroid. Our results show that targeted vessel ablation can be a valuable addition to conventional MR-HIFU treatment. However, a

limitation of the method as we implemented it is the use of contrast-enhanced MRA of the uterine arteries. The American Food and Drug Administration currently has not given permission for MR-HIFU ablation of tissue that might contain a gadolinium-based contrast agent, since this could possibly lead to the release of toxic chelates. Therefore, CE-MRI and CE-MRA are unusable for pre-treatment imaging. For this reason, non-invasive MRA techniques, such as time of flight (TOF) and arterial spin labeling (ASL) should be explored[53]. TOF or inflow angiography is an MRA technique dependent on the flow and movement of protons in blood through the imaging plane. TOF is routinely used in cerebral imaging. The signal in the imaging slice is saturated with rapid radiofrequency (RF) pulses. These pulses suppress stationary tissues, while fresh blood entering the slice or volume retains its signal intensity and creates bright contrast between blood and background tissue. Slow blood flow, tortuous vessels, or vessels in the same plane as the image slice result in saturation of the blood flow in the image volume, leading to poor vessel visualization[54, 55]. ASL is an MRA technique using arterial blood as endogenous contrast agent by magnetically labeling the blood flowing into the slices of interest using radiofrequency pulses. After the initial labeling there is delay to allow the labeled arterial hydrogen protons to pass through the arterial vasculature. Imaging is repeated without labeling of arterial blood to acquire a control image. Vessel visualization is based on the difference in magnetization between the labeled and unlabelled images.[56, 57] ASL is also predominantly used in cerebral imaging[58], however its clinical use is currently expanded to measurement of kidney perfusion[59]. However, non-contrast enhanced MRA techniques generally have longer acquisition times than CE-MRA and are highly susceptible to motion artifacts. In brain imaging motion is not a major concern since the brain is a relatively stationary organ. Pelvic organs are however more susceptible to motion, induced by bowel movement and filling of the bladder. Further research is necessary to assess the role of non-invasive MRA techniques for pre-treatment pelvic vessel visualization.

In clinical practice, contrast-enhanced T1-weighted MR imaging is used to assess the treatment effect. Ablated tissue appears as a non-enhancing, devascularized region (referred to as the non-perfused volume, or NPV). In general, the NPV observed after HIFU ablation is larger than expected considering the planned treatment volume. Most likely this is caused by down-stream necrosis after ablation of small vessels[23, 60]. Peri-procedural evaluation of the effectively treated area would be relevant since this tissue does not require further ablation, which can in turn lead to an increase in treatment efficacy and to further decrease in treatment time. Since patients are post-treatment also scheduled for regular follow-up MRI scans (every three months post-treatment), non-enhanced scan techniques to visualize the treated area would be more patient friendly. We have investigated the feasibility of using diffusion-weighted MR imaging (DWI) subsequent apparent diffusion coefficient (ADC) mapping for post-treatment

evaluation of the MR-HIFU procedure (results presented in chapter 7). DWI is an MRI technique that can be used to show tissue characteristics based on diffusion of water molecules within the intra- and extracellular space, using strong additional gradient lobes in the MRI pulse sequence. The strength, duration and timing of additional gradient lobes (expressed in the *b*-value in seconds/mm^2) determine the amount of diffusion weighting. When diffusive motion of water molecules is decreased, DWI shows high signal intensity in those regions corresponding to a lower diffusion coefficient (D in mm^2/s). However, signal loss on DWI is also caused by other mechanisms causing motion of water molecules, such as perfusion effects due to capillary flow. Therefore, it is preferred to refer to the measured diffusion coefficient (D) as the apparent diffusion coefficient (ADC) of water. The ADC is an indicator of the average mobility of water molecules in each voxel of a certain tissue. When mobility is low, the ADC value is also low, and vice versa. The ADC value can be calculated by fitting a model for signal loss as a function of the diffusion coefficient to DWI signal intensities acquired at different *b*-values. At least two *b*-values are required to calculate the ADC. Use of low *b*-values results in a stronger reflection of perfusion effects in the ADC values, whereas use of higher *b*-values results in diffusion effects without perfusion influences[61]. In addition to the current literature available on DWI for post-MR-HIFU imaging[62-64], we used different *b*-value combinations for calculation of the ADC resulting in different sensitivities for diffusion and perfusion effects. We showed that identification of the treated area is possible without the use of intravenous contrast agents.

