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The role of MRI before and after uterine fibroid embolisation

PhD thesis

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List of abbreviations

ACR	American College of Radiology
ADC	Apparent diffusion coefficient
CE	Contrast enhancement
CE MRI	Contrast-enhanced magnetic resonance imaging
CIRSE	Cardiovascular and Interventional Radiological Society of Europe
CNGOF	College National des Gynecologues et Obstetriciens Francais
CT	Computed tomography
DWI	Diffusion weighted imaging
FEMME	A Randomized Trial of Treating Fibroids with Either Embolisation or Myomectomy to Measure the Effect on Quality of Life Among Women Wishing to Avoid Hysterectomy
FIGO	International Federation of Gynecology and Obstetrics
FIRSTT	Fibroid Interventions: Reducing Symptoms Today and Tomorrow
GnRH	Gonadotropin releasing hormone
HCP	High-contrast phase
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drugs
PCP	Precontrast phase
PVA	Polyvinil alcohol
QOL	Quality-of-life
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RCOG	Royal College of Obstetricians & Gynecologists
ROC	Receiver operating characteristic
SD	Standard deviation
SI	Signal intensity
SIR	Society of Interventional Radiology
SOGC	Society of Obstetricians and Gynaecologists of Canada

SPRM	Selective progesterone receptor modulator
T1W	T1 weighted
T2W	T2 weighted
UAE	Uterine artery embolization
UFE	Uterine fibroid embolization
UFS-QoL	Uterine Fibroid Symptom – Quality of Life
US	Ultrasound
VR	Volume reduction

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1. Introduction

1.1. General characteristics of uterine fibroids

Uterine fibroids (also called myomas and leiomyomata) are the most common benign neoplasms in women of reproductive age. Fibroids affect up to 20-40% of women in reproductive age (Deshmukh et al, 2012). The estimated cumulative incidence may be as high as 80% by the age of 50 years (Baird et al, 2003). Studies have shown that race, body-mass-index, and parity are factors affecting the prevalence, although the exact cause of fibroids is still unknown. Family history, time since last birth, premenopausal state, hypertension, and diet are also considered to be risk factors (Marsh et al, 2018). Arising from a single smooth muscle cell, fibroids are composed of connective tissue and multiple layers of smooth muscle fascicles surrounded by a pseudocapsule of compressed muscle fibers. Fibroids are hormonally responsive tumors. In high-estrogen states, such as pregnancy and during oral contraceptive use, they may show an accelerated growth rate. For the same reason they generally regress in size after menopausa. Most often there are multiple lesions, but they may also be solitary (Kassam et al, 2017). As the uterus, uterine fibroids get their blood supply via the uterine artery. As they grow, they may be parasitically diverting blood flow from the supplying arteries of adjacent structures. The ovarian arteries affected most commonly, but aberrant blood supply from the inferior and superior mesenteric artery and the round ligament artery are also possible (Pelage et al, 2005; Song et al, 2014; Bérczi et al, 2021).

If uterine fibroids outgrow their blood supply, they can undergo different kinds of degenerative processes. Degenerated fibroids are more heterogenous and have atypical characteristics compared to non-degenerated ones. In case of hyaline degeneration, proteinaceous tissue accumulates in the extracellular space and calcified foci appear. This phenomenon happens in as high as 60% of fibroids. Fibroids with myxoid degeneration appear as a complex cystic mass. These fibroids are hypocellular, have a myxoid matrix, and are filled with gelatinous material. Interstital edema and lymphedema can both happen in case of fibroids. Cystic areas with high T2 signal intensity and without contrast enhancement are characteristics of cystic degeneration which represents areas of edematous connective tissue microscopically. Red degeneration (also known as carneous degeneration) is the commonest type of degeneration during pregnancy. It represents the

painful infarction of fibroids, caused by peripheral venous thromboses or intratumoral arterial ruptures (Bolan et al, 2016; Ricci et al, 2017).

Uterine leiomyosarcomas are rare gynaecological malignancies (<0.13% of uterine smooth muscle tumors) that may represent a de novo lesion or originate from a benign fibroid. The rate of malignant transformation of benign uterine fibroids is low. The reported prevalence of sarcomatous change is 0.1%-0.8%. Less than 1% of hysterectomy specimens contained sarcomatous tissue when the operation was indicated because of benign uterine fibroids (Ricci et al, 2017). Smooth muscle tumor of uncertain malignant potential (STUMP) is a rare heterogeneous tumor that cannot be definitively classified histologically as leiomyoma or leiomyosarcoma. STUMP mimics fibroids and sarcomas as well, there have unfortunately no specific MR features. Based on MR imaging appearance they are indistinguishable. After removal they have a high rate of recurrence (7.3%–12.5%) and may recur as low-grade leiomyosarcoma; therefore, long-term follow-up is needed (Nougaret et al, 2020; De Mulder et al, 2018).

1.2. Classification of uterine fibroids

Uterine fibroids are classified based on their localisation. Initially they develop from the myometrium as intramural fibroids. As they grow, they may reach a subserosal or submucosal position. In accordance with the International Federation of Gynecology and Obstetrics (FIGO) classification system, they can be further subdivided into 8 categories (Fig. 1). FIGO category number 0 and 7 represent pedunculated fibroids. Pedunculated fibroids have their center located outside of the myometrium. They are attached to the uterus by a stalk. The stalk's diameter - by definition - must be narrower than 50% of the fibroid diameter. For fibroids that are not directly related to the myometrium of the uterine corpus FIGO category number 8 is used (Munro et al, 2011). These may be located in the cervix (5% of all fibroids), or in the broad or round ligaments. Rarely, fibroids as they adhere to pelvic structures other than the uterus, develop an auxiliary blood supply, and lose their original attachment to the uterine vasculature – these lesions termed as „parasitic" fibroids. Rarely, leiomyomas occur in unexpected locations, such as diffuse peritoneal leiomyomatosis, intravenous leiomyomatosis, or benign metastasizing leiomyoma (Fasih et al, 2008).

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SM - Submucosal	0	Pedunculated intracavitary
	1	≤50% intramural
	2	≥50% intramural
O - Other	3	Contacts endometrium, 100% intramural
	4	Intramural
	5	Subserosal, ≥50% intramural
	6	Subserosal, ≤50% intramural
	7	Subserosal pedunculated
	8	Other (specify e.g. cervical, parasitic)
Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separeted by a hyphen. By convention, the first refers to the relatioship with the endometrium, while the second refers to the relationship with the serosa. One example is below:	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometriual and peritoneal cavities, respectively.

Figure 1. FIGO classification system of uterine fibroids (Based on Munro et al, 2011).

1.3. Symptomatology

Bleeding (e.g., menorrhagia: abnormally heavy and/or prolonged bleeding that occurs at regular intervals, or metrorrhagia: irregular menstrual bleeding or bleeding between periods) is the most common symptom at presentation. The amount and frequency of the abnormal bleeding are variable, but generally the bleeding is heavier and/or has a longer duration. The exact patomechanism of the abnormal bleeding is still unknown, however, there are three accepted, yet unproven theories. All three theories are connected to the spatially distortive nature of uterine leiomyomata. Firstly, they may alter the the normal contractile function of the myometrium which may be responsible for bleeding from the subendometrial vascular bed. Secondly, the distorted and compressed endometrium may fail to respond to the cyclic change of the estrogen/progesterone hormone levels, which may result in incomplete sloughing of the endometrium during menstruation. Thirdly, the compression may lead to the necrosis of the overlying endometrial tissue, exposing vascular surfaces that may bleed excessively. Significant acute blood loss due to leiomyomata is a rarity. In contrast, development of chronic iron-deficiency anaemia is quite common (Beckmann et al, 2014).