Future directions

Women are increasingly interested in minimally invasive uterus preserving treatments for uterine fibroids such as UAE and MR-HIFU, because of potential advantages such as faster recovery times and decreased complication rate. Patients and gynecologists should be well aware of the different techniques that are available. When patients consider UAE or MR-HIFU, close collaboration between gynecologists and interventional radiologists is extremely important. The interventional radiologist has an important role in combining both clinical patient information and screening MR imaging to decide whether a patient is a suitable candidate for treatment. Ideally, potential patients should visit the interventional radiologist at the outpatient clinic to discuss the results of screening MR imaging and to be informed about different treatment techniques. Attention must be paid to the risk of additional interventions after treatment because of insufficient symptom relief. By providing transparent information, women can choose the treatment that suits their lives and health perspective best. Treatment information for patients and referring gynecologists must be available at all times, and interventional radiologists should be accessible for questions regarding UAE and MR-HIFU. A website containing dedicated treatment information and a contact form is a good medium to accomplish this.

A multidisciplinary approach to treatment of symptomatic uterine fibroids using minimally invasive treatments is important. Gynecologists have excellent knowledge on uterine fibroids and their related symptoms, while interventional radiologists have the technical skills and equipment to perform the treatments. Both gynecologists and radiologists should be involved in post-treatment follow-up: gynecologists focusing on clinical symptoms and radiologists on imaging characteristics.
Although the use of UAE is widespread throughout Europe, the number of procedures per center is relatively low, also in The Netherlands[19]. A recent publication by van der Kooij et al. proposed some recommendations for the implementation of UAE in The Netherlands, for instance the addition of UAE to the Dutch guideline for management of menorrhagia[65]. Education of gynecologists regarding UAE, adequate patient information using leaflets and a website, and arranging of a standard treatment protocol in a multidisciplinary team are other recommendations. In our opinion, the same advices will apply for the implementation of MR-HIFU treatment in a clinical setting.

The technique of MR-HIFU is still rapidly evolving which will result in an increasing number of clinical applications and an increase in patients suitable for treatment. Similar to UAE, MR-HIFU was recently approved for treatment of adenomyosis (presence of ectopic glandular tissue in the myometrium of the uterus) and the first clinical studies have been published showing promising results[66-69]. Faster MR-HIFU treatment is the key issue for future developments. Technical optimization of targeted vessel ablation could result in better treatment results. Larger treatment volumes per sonication will also decrease treatment time. Peri-procedural MR imaging should be limited to a minimum number of series to reduce acquisition time. Targeted vessel ablation can result in more pain experience by patients during treatment, most likely due to induced ischemia. Regular thermal ablation results in quick tissue necrosis, while targeted vessel ablation induces tissue ischemia subsequently leading to tissue necrosis, a process that takes longer to evolve. This makes adequate pain management increasingly important. Current treatments are performed using only mild conscious sedation and analgesics. When treatment is painful patients use the patient emergency stop button that immediately aborts the active sonication. If considered necessary, the interventional radiologist can administer additional pain medication. These procedures cost valuable treatment time. A solution could be the use of stronger pain medication such as a combination of fentanyl citrate and benzodiazepines, or using propofol. However, this requires the peri-procedural presence of an anesthesiologist for monitoring of the patients vital functions.

Studies assessing long-term outcome after MR-HIFU are important to evaluate if the treatment results found on the short-term will persist. The ultimate goal would be

to perform a randomized controlled trial (RCT) comparing UAE with MR-HIFU as treatments for symptomatic uterine fibroids. Patients included for randomization in this study should be suitable candidates for both UAE and MR-HIFU, based on screening MR imaging and clinical patient information. Recently, the study design of the FIRSTT (Fibroid Interventions: Reducing Symptoms Today and Tomorrow, Clinical Trial Registration NCT00995878) trial was published, to our knowledge the only RCT currently recruiting and randomizing patients for either UAE or MR-HIFU treatment[70]. The primary endpoint of this trial is the need for additional interventions for fibroid related symptoms following treatment. Differences in symptom improvement, recovery, health-related quality of life, ovarian reserve, procedural complications, and economic impact will also be evaluated. Hopefully, this study will provide the definitive answer how MR-HIFU compares to UAE with regard to clinical efficacy.