Pelvic pressure, pelvic fullness, and the pelvic mass sensation are also common symptoms. Seldomly, enlarging fibroids may press the ureters to the brim of the pelvis resulting in hydroureter and hydronephrosis. A rapidly enlarging fibroid may also cause pain symptoms and as such, they may be the cause of secondary dysmenorrhoea. In case of pedunculated fibroids, torsion, and prolapse through the cervical canal may occur, leading to acute pain and cramps. Problems with urination and defecation may also appear (Testa et al, 2016).

Fibroids could as well interfere with fertility. Up to 27% of patients seeking reproductive care have uterine fibroids (Hur et al, 2019). Submucosal fibroids have distortive effects on the uterine cavity which results decreased clinical pregnancy rates and delivery rates. Moreover, patients with submucosal fibroids have a threefold risk of spontaneous abortion. Pritts et al. in their systematic review from 2009 concluded that submucosal fibroids result in decreased rates of clinical pregnancy, implantation, ongoing pregnancy, and live birth, as well as increased rates of spontaneous abortion, thus their removal seems to confer benefit (Pritts et al, 2009).

Intramural fibroids also caused decreased rates of implantation and ongoing pregnancy, and increased rates of spontaneous abortion when compared with controls without fibroids. The underlying mechanisms are not precisely known. Possible mechanisms among others include interference with sperm transport due to anatomical distorsion, fallopian tube obstruction and adnexal distorsion leading to failure of ovum capture, and increasing myometrial contractions (Ludwig et al, 2020).

Uterine leiomyomata may also disturb affected women's social life as they negatively impact physical and social activities, women's health-related quality of life, and work productivity. The resultant economic burden of fibroids is as high as 34.4 billion USD annually in the United States (Cardozo et al, 2012).

1.4. Diagnosis of fibroids

1.4.1. Physical examination and ultrasound diagnosis

The diagnosis of fibroids is based on gynecological physical examination and imaging studies. On bimanual examination fibroids usually present as a large, solid, mobile mass. The most often used imaging modality to confirm the diagnosis is ultrasound. Ultrasound

is an easily accessible, harmless, and inexpensive modality. Transabdominal or transvaginal approach may be used depending on the desired focus. With transabdominal examination, wider field of view is available, other organs can be easily visualized, and it is more flexible than an endocavitary approach. These abilities make transabdominal approach the preferred one in case of subserosal or giant fibroids, parasitic fibroids, and in case of possible peritoneal involvement. Since an endocavitary route enables the transducer to get closer to the lesion, higher frequency transducers can be used, which provide a better resolution. The method also helps the more precise evaluation of endometrial thickness and other uterine and adnexal abnormalities. Combination of these two methods gives the best result regarding the detection, characterisation, and mapping of uterine fibroids (Testa et al, 2016).

A usual fibroid appears as a well-defined, large, solid lesion with inhomogeneous echostructure and radial shadowing (also known as Venetian blind, or rain shower appearance). Generally, the lesions are hypoechoic, but even non-degenerated leiomyomas can be iso- or hyperechoic compared to the myometrium. The variable echogenicity depends on the composition of the lesion. Calcification and cystic areas may be seen when a fibroid is degenerated (Hur et al, 2019).

1.4.2. Computed tomography (CT) diagnosis

CT examination plays a marginal role in the diagnosis of uterine leiomyomata. Fibroids appear as spatially distortive pelvic soft tissue masses often with coarse calcification. They have an atypical, variable enhancement pattern (Wilde et al, 2009).

1.4.3. Magnetic resonance imaging (MRI) characteristics and types of degeneration

On MR imaging, non-degenerated leiomyomas appear as well delineated round lesions. Fibroids have generally homogeneously hypointense signal intensity on T2-weigted images and isointense signal intensity compared to the outer myometrium. Their enhancement pattern – just as on CT images – is variable and heterogenous. Around the lesion dilated lymphatic vessels and veins may cause a pseudocapsule of edema, which may appear as a T2-hyperintense rim (Mittl et al, 1991). Generally, within fibroids there is no restricted diffusion. They have low signal intensity on diffusion-weighted images (DWI) and in the apparent diffusion coefficient (ADC) map (DeMulder et al, 2018).

Two histologic subtypes of uterine fibroids with slightly different signal characteristics can be distinguished. Cellular fibroids contain more smooth muscle cells and less connective tissue. This compositional difference makes them appear more hyperintense on T2-weighted images and they may also have an avid contrast enhancement (Deshmukh et al, 2012). Uterine lipoleiomyoma is a rare histological variant usually seen in postmenopausal women. Apart from the muscular and fibrous component they also contain fat. This makes them hyperintense both on T1- and T2-weighted (T1W, T2W) images. Because of their fat content characteristic signal loss appears on fat-saturated images (DeMulder et al, 2018).

As already mentioned, fibroids tend to degenerate when they outgrow their blood supply. Different kinds of degenerations all have their own – more or less specific – MR signal characteristics. Fibroids with hyaline degeneration have lower signal intensity on T2W images. It is difficult to distinguish them from normal, non-degenerated fibroids, although their contrast enhancement is usually lower (Arleo et al, 2015). In cystic degeneration, cystic areas have high signal intensity on T2W images and have no contrast enhancement. In myxoid degeneration fibroids contain mucinous areas. These fibroids have an extremely high T2 signal intensity and enhance well, except for the mucinous foci (Ueda et al, 1999). In case of haemorrhagic degeneration, fibroids usually have a high T1W signal intensity either diffusely or peripherally due to the proteinaceous content of the blood and/or by the T1-shortening effect of methemoglobin. Calcific foci cause signal voids in all kinds of degenerations (Nougaret et al, 2020).

1.4.4. The role of DWI and ADC

Diffusion-weighted imaging (DWI) is a functional MRI technique which creates signal based on the differences of the Brownian motion of water molecules. The technique provides information regarding cellularity and micro-architecture of biologic tissues. Apparent diffusion coefficient (ADC) is a DWI-derived quantitative parameter calculated automatically by imaging softwares. It represents the magnitude of diffusion and as such, restricted areas appear with lower signal intensity on ADC maps. ADC values are widely used to monitor and predict treatment response of different benign and malignant lesions throughout the body (Baliyan et al, 2016).

Previous studies examined the potential predictive role of ADC values regarding the uterine artery embolization (UAE) treatment of uterine leiomyomas. They found significant correlation between preprocedural ADC values and postprocedural volume reduction rates: high ADC of a leiomyoma was found to be associated with a greater volume reduction after embolization (Hecht et al, 2011). The real reason for the correlation between pre-UAE ADC and VR after embolization still remains unknown; it is suspected that leiomyomas with lower ADC were more hyalinized (or fibrotic) and would shrink less after embolization (Hecht et al, 2011; Cao et al, 2014).

Dao et al. conducted a systematic review and metaanalysis in 2019 on the subject. Their main objectives were to examine whether baseline ADC values can predict fibroid size reduction (i.e., volume reduction in patients undergoing UAE for symptomatic uterine fibroids) and to examine whether changes in ADC (from baseline to postembolization) could predict fibroid volume reduction. Eleven studies with 258 patients were included. The metaanalysis demonstrated high heterogeneity of data and found no correlation between baseline ADC values and fibroid volume reduction at approximately 6 months after the procedure (r=0.40; 95% CI, -0.07 to 0.72; I2=69.7%). They concluded that the potential of both baseline and changes in ADC (before and after embolization) for predicting treatment response to UAE is unclear. The authors named several factors that may be responsible for the high heterogeneity: technical factors (e.g., the radiologist' measurement definitions, MRI vendor or system used), the DWI assessment and sequencing methods used (e.g., selection of b values), biological characteristics of uterine leiomyomas, embolization agent size and type, the embolization technique, endpoints used, different sample sizes and patient selection (Dao et al, 2019).

1.5. Patient management, treatment options

Regarding patient management, different factors should be considered: patient's age, symptom type and severity, size and location of the lesions, desire to maintain fertility, access to treatment, desire of the patient to one or other treatment option, and physician's experience. The ideal treatment should aim symptomatic relief, size reduction of fibroids, and maintenance of fertility (if desired). Unnecessary harm should always be avoided. Apart from expectant management, medical, interventional radiological, and surgical therapies are available (De La Cruz et al, 2017).

In premenopausal women, 3-7% of untreated fibroids regress in size in three years and most of them decrease in size postmenopausally. Expectant management is preferred in case of asymptomatic fibroids since the chance of malignant transformation is minimal. Currently there is no evidence regarding the usefulness of repeated imaging.

1.5.1. Drug therapy

Drug therapy is most often the first line treatment. Their aim is to reduce abnormal uterine bleeding caused by uterine fibroids. Available medical treatments include anti-fibrinolytic agents, non-steroidal anti-inflammatory drugs (NSAIDs), combined hormonal contraceptives, progesterone-only treatments, selective progesterone receptor modulators (SPRMs), anti-progestins, aromatase inhibitors, and gonadotropin releasing hormone (GnRH) agonists or antagonists (Giuliani et al, 2020).

Since NSAIDs have a low cost, relatively low chance for adverse effects and wide availability, they are the first agent to apply in most of the cases. Ibuprofen and naproxen are the two most widely used drugs. NSAIDs work by inhibiting the enzyme cyclooxygenase, lowering the production of pro-inflammatory prostaglandins and have been shown to improve dysmenorrhea and menorrhagia compared to placebo (Lethaby et al, 2013).

Hormonal contraceptives are another commonly applied therapeutical option. Combined estrogen-progesteron contraceptives either in form of pills or intrauterine devices decrease the volume of blood loss mainly by stabilizing the endometrium. Abnormal uterine bleeding, hemoglobin concentration, and quality of life were found to be improved in women who used combined oral contraceptives compared to placebo (Moroni et al, 2015). Moreover, the levonorgestrel-releasing intrauterine system (Mirena) was proved to induce a significantly greater reduction in menstrual blood loss versus oral contraceptives (Sayed et al, 2011).

Tranexamic acid is a commonly used oral antifibrinolytic agent that significantly reduces menstrual blood loss compared with placebo (Lukes et al, 2010). Because of the heavy blood loss, iron supplementation is a necessary adjuvant treatment to avoid serious iron deficiency anaemia (Laughlin-Tommaso et al, 2018).

1.5.2. Surgical management

Current surgical management strategies include hysterescopic and laparoscopic myomectomy, laparoscopic, vaginal or laparotomic hysterectomy, laparoscopic cryomyolysis and thermo-coagulation, and laparoscopic occlusion of the uterine arteries (Donnez et al, 2016).

Hysterescopic myomectomy is currently the mainstay of minimally invasive surgical therapy in case of small (<2 cm) submucous fibroids, especially in the case of small pedunculated submucous fibroids. The procedure is usually carried out in an outpatient setting. Depending on the gynecologist's experience and the available equipment, different technical approches may be used. Resectoscopic loop or a laser fiber may be used to cut the pedicle of the fibroid. The mass may be extracted by forceps or left in place. Another commonly used technique is the slicing technique, where the fibroid is cut into small chips. Two-step approch is also an option, especially for larger, FIGO type 1-3 fibroids (fibroids with a submucous and an intramural component as well). First, the intracavitary component is resected, then the intramural component rapidly migrate into intracavitary positon, enable the second step hysterescopy to excise the portion. If the fibroid is larger (>3 cm in diameter), there is an increased risk of operative complications (perforation, bleeding and fluid intravasation) and damage to surrounding myometrium due to use of electrosurgery. Postprocedural pregnancy rates range is from 16.7% to 76.9%, with a mean of 45% (Donnez et al, 2014).

Laparoscopic myomectomy is the preferred procedure for intramural and subserosal fibroids. The approach yields lower blood loss and morbidity, shorter hospital stay, and less post-operative pain than open myomectomies (Pitter et al, 2014). Contraindication of laparoscopic myomectomy includes large (>10-12 cm), and multiple fibroids in different locations due to the increased number of incisions. In a review of prospective and retrospective studies, Donnez and Jadoul reported a pooled pregnancy rate of 49% (95% CI 46–52) in patients who underwent laparoscopic myomectomy (Donnez et al, 2009).

Despite the rapid technological development and increasing number of options, laparoscopic hysterectomy remained the only definitive treatment option for symptomatic uterine fibroids. The procedure is only appropriate for women who do not wish to maintain fertility and also not appropriate if the patient has a will to retain her uterus. The

main indiciation of hysterectomy overall are fibroids. In the last decades, laparoscopic approach became the ideal technique and largely replaced laparotomy. In some departments, the rate of laparoscopic hysterectomy exceeds 90% (Donnez et al, 2009). Vaginal hysterectomy also remains indicated in some cases, depending on the skill and personal experience of the surgeon. (Aarts et al, 2015). Sharp morcellation techniques can be used to remove fibroids and/or myomatous uteri in well counseled women. Although the prevalence of sarcoma is low in fibroids (<0.3%), the risk of specimen fragment dispersion with morcellation remains a serious and highly debated concern (Donnez et al, 2016). Incidence of major complications after hysterectomy is reported to be 0.4%. After hysterectomy, the majority of women experience symptomatic relief and report a significant improvement in quality of life (Pitter et al, 2014).

1.5.3. Uterine artery embolisation (UAE)

Uterine artery embolisation (UAE, also known as uterine fibroid embolisation, UFE) is a minimal invasive, image-guided, interventional radiological procedure. The aim of the procedure is to induce ischaemic necrosis of the uterine fibroids. To achieve this, occluding agents (usually 500-700 μm PVA particles) are injected into both of the uterine arteries via a catheter from a peripherial transcutaneus access (mostly common femoral artery, in some centres brachial artery). UAE is a good treatment option for women who wish to preserve their uterus, or avoid surgery because of comorbidities or personal preferences. The procedure provides a safe and effective option even in case of multiple and large (>10 cm) fibroids (van Overhagen et al, 2015; Dariushnia et al, 2014; Bérczi et al, 2015). According to randomised trials, UAE provides similar improvement in quality of life as surgical therapies, but with a shorter in-hospital time, and an earlier resumption of normal activities (Gupta et al, 2012). Contraindications include pregnancy, active uterine or adnexal infections, allergy to intravenous contrast media, and renal insufficiency (De La Cruz et al, 2017).

As reported in a study which examined how fibroid related heavy menstrual bleeding change after UAE in 81 patients, the symptom resolved at two years follow-up in 62% of the patients, while this number increased to 83% at five years (de Bruijn et al, 2016).

Despite the encouraging results regarding symptomatic relief and avoided surgery-associated risks, studies reported that 19-38% of patients will have reintervention for

persisting symptoms (Hartmann et al, 2017). In the first five-year period after UAE, hysterectomy as a form of reintervention was needed in 28% of cases as reported by a multicenter, randomized controlled trial (van der Kooij et al, 2010). The rate of major complications (i.e., rehospitalization, ovarian failure, pulmonary embolism, and unplanned hysterectomy) is between 1 to 12% (Carillo et al, 2008). Fever, pain, nausea, pelvic infection, postembolization syndrome, and vaginal discharge may appear as minor complications (Rezk et al, 2021).

Data are conflicting regarding reproductive outcomes after UAE compared to myomectomy. Due to a potential post-procedure decline in ovarian function and increased risk of pregnancy-related complications in UAE, these should be considered in patient counselling and in the final decision of the desired treatment (expectant, medical, embolization, or surgery). Regarding pregnancy-related complications, UAE for uterine fibroids is associated with an increase of miscarriage (35.2% versus 16.5%; OR, 2.8; 95% CI, 2.0–3.8), cesarean delivery (66% versus 48.5%; OR, 2.1; 95% CI, 1.4–2.9), and postpartum hemorrhage (13.9% versus 2.5%; OR, 6.4; 95% CI, 3.5–11.7) compared to expectant management (Homer et al, 2010).