To conclude, UAE and MR-HIFU are both non-surgical, respectively minimal- and non-invasive treatment options for symptomatic uterine fibroids with promising clinical results. Technical developments and increasing clinical experience will further improve treatment efficacy. Future research is necessary to fill in the current gaps in knowledge about deciding which patients benefit most from both treatments. A multidisciplinary treatment approach including gynecologists and radiologists is mandatory for good patient care.

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Chapter 9

Summary

Samenvatting

This thesis assesses clinical results and technical developments of two minimally invasive treatments for symptomatic uterine fibroids: uterine artery embolization (UAE) and magnetic resonance-guided high intensity focused ultrasound (MR-HIFU). In the introduction both techniques are briefly described.

Part I: Uterine artery embolization for treatment of symptomatic uterine fibroids: European practice and clinical results

In **chapter 2**, the results of a survey on clinical practice of UAE in European countries are described. A total of 167 respondents from different treatment centers in twenty-four European countries performing UAE were included in this study. Forty-eight percent of the included centers had 5 to 10 years of clinical experience with UAE, and the majority of centers (53%) performed 10 to 50 procedures per year. These results show that although UAE is widespread in Europe as an alternative treatment for hysterectomy or myomectomy, the impact on management of patients with symptomatic uterine fibroids is still relatively low according to the overall number of UAE procedures. For better implementation of UAE in clinical practice, collaboration between referring gynecologists and interventional radiologists is mandatory. Moreover, transparent treatment information should be available for both patients and referring physicians.
Clinical results of UAE assessed up to five years post-treatment in 100 women are described in **chapter 3**. At final follow-up (median 54 months, range 45-87), 93 women were available for evaluation. Continued symptom relief was observed in 72% of these patients. Twenty-three women underwent additional major treatment (i.e. hysterectomy, myomectomy, or repeat UAE) because of insufficient symptom relief, formation of new fibroids or complications. At final follow-up, 90% of all women were satisfied or very satisfied with UAE treatment and the result, even though some of them needed an additional intervention. Predictors of failure (defined as major intervention or no improvement at final follow-up) as determined with Cox proportional-hazards regression analysis, were lack of improvement in symptoms of bleeding or pain at 1-year follow-up, and volume reduction of the dominant fibroid (percentage of reduction was inversely proportional to risk of failure).
In **chapter 4** the results of a study assessing the effects of UAE on psychological and sexual well-being in 141 women are reported. Sexual and psychological well-being both improved significantly three months after UAE. Thirty-four percent of women reported an increase in sexual activity after UAE, and 37% an increase in sexual desire. The percentage of women reporting problems with sexual functioning concerning lubrication, orgasm, or pain during sexual activity decreased by respectively 7%, 36% and 14%. The total score on the SCL-90 decreased significantly from 133 to 116 points, indicating a decrease in emotional and somatic concerns.

Part II: Volumetric magnetic resonance-guided high intensity focused ultrasound for uterine fibroids: First clinical results and future technical developments

MR-HIFU treatment with a point-by-point ablation technique has been used for uterine fibroid treatment since its introduction in 2004. In 2009 a new volumetric MR-HIFU technique, developed by Philips Healthcare and the group of Prof. dr. C.T. Moonen in Bordeaux, was introduced. In **chapter 5** the results of the first prospective clinical trial assessing safety and technical feasibility of the volumetric MR-HIFU approach are presented. Treatment capability and technical feasibility were assessed by comparison of the non-perfused volumes (NPVs) with MR thermal dose predicted treatment volumes. The mean NPV calculated as a percentage of the total fibroid volume was 21.7%. We found a very strong correlation between the predicted treatment volumes and NPVs (correlation coefficient r = 0.87). All treatments were performed on an outpatient basis, and women tolerated the treatment well. Safety was determined by evaluation of complications or adverse events and unintended lesions. No serious adverse events or unintended lesions were reported and the recovery to normal daily activities was fast (mean 2.3 ± 1.8 days). These initial results show that volumetric MR-HIFU is safe and technically feasible for treatment of symptomatic uterine fibroids.