Results of the FEMME (A Randomized Trial of Treating Fibroids with Either Embolisation or Myomectomy to Measure the Effect on Quality of Life Among Women Wishing to Avoid Hysterectomy) trial, a multicenter, randomized, open-label trial of 254 women concluded that those women who underwent myomectomy had a better fibroid-related quality of life at 2 years than those who underwent uterine-artery embolization. The difference though, was relatively small: in the intention-to-treat analysis, the mean±SD score on the health-related quality-of-life domain of the UFS-QOL questionnaire at 2 years was 84.6±21.5 in the myomectomy group and 80.0±22.0 in the uterine-artery embolization group; the overall incidence of perioperative and postoperative complications was similar in the two groups, 29% of the women in the myomectomy group and in 24% of the women in the uterine-artery embolization group (Manyonda et al, 2020).

There are plenty of available standards of practice and quality improvement guidelines regarding UAE of uterine fibroids. The aim of these guidelines is universally the same: to synthetise current scientific evidence and expert opinions in order to provide help for

clinicians regarding appropriate patient selection and counselling. Chen et al. evaluated 11 guidelines (from 2007 to 2015) in a systematic review to report on the concordance and divergence regarding the recommended use of UAE. The guidelines were found to be consistent on the indications of the procedure: to treat symptomatic uterine fibroids (causing heavy and/or prolonged menstrual bleeding, pain, mass effect); other indications included symptomatic fibroids in women who had previous unsuccessful surgery because of uterine fibroids, wish to preserve their uterus, or unsuitable for surgery (Chen et al, 2018).

The absolute contraindications were also straightforward in all of the guidelines: viable pregnancy and active infection. They did not find however, the similar level of consistency about the relative contraindications of the procedure. Common relative contraindications were immunocompromise, endovascular contraindications (impaired renal function, contrast agent allergy, coagulopathy). Apart from these points, the Cardiovascular and Interventional Radiological Society of Europe's (CIRSE) guideline from 2015 adds that the presence of utero-ovarian anastomoses, or a common artery supplying the uterus and ovaries, should be also considered a relative contraindication just as concomitant gynaecological malignancy which makes the patient more suitable for hysterectomy (van Overhagen et al, 2015).

Specific characteristics of fibroids may also appear as a relative contraindication. UAE of pedunculated fibroids is a long debated and controversial point of guidelines. Of the aforementioned 11 guidelines, 7 discuss this point: according to The Royal Australian and New Zealand College of Obstetricians and Gynaecologists' (RANZCOG 2020) and the Royal College of Obstetricians & Gynecologists' (RCOG 2013) guidelines, all pedunculate fibroids, according to the Society of Obstetricians and Gynaecologists of Canada's (SOGC, Lefebvre et al, 2004) guideline all pedunculated and submucosal fibroids, according to the CIRSE guideline (2015) pedunculated subserosal fibroids are considered to be a relative contraindication. The guideline published by the College National des Gynecologues et Obstetriciens Francais (CNGOF, Marret et al, 2012) states that single peduculated fibroids are relative contraindication of the procedure, while the guidelines of the Society of Interventional Radiology (SIR, Dariushnia et al, 2014) and American College of Radiology (ACR, Burke et al, 2009) mention no morphologic characteristics of fibroids as relative contraindication.

Uterine fibroid embolisation has been done since 2008 in our centre, one out of the two major centres in Hungary. More than 750 patients has been treated until December 2021, the number of 50-70 patient/year is considered high for one center even in international standards. The collaboration with the Department of Obstetrics and Gynaecology of Semmelweis University is essential and fruitful, we are very grateful for their support and collaboration.

1.5.4. Magnetic resonance-guided focused ultrasound surgery (MRgFUS)

Magnetic resonance-guided focused ultrasound surgery (MRgFUS) is a minimally invasive procedure that involves continuous waves of ultrasound energy of numerous transducers (e.g., appr. 200 ultrasound probes) focused to a small area (e.g., appr. 2-4 to 8-10 mm prism) over a 2 to 3 hour period under MR guidance. Eventually, the goal is to heat the entire fibroid to >57 ^{o}C for at least 1 second to induce coagulative necrosis. The approach offers short recovery time and symptomatic relief, making it a viable option for women with symptomatic fibroids when other procedures are contraindicated or not desired. Since the procedure require dynamic MR guidance, contraindications to MR examinations (pacemakers, metallic objects, ferromagnetic aneurysm clips etc.) are also contraindications of the procedure. Multiple, or pedunculated fibroids, non-enhancing fibroids, giant fibroids (>10 cm), post-menopausal status, severe adenomyosis are also considered as contraindications. Rarely, reversible pelvic neuropathy and local skin burns appear after treatment with MRgFUS. For this reason, the procedure is not recommended for women with prior extensive abdominal/pelvic surgeries or abdominal scarring (Taran et al, 2009; Giuliani et al, 2019).

This technique is currently not available in Hungary. However, it was available for approximately 5 years 15 years ago. Our early results were summarised as a single centre prospective study on 38 patients with uterine fibroids who were treated by MRgFUS. Follow-up MRI examinations were performed at 3 and 6 months after the procedure. Total fibroid volumes and non-perfused volumes were evaluated. The study reported a significant reduction in fibroid volumes at 3 and 6 month follow-ups (10±19%, $p=0.022$ and 19±29%, $p<0.001$, respectively). Moreover, the study found positive correlation

between early non-perfused volumes and the total fibroid volume loss at follow-up examinations (Várallyai et al, 2009).

The low T2 signal intensity of fibroids compared to skeletal muscle on preprocedural MR images and percentage of non-perfused volume immediately after treatment were found to be independent predictive factor of volume reduction and symptomatic relief. It is hypothesized that lower T2 signal intensity represents lower cellularity and/or vascularisation making it easier to obtain adequate temperature elevation with sonication within the fibroid (Lénárd et al, 2008).

A study on 359 patients reported that the symptom severity score at 3 months after MRgFUS was significantly lower from baseline (Stewart et al. 2007). The impact of learning curve was analysed in a study on 287 patients, a mean non-perfused volume ratio (the sum of the non-perfused volume of all treated fibroids divided by the volume of all uterine fibroids, treated and untreated) of 39% for patients treated between 2003–5 and 54% for patients treated between 2005–6 was reported (Okada et al, 2009).

The Fibroid Interventions: Reducing Symptoms Today and Tomorrow (FIRSTT), a randomized controlled trial of uterine artery embolization (UAE) versus magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS) of 37 premenopausal women with symptomatic uterine fibroids reported that similar fibroid volume reduction was seen for the MRgFUS and UAE treatments. They found that nonperfused volume 24 months after the procedure was higher in the UAE arm than in the MRgFUS arm (Laughlin-Tommaso et al, 2021).

A non-randomised comparative study of 192 patients treated by MRgFUS or abdominal hysterectomy concluded that MRgFUS treatment of uterine leiomyomas leads to clinical improvement with fewer significant clinical complications and adverse events compared to hysterectomy at 6 months follow-up (Taran et al, 2009).

A meta-analysis of Xu et al on 31 studies containing totally 42103 patients was conducted to compare the re-intervention rates of myomectomy, UAE and MRgFUS. They concluded that myomectomy has the lowest short-term and long-term re-intervention rate of the three regimens while the MRgFUS has the highest. The rate of reintervention for

MRgFUS increased rapidly between 36th and 60th months after the treatment (Xu et al, 2021).

Although preexisting data are promising and reassuring regarding the reproductive outcomes after MRgFUS, there is no published prospective data regarding women who wish to become pregnant and have been treated with MRgFUS. Therefore, a reccomendation on the use of MRgFUS prior to a planned pregnancy cannot be made for women who wish to conceive (Lozinski et al, 2019; Kröncke et al, 2019).

Relevant side effects and complications during and after MRgFUS therapy are: pain, skin burns, inflammation of subcutaneous adipose tissue and the musculature of the abdominal wall, paresthesia of the leg due to nerve irritation or damage deep vein thrombosis (very rare), bowel perforation (extremely rare). Gorny et al in their retrospective review of 130 patients with symptomtic uterine fibroid trated with MRgFUS observed that treatment related complications in 17 patients (13.1%); only one of the 17 had major complication (deep vein thrombosis) (Gorny et al, 2011).

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2. Objectives

The aim of our first study is to evaluate prognostic value of pretreatment pelvic magnetic resonance imaging features in uterine artery embolisation for symptomatic fibroids:

- To compare the signal intensity (SI) of fibroids with that of myometrium and skeletal muscle on T1- and T2-weighted images.
- To compare contrast enhancement of the fibroids and the myometrium
- To compare fibroid volume decrease as a function of location (submusosal, sebserosal, intramural).
- To assess numerical analogue quality-of-life (QOL) score for clinical effectiveness before and after UAE

The purpose of our second study was to evaluate whether the size of the dominant fibroid would influence the complication rate and effectiveness in a large single-center cohort.

- To compare numerical analogue quality-of-life (QOL) score as clinical outcome of large fibroids (> 10 cm largest diameter) of UAE in patients with regular size fibroids <10 cm
- To compare risk (minor and major complications) of large fibroids (> 10 cm largest diameter) of UAE in patients with regular size fibroids <10 cm

3. Results

3.1. Pre-embolization MRI parameters of fibroids as prognostic values for the effectiveness of UFE

3.1.1. Patients

Pre- and postprocedural pelvic magnetic resonance imaging of 70 consecutive patients (mean age 42±21; range 27–52 years) with uterine fibroids who have undergone uterine artery embolization in our institution (Semmelweis University, Medical Imaging Centre) between May 2011 and June 2014 was used to retrospectively evaluate the relationship between imaging features of fibroids and treatment response (Kalina et al, 2018). Inclusion criteria: patient had both pre- and post-UFE MRI, and the images were available. Exclusion criteria: pre- or post-UFE MRI was not done or images were not available. The main complaints of patients were menorrhage, dysmenorrhea, pelvic pain and bulk-related symptoms. Pelvic MRI scans were obtained 1.8±1.3 (SD) months before and 6.6±1.8 months after the embolization.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in this study. Due to the retrospective manner of this study, no ethical approval was necessary.

3.1.2. MRI technique

The MRI devices used for imaging were: Philips Achieva 3T; Philips Achieva 1.5 T; and Siemens Magnetom Harmony 1T. Details are given in Table 1. Gadolinium-based intravenous contrast material (Optimark, Mallinckrodt, Inc.; Gadovist, Bayer AG; Dotarem, Guerbet LLC; Magnetolux, Sanochemia Pharmazeutika) was used to obtain contrast-enhanced sequences.

Table 1.. Detailed magnetic resonance imaging (MRI) protocols used for imaging (Kalina et al, 2018).

	Philips Achieva 3T			Philips Achieva 1,5T			Siemens Magnetom Harmony 1T		
	T1WI	T2WI	T1WI + IV contrast	T1WI	T2WI	T1WI + IV contrast	T1WI	T2WI	T1WI + IV contrast
Sagittal									
TR/TE (ms)	5/2	6100/80	8/4	495/10	7500/90		-	3200/113	130/4
Flip angle (°)	20	90	20	90	90	90	-	150	70
Matrix size	672x672	384x384	528x528	720x720	384x384	720x720	-	512x512	512x512
Field of view (mm)	300	250,4	300	350	350	350	-	250	280
Section thickness (mm)	3	4	3	4	4	4	-	5	6
Inter-section gap (mm)	1	1	1	1	1	1	-	1.3	1.8
Coronal									
TR/TE (ms)	5/2	1900/80	8/4	-	6400/90	-	-	6000/116	-
Flip angle (°)	20	90	20	-	90	-	-	150	-
Matrix size	672x672	512x512	528x528	-	400x400	-	-	512x512	-
Field of view (mm)	300	362.3	300	-	380	-	-	380	-
Section thickness (mm)	3	4	3	-	4	-	-	5	-
Inter-section gap (mm)	1	1	1	-	1	-	-	1	-
Axial									
TR/TE (ms)	5/2	-	8/4	619/10	4700/100	697/10	351/12	4200/105	138/4
Flip angle (°)	20	-	20	90	90	90	90	150	70
Matrix size	672x672	-	528x528	704x704	704x704	704x704	512x512	256x320	512x512
Field of view (mm)	403.2	-	404.1	333	330.7	333	250	160	280
Section thickness (mm)	1.9	-	1.9	4	4	4	6	5	6
Inter-section gap (mm)	-1	-	-1	1.5	1.5	1.5	1.8	0.5	0.6

3.1.3. Image analysis

All pre- and postprocedural MR images were evaluated by a radiologist with experience in female pelvic imaging. Fibroids with submucosal, intramural and subserosal localization with a largest diameter of at least 3 cm were included in the analysis. The signal intensity (SI) of fibroids were compared with that of myometrium and skeletal muscle (iliacus muscle) on T1- and T2-weighted images.

When compared to myometrium, fibroids were considered ’hyperintense’ if their T1 SI was higher than that of myometrium, and ’isointense/hypointense’ if their T1 SI was equal to or lower than that of myometrium. On T2-weighted images, fibroids with a SI equal to or higher than that of myometrium were grouped as ’isointense/hyperintense’, and ’hypointense’ if their SI was lower than that of myometrium.

When compared to skeletal muscle, fibroids were considered ’hyperintense’ if their T1 SI was greater than that of skeletal muscle, and ’isointense/hypointense’ if their SI was equal to or lower than that of skeletal muscle. On T2-weighted images, fibroids were grouped as ’hyperintense’ if their SI was greater than that of skeletal muscle, and ’isointense/hypointense’ if their SI was equal to or lower than that of skeletal muscle.

On gadolinium-enhanced T1-weighted images, the SI of fibroids were compared with that of myometrium. Fibroids were grouped as ’isointense/hyperintense’ if their SI was equal

to or greater than that of myometrium, and 'hypointense' if their SI was lower than that of myometrium.

Fibroids were grouped into each of the above-listed categories if their largest diameter was predominated by each of these features (i.e., at least half of the largest diameter). Locations of fibroids were classified as submucosal, intramural and subserosal, according to the FIGO classification system described by Munro et al (Munro et al, 2011). Fibroid volume was calculated according to the ellipsoid formula (length x width x height x 0.5233) (Volkers et al, 2008). The volume reduction (VR) rate of fibroids was determined by the following formula: $VR = (V_{pre} - V_{post})/ V_{pre}$, where V_{pre} and V_{post} represent fibroid volumes pre- and post-UAE, respectively (Noda et al, 2015).

To rule out therapeutic failure as the cause of insufficient post-embolization volume reduction, we determined the percentage of infarction of fibroid tissue at control imaging by using three categories previously described by Kroencke et al (complete = 100%, almost complete = 90%–99%, and partial = 0%–89%) in 68 patients; the remaining two patients were scanned without administration of intravenous gadolinium at the control imaging (Kroencke et al, 2010).