Treatment efficacy is an important issue to address during MR-HIFU treatment, since uterine fibroids are generally large resulting in relatively long treatment times. **Chapter 6** describes the first clinical experience of targeted vessel ablation (a method to deliberately ablate fibroid supplying blood vessels during MR-HIFU treatment) in two symptomatic patients with a total of three fibroids. This resulted in almost total fibroid devascularization (non-perfused volume to total fibroid volume ratio ranging from 68 to 86%). There was a reduction in fibroid related symptoms, and an increase in quality of life up to six months after treatment. Volume reduction of the treated fibroids ranged from 31-59%. Although there are technical issues that need to be resolved, targeted vessel ablation has the potential to increase treatment efficacy in clinical practice.

Non-contrast agent dependent methods to visualize the non-perfused volume may sometimes be preferred for evaluation of the result after MR-HIFU treatment for uterine fibroids. In **chapter 7** the results of a study investigating the use of different *b*-value combinations for diffusion weighted MR imaging (DWI) and apparent diffusion coefficient (ADC) mapping for evaluation of treatment results are described. There is a significant decrease in the ADC of treated fibroid tissue when low *b*-values (0 and 200 s/mm^2) were used for calculation of the ADC. This also resulted in the best agreement of lesion detection on ADC maps with the visualization of treated fibroid tissue in contrast-enhanced MRI scans. This probably reflects decreased perfusion in treated regions. When higher *b*-values were used (400, 600 and 800 s/mm^2), we found a significant increase in ADC. This increased diffusivity is thought to reflect

the direct thermal damage done to the treated fibroid tissue, resulting in damaged cell membranes. DWI and ADC mapping can therefore be used for evaluation of treatment results after volumetric MR-HIFU treatment of uterine fibroids.

In **chapter 8** the results of our findings are summarized by subject. The relevance of our findings is discussed in the context of the current literature. In summary this thesis explored the clinical results and technical feasibility of UAE and MR-HIFU as minimally invasive treatment options for symptomatic uterine fibroids. Both treatments showed promising clinical results. Technical developments and increasing operator and clinical experience will further improve treatment efficacy. Adequate selection of the best suitable candidates for each treatment in a multidisciplinary approach by both gynecologists and radiologists is a future challenge that necessitates future research, but has the potential to result in better treatment results.

Chapter 9

Summary

Samenvatting

Dit proefschrift beschrijft de klinische resultaten en technische ontwikkelingen van twee minimaal invasieve behandelingen voor symptomatische uterus myomen: embolisatie van de arteria uterina (UAE) en magnetische resonantie-geleide high intensity focused ultrasound (MR-HIFU). In de introductie worden beide technieken kort beschreven.

Deel I: Embolisatie van de arteria uterina ter behandeling van symptomatische uterus myomen: De Europese praktijk en klinische resultaten

In **hoofdstuk 2** worden de resultaten beschreven van een studie naar de klinische praktijk van UAE in Europese landen. In totaal werden 167 respondenten van verschillende behandelcentra die UAE uitvoeren in vierentwintig Europese landen geïncludeerd in deze studie. Achtenveertig procent van de geïncludeerde centra had 5 tot 10 jaar klinische ervaring met UAE, en de meerderheid van de centra (53%) voerde 10 tot 50 procedures per jaar uit. Deze resultaten laten zien dat, ook al is UAE wijd verspreid in Europa als alternatieve behandeling voor hysterectomie of myomectomie, de impact op de behandeling van patiënten met symptomatische uterus myomen nog steeds relatief laag is afgaande op het aantal uitgevoerde UAE procedures. Voor betere implementatie van UAE in de klinische praktijk is samenwerking tussen verwijzende gynaecologen en interventieradiologen een vereiste. Duidelijke behandelinformatie moet beschikbaar zijn voor zowel patiënten als verwijzende artsen.
Klinische resultaten tot vijf jaar na UAE behandeling van 100 vrouwen staan beschreven in **hoofdstuk 3**. Aan het einde van de follow-up (mediaan 54 maanden, range 45-87) waren 93 vrouwen beschikbaar voor evaluatie. Aanhoudende verlichting van symptomen werd geobserveerd in 72% van deze patiënten. Drieëntwintig vrouwen ondergingen een ingrijpende aanvullende behandeling (hysterectomie, myomectomie, of herhaalde UAE) vanwege onvoldoende symptoomverbetering, formatie van nieuwe myomen, of complicaties. Aan het einde van de follow-up, was 90% van alle vrouwen tevreden of zeer tevreden met de UAE behandeling en het resultaat, ook al was een aanvullende behandeling voor sommigen van deze vrouwen noodzakelijk. Voorspellers van falen van de behandeling (gedefinieerd als een ingrijpende aanvullende behandeling of geen verbetering van klachten bij laatste follow-up) werden bepaald met behulp van Cox proportional-hazards regressie analyse, en waren gebrek aan verbetering in symptomen van bloeding of pijn na 1 jaar follow-up, en volumereductie van het dominante myoom (percentage van reductie was omgekeerd evenredig met het risico op falen).
In **hoofdstuk 4** worden de resultaten beschreven van een studie die de effecten van UAE op psychologisch en seksueel welbevinden in 141 vrouwen onderzocht. Seksueel en psychologisch welbevinden verbeterden beiden significant drie maanden na UAE. Vierendertig procent van de vrouwen rapporteerden een stijging in seksuele activiteit