3.1.4. Embolization procedure

All embolization procedures were performed by the same interventional radiologist with an experience of more than 10 years using a standard procedure. Unilateral right common femoral arterial access was used to catheterize and obtain superselective angiography of both uterine arteries with 4F catheters. Embolization was achieved by the injection of nonspherical polyvinyl alcohol particles into each uterine arteries (500-710 μm, COOK PVA-500, Bloomington, Indiana, USA; 500–700 and 355–500 μm Contour; Boston Scientific-Target Therapeutic, Fremont, CA) until near-stasis flow was reached. The puncture site was compressed manually after the procedure. Patients routinely received antibiotic prophylaxis (amoxicillin-clavulanic acid or clindamycin). For postprocedural pain control, tramadol, meloxicam, metamizol-Na, nalbuphin or drotaverin were used. After UAE, patients were kept in the hospital overnight for observation.

3.1.5. Predictive features of preembolisation MRI

UAE was completed in all patients without any major complications. Altogether 109 fibroids in 70 patients were evaluated. The mean fibroid volume before embolization was 116±200 cm^3 (range, 5-1,271 cm^3), and decreased by 51.1±30.8% (range, -112.1-99%) to 59±114 cm^3 (range, 0.1-809 cm^3) during the 6.6±1.8 month follow-up period ($p<0.001$). Out of 109, 104 fibroids (95.4%) showed a VR; their volume decreased by 55.1±23.9% (range, 5.1-99%). On post-embolization images (n=106 fibroids, as two patients with three fibroids have not received contrast medium on the control MRI), complete infarction was found in 89 fibroids (84%), almost complete infarction in five fibroids (4.7%), and partial infarction in 12 fibroids (11.3%).

Fibroid location, T2 SI, contrast enhancement (CE), and size showed significant association with the degree of VR after UAE (Table 2).

Out of 109 fibroids, 71 (65.1%) were intramural, 27 (24.8%) were subserosal, and 11 (10.1%) were submucosal. The mean VR of submucosal fibroids was 82.1±18.5%, which was significantly greater than the VR of intramural (49.4±30.7%) and subserosal (43±28.3%) fibroids ($p<0.001$ for both). The VR of intramural and subserosal fibroids did not differ significantly ($p=0.79$; Fig 2).

Eighteen fibroids (16.5%) that were isointense or hyperintense to myometrium on pretreatment T2-weighted images showed a mean VR of 63.7±25.8%, whereas the other 91 fibroids (83.5%) that were hypointense to myometrium showed a VR of 48.6±31.3% ($p=0.041$; Figs 2 and 3).

Twenty-nine fibroids (27.4%) with isointense or hyperintense signal compared to myometrium on contrast-enhanced images showed a volume reduction of 61.3±27.4% which was significantly greater then the volume reduction of 47.6±31.6% showed by the 77 fibroids (72.6%) with hypointense signal compared to myometrium ($p = 0.035$; Figs 3 and 4; two patients with three fibroids had only non-contrast MRI).

Table 2. Pre-embolization imaging parameters that showed significant association (p<0.05) with the degree of volume reduction. Statistical analysis was performed using Kruskall-Wallis test for categorical parameters (location, signal intensity); Mann-Whitney U test for continous variables (i.e. volume); and paired Wilcoxon signed-rank test for volume reduction (pre- vs. postembolization volume) (IBM SPSS Statistics 22 and GraphPad Prism 6.01) (Kalina et al, 2018).

Parameter (number of fibroids)	Mean fibroid VR ± SD (%)	Difference between means of VR (%)	*p* -Value
Submucosal localisation (n=11) Subserosal localisation (n=27)	82.1±18.5 43±28.3	39.1	<0,001
Submucosal localisation (n=11) Intramural localisation (n=71)	82.1±18.5 49.3±30.7	32.7	<0,001
Iso-/hyperintense T2 signal compared to myometrium (n=18) Hypointense T2 signal compared to myometrium (n=91)	63.7±25.8 48.6±31.3	15.1	0.041
Iso-/hyperintense signal to the myometrium on CE-T1WI (n=29) Hypointense signal to the myometrium on CE-T1WI (n=77)	61.3±27.4 47.6±31.6	13.7	0.035
Fibroid volume <50 cm^3 (n=59) Fibroid volume ≥50 cm3 (n=50)	54.9±37.1 46.7±20.6	8.2	0.021

Fibroids with a baseline volume of <50 cm^3 (n=59; 54,1%) showed a VR of 54.9±37.1% (range, -112.1–99%), which was significantly greater than the degree of VR showed by fibroids ≥ 50 cm^3 (n=50; 45,9%; 46.7±20.6%; range, 5.1–90.3%; p=0.021). No statistically significant associations were found between fibroid T2 SI compared to skeletal muscle (p=0.421), T1 SI compared to myometrium (p=0.270) and skeletal muscle (p=0.14) and subsequent VR.

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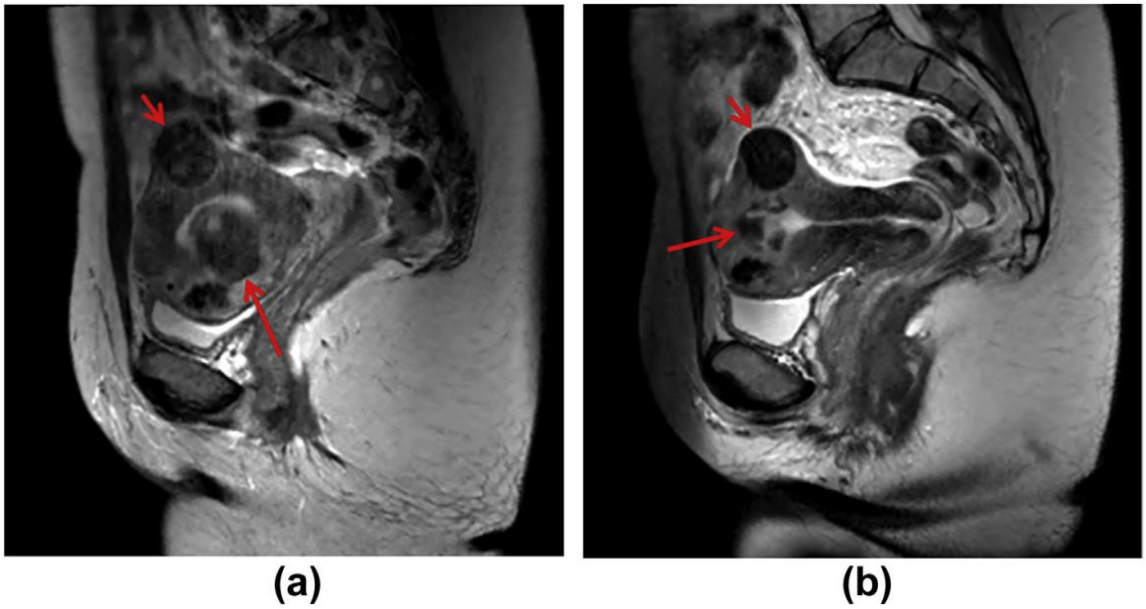

Figure 2. (a) Pre-embolization sagittal T2-weighted image showing submucosal (long arrow) and subserosal (short arrow) fibroids. (b) Six months after UAE, the submucosal fibroid (long arrow, 96% decrease in volume) had undergone a greater VR than the subserosal fibroid (short arrow, 50% decrease in volume) (Kalina et al, 2018).

Numerical analogue quality-of-life (QOL) score (0: intolerable symptoms, 100: perfect quality of life) was obtained before and 36.0±11.5 months after the embolization in 62/70 patients (86.1%) in order to assess clinical efficacy of the procedure. Mean QOL score before UAE was 38.5±24.3 points, which improved by 48.2±27.6 points to 86.7±15.9 points at 36.0±11.5 months after the procedure ($p<0.001$) (paired Wilcoxon signed-rank test). Assessment of any connections between initial fibroid imaging characteristics and post-treatment QOL score changes would make sense only in cases of solitary fibroids. Thus, due to the small number of such cases, such analyses would have been of slight relevance. A separate study of patients with solitary fibroids should address this question.

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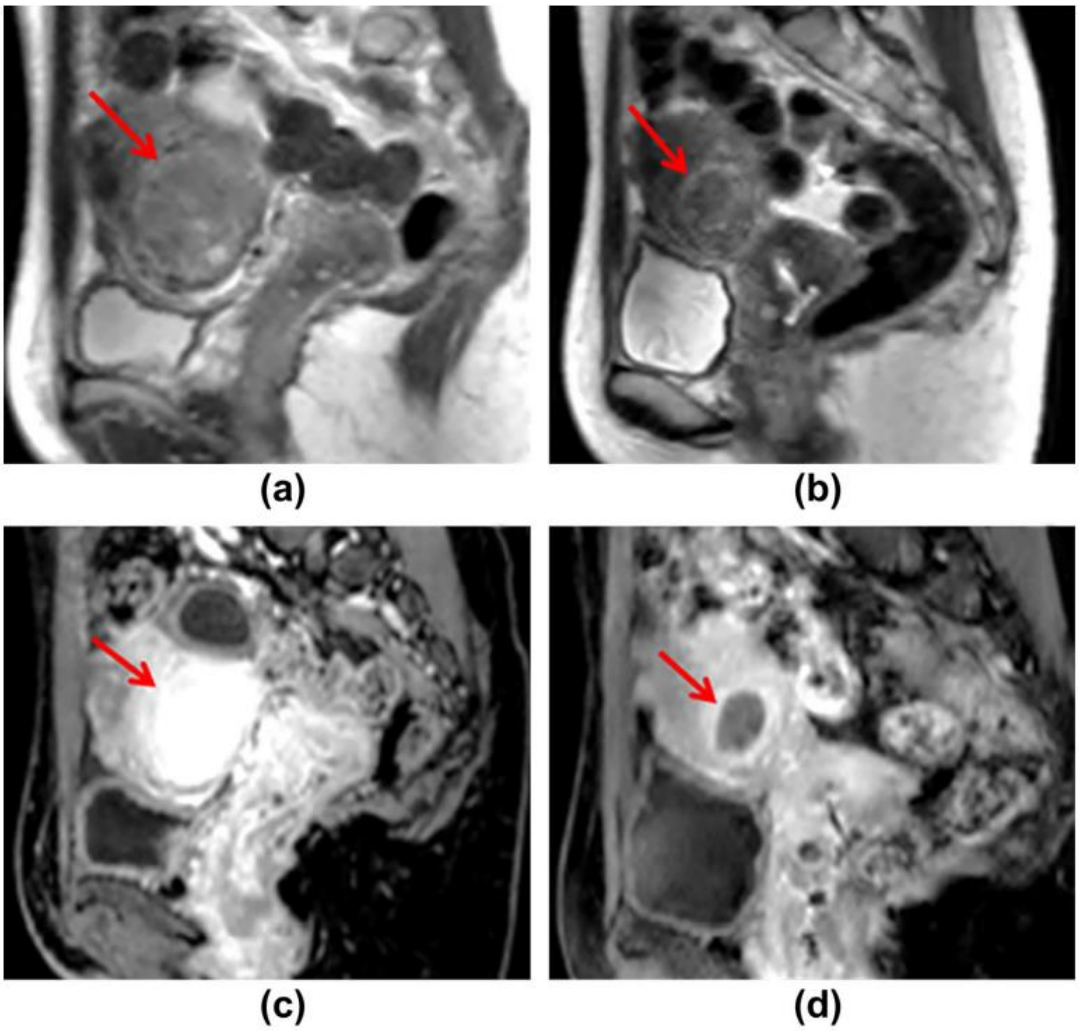

Figure 3. (a) Sagittal T2-weighted images showing an intramural fibroid with isointense/hyperintense signal compared to myometrium, which reduced by 77% nine months after the embolization (b, d). (c) Before UAE, the fibroid had also shown hyperintense signal compared to myometrium on contrast-enhanced T1-weighted images (Kalina et al, 2018).

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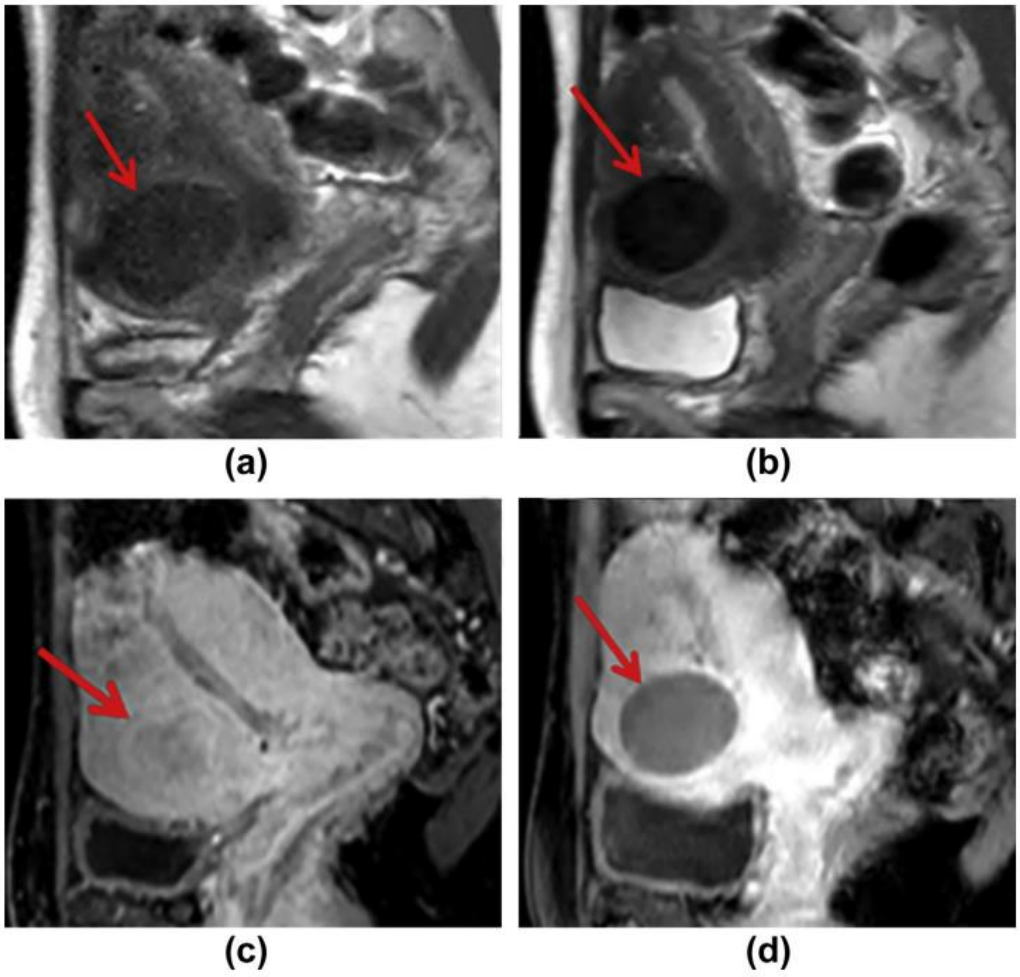

Figure 4. T2-weighted MRI images obtained from the same patient shown in Fig 2 in another sagittal plane. (a) The intramural fibroid of low T2 SI on pre-embolization images had undergone only 32% VR 9 months after UAE (b, d). (c) The signal of this fibroid appears hypointense on preembolization contrast-enhanced T1-weighted sequence (Kalina et al, 2018).