na UAE, en 37% een verbetering in seksueel verlangen. Het percentage vrouwen dat seksuele problemen rapporteerde op het gebied van lubricatie, orgasme, of pijn tijdens seksuele activiteit daalde met respectievelijk 7%, 36% en 14%. De totale score op de SCL-90 daalde significant van 133 naar 116 punten, wat duidt op een verlaging van emotionele en lichamelijke zorgen.

Deel II: Volumetrische magnetische resonantie-geleide high intensity focused ultrasound voor uterus myomen: Eerste klinische resultaten en toekomstige technische ontwikkelingen

MR-HIFU behandeling met de punt-ablatie techniek wordt sinds de introductie in 2004 gebruikt voor de behandeling van uterus myomen. In 2009 werd een nieuwe volumetrische MR-HIFU techniek geïntroduceerd, ontwikkeld door Philips Healthcare en de groep van Prof. dr. C.T. Moonen uit Bordeaux. In **hoofdstuk 5** worden de resultaten gepresenteerd van de eerste prospectieve klinische studie naar de veiligheid en technische uitvoerbaarheid van de volumetrische MR-HIFU methode. Bekwaamheid van de behandeling en technische uitvoerbaarheid werden onderzocht door het vergelijken van de non-geperfundeerde volumina (NPVs) met de MR thermale dosis voorspelde behandelvolumina. Het gemiddelde NPV berekend als percentage van het totale myoomvolume was 21.7%. De correlatie tussen voorpelde behandelvolumina en NPVs was erg sterk (correlatiecoëfficiënt r = 0.87). Alle behandelingen werden poliklinisch uitgevoerd en werden goed verdragen door de vrouwen. Veiligheid werd bepaald door evaluatie van complicaties of bijwerkingen en onbedoelde laesies. Er werden geen ernstige bijwerkingen of onbedoelde laesies gerapporteerd en het herstel naar normale dagelijkse activiteiten was snel (gemiddeld 2.3 ± 1.8 dagen). Deze initiële resultaten laten zien dat volumetrische MR-HIFU veilig en technisch uitvoerbaar is voor de behandeling van symptomatische uterus myomen.

Efficiëntie van de behandeling is een belangrijke kwestie tijdens de MR-HIFU ablatie, aangezien uterus myomen in het algemeen groot zijn, resulterend in lange duur van de behandeling. **Hoofdstuk 6** beschrijft de eerste klinische ervaring met gerichte vaatablatie (een methode om opzettelijk de bloedvoorzienende vaten van het myoom te ableren tijdens de MR-HIFU behandeling) bij twee symptomatische patiënten met in totaal drie myomen. Dit resulteerde in bijna volledige devascularisatie van de myomen (ratio van non-geperfundeerd volume ten opzichte van totale myoom volume varieerde van 68 tot 86%). Er werd een reductie in myoom-gerelateerde symptomen gerapporteerd, en een stijging van de kwaliteit van leven zes maanden na behandeling. Volume reductie van de behandelde myomen varieerde van 31-59%. Hoewel er technische kwesties zijn die nog opgelost dienen te worden, heeft gerichte vaatablatie potentieel om de behandelefficiëntie te verhogen in de klinische praktijk.

Niet-contrastmiddel afhankelijke methoden om het non-geperfundeerde volume te visualiseren kunnen soms de voorkeur hebben voor evaluatie van het resultaat

na MR-HIFU behandeling van uterus myomen. In **hoofdstuk 7** worden de resultaten beschreven van een studie die het gebruik van verschillende *b*-waarde combinaties voor diffusie gewogen MRI (DWI) en apparent diffusion coefficient (ADC) mapping onderzoekt voor evaluatie van het behandelresultaat. Als lage *b*-waarden (0 en 200 s/mm^2) gebruikt werden voor berekening van de ADC werd een significante verlaging gevonden in de ADC van behandeld myoomweefsel. Dit resulteerde ook in de beste overeenstemming tussen laesie detectie op ADC maps en visualisatie van behandeld myoom weefsel op MRI beelden na toedienen van contrastmiddel. Dit is mogelijk een reflectie van de verlaagde perfusie in behandeld gebied. Als hogere *b*-waarden gebruikt werden (400, 600 en 800 s/mm^2) vonden we een significante verhoging van de ADC. Deze verhoogde diffusiviteit reflecteert mogelijk de directe thermale schade aan behandeld myoomweefsel, resulterend in schade aan celmembranen. DWI en ADC mapping kunnen dus gebruikt worden voor evaluatie van het behandelresultaat na MR-HIFU behandeling van uterus myomen.
In **hoofdstuk 8** vatten we de resultaten van onze bevindingen samen per onderwerp. De relevantie van onze bevindingen wordt bediscussieerd in de context van de beschikbare literatuur. Samenvattend onderzoekt dit proefschrift de klinische resultaten en technische uitvoerbaarheid van UAE en MR-HIFU als minimaal invasieve behandelopties voor symptomatische uterus myomen. Beiden behandelingen laten veelbelovende resultaten zien. Technische ontwikkelingen en vergroten van de klinische ervaring zullen de behandelefficiëntie verder verbeteren. Adequate selectie van de meest geschikte kandidaten voor iedere behandeling met een multidisciplinaire benadering door zowel gynaecologen als radiologen is een uitdaging voor de toekomst die nader onderzoek noodzakelijk maakt, maar potentieel heeft om te resulteren in betere behandelresultaten.

Chapter 10

List of Publications

Dankwoord

Curriculum Vitae

Journal Articles

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Grants and Awards

Young Investigator Award, International Symposium on MR-guided Focused Ultrasound, Washington, USA, October 2010

Grant ZonMw Doelmatigheidsonderzoek: Vroege Evaluatie Medische Innovaties (VEMI). Project name: '*Minimal Invasive versus Non Invasive treatment for symptomatic uterine fibroids: A randomized controlled trial comparing uterine artery embolisation with magnetic resonance guided focused ultrasound (MINI-TRIAL)*' (project number 171001001)

Chapter 10

List of Publications

Dankwoord

Curriculum Vitae

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Lieverds, ik hou van jullie. Het leven met jullie is mooi!

Chapter 10

List of Publications

Dankwoord

Curriculum Vitae

Marianne Jeannette Voogt was born April 14th, 1982 in Ridderkerk, The Netherlands. In the year 2000 she completed secondary school at the Onze Lieve Vrouwe Lyceum in Breda, and in that same year she started medical training at the Erasmus University, Rotterdam. She followed two years of clinical internships in the Sint Elisabeth Hospital in Tilburg. As part of her medical training she performed scientific research focusing on uterine artery embolization treatment of uterine fibroids at the department of Obstetrics and Gynecology (Dr. P.F. Boekkooi) and the department of Radiology (Dr. P.N.M. Lohle) in Tilburg. She obtained her medical degree in 2006 and started working for one year as a resident in Obstetrics and Gynecology at the Sint Elisabeth Hospital. In 2008 she started her PhD studies at the Department of Radiology, University Medical Center Utrecht (Prof. dr. M.A.A.J. van den Bosch and Prof. dr. W.P.Th.M. Mali). Results of this research are presented in this thesis. In February 2011 she started her residency in Radiology at the University Medical Center Utrecht (Prof. dr. J. van Schaik). She is married to Vincent van Beusekom since 2009. Together they have a daughter Sara, who was born in May 2011.