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3.2. Safety and effectiveness of UFE in fibroids larger than 10 cm

Between 28 April 2008 and 31 December 2012, 303 UAE were performed in our department (Semmelweis University, Medical Imaging Centre), all patients were included in the study (Bérczi et al, 2015). The mean age of the patients was 42.3 years (range 24–54 years). Leading symptoms were strong menstrual bleeding accompanied by pelvic pain, anemia, and urgent sensation of urination. Some of our patients reported fertility problems or subsequent desire for pregnancy. All treated patients had full documentation of symptoms (Table 3.), previous gynecological history, diameters of the largest fibroid, and follow-up information including complications.

Table 3. Complaints of fibroid patients before UFE (Bérczi et al, 2015).

Complaints (n = 303, 100 %)		n	%
Distribution of menstruation			
	Dysmenorrhea	277	91.4
	Anaemia	50	16.5
Pain			
	Pelvic pain	64	21.1
	Lumbar pain	20	6.6
	Dyspareunia	6	2.0
Pressure			
	Pelvic pressure	32	10.6
	Frequent urination	107	35.3
	Obstipation	5	1.7
Fertility			
	Subfertility/infertility	4	1.3

In 19 cases (all belonged to Group 1), only unilateral embolization was done because of tortuous origin of the uterine artery, early venous filling, retrograde filling of the ovarian artery, or unidentifiable uterine artery.

Table 4. Satisfaction analysis (4A) and summary of pre- and postprocedural quality-of-life scores (4B). Numerical analog quality-of-life score presents major improvement of symptoms in both groups with no significant differences between scores of the two groups (Mann-Whitney U test).

(A)	Group 1 (239/262)		Group 2 (36/41)		
Satisfaction					
Has UFE improved your symptoms?					
Yes	184	77.0%	28	77.8%	
Partially	42	17.6%	5	13.9%	
No	13	5.4%	3	8.3%	
Would you recommend this treatment to other patients?					
Yes	236	98.7%	35	97.2%	
No	3	1.3%	1	2.8%	
(B) Score	Group 1 (239/262)		Group 2 (36/41)		*p*
Numerical analog quality-of-life score					
Preprocedural	33.3±23.5		33.5±24.1		0.940
Postprocedural	85.6±16.0		81.5±23.5		0.365

Before embolization, imaging of the uterus was typically done by pelvic CE-MR. For 7 out of 303 patients, MR was not done predominantly due to claustrophobia, for these patients, transabdominal or transvaginal ultrasound was performed. Clinical efficacy was assessed using numerical analog quality-of-life score (0-unbearable symptoms; 100-perfect quality of life) before and after the procedure. All periprocedural and postprocedural complications were listed during the procedure and at the follow-up interviews. Minor complications included temporary fever (not longer than 4 weeks without any need of antibiotics), temporary amenorrhea, long-lasting postprocedural menstrual bleeding, postprocedural dysmenorrhea, aspecific infection (fever without pelvic complication and need for antibiotics). These complications did not require hospitalization or remarkable medication. Major complications were determined as fibroid expulsion, emergency myomectomy, or emergency hysterectomy due to infectious complication of the necrotized fibroid. Elective myomectomy or elective hysterectomy was also listed.

The patients were divided into two groups based on the largest diameter of the largest fibroid; Group 1: diameter ≤10 cm, and Group 2: diameter >10 cm. Statistical analysis

of the relationship between fibroid diameter and complications was performed using Fisher's exact test. Mann–Whitney *U* test was applied for the statistical analysis of quality-of-life score in the two groups.

3.2.1. Clinical Efficacy in Group 1 (≤10 cm) and Group 2 (>10 cm)

The number of patients in Group 1 (≤10 cm) and Group 2 (>10 cm) was 262 and 41, respectively. Follow-up is available on 275 patients (275/303 = 90.8 %) (Group 1: 239/262 = 91.2 %; Group 2: 36/41 = 87.8 %). Mean follow-up time was 7.79 ± 5.16 (SD) month (7.6 ± 4.9 for Group 1, and 8.98 ± 6.7 for Group 2). Symptoms improved at least partially in 94.6 and 91.7 % in Group 1 and Group 2, respectively (Table 4A). Quality-of-life score was 33.3 ± 23.5 and 33.5 ± 24.1 before, whereas 85.6 ± 16.0 and 81.5 ± 23.5 after UAE in Group 1 and Group 2, respectively; (Mann–Whitney *U* test one-sided, $p = 0.365$) (Table 4B).

3.2.2. Complications in Group 1 (≤10 cm)

The vast majority of these complications were minor, such as fever (12 cases), temporary amenorrhea (7 cases), prolonged menstruation (4 cases), aspecific infection (2 cases), intermittent menorrhagia (4 cases) and postprocedural dysmenorrhea (23 cases). Among major complications, expulsion of a fibroid was reported in 4 cases, all of them appeared in between the 2 weeks and 3 month following UFE; one of these patients needed supplementary surgical gynecological intervention to complete the expulsion. In 2 cases, acute hysterectomy was necessary on the 5th and 9th postprocedural week followed by appearance of strong pelvic pain, fever, and elevated septic blood parameters in both patients. Elective myomectomy was done because of persistent symptoms, 7.5 months following UFE (Table 5).

All 19 patients who had unilateral embolization belonged to Group 1, follow-up is available in 12 cases and none of them had remarkable complications.

3.2.3. Complications in Group 2 (>10 cm)

The following minor complications were documented: fever (5 cases), temporary amenorrhea (1), aspecific infection (1), postprocedural dysmenorrhea (2), and intermittent menorrhagia (1). Major complications as fibroid expulsion of the fibroid were reported in 1 case, the necrotized fibroid tissue appeared in the cervical canal in

the 6th post-interventional month. As septic complications, one emergency myomectomy occurred in the 6th postprocedural week; acute hysterectomy was reported in 2 cases, 3, and 6 weeks following UAE (Table 5).

An elective myomectomy was reported 8 months after UAE because the embolized fibroid grew back to the pre-embolization size resulting in symptom recurrence. In another case, the large uterine mass was unchanged in size and unusually strong post-interventional blood flow was detected during transvaginal ultrasound, malignancy was suspected. Hysterectomy was decided, elective surgery was performed 8 months after UAE; subsequent histology, however, excluded malignancy (Table 5).

Table 5. List of minor and major complications following UFE in patients with fibroids ≤10 cm (Group 1) and >10cm (Group 2). Statistical analysis was performed using Fisher's exact test.

	Group 1 (239/262)		Group 2 (36/41)		
	(n)	(%)	(n)	(%)	p value
Complications					
Fever	12	5.0	5	13.9	0.063
Temporary amenorrhea	7	2.9	1	2.8	1.0
Prolonged menstruation	4	1.7	0	0.0	1.0
Aspecific infection	2	0.8	1	2.8	0.354
Postprocedural dysmenorrhea	23	9.6	2	5.6	0.550
Intermittent menorrhagia	4	1.7	1	2.8	0.519
Myoma expulsion	4	1.7	1	2.8	0.519
Acute myomectomy	0	0.4	1	2.8	-
Elective myomectomy	1	0.0	1	2.8	0.090
Acute hysterectomy	2	0.8	2	5.6	0.253
Elective hysterectomy	0	0.0	1	2.8	-

4. Discussion

4.1. Pre-embolization MRI parameters of fibroids as prognostic values for the effectiveness of UFE

UAE has been shown to be effective in reducing fibroid volumes and improving QOL in our study group of 70 patients. The average fibroid volume reduction of 51.1% in our study population is comparable with literature data. Literature data show that within 3–6 months after the procedure, the observed reduction in the volume of fibroids was 25%–60% (Burn et al, 2000; Szkodziak et al, 2020). Furthermore, on post-embolization images, we have found complete infarction in 89 fibroids (84.0%), almost complete infarction in 5 fibroids (4.7%) and partial infarction in 12 fibroids (11.3%). The ratio of fibroids having partial infarction in our study is similar to the findings of Kroencke et al (20%) (Kroencke et al, 2010). These data suggest that the effectiveness of the embolization protocol used in our study group reached international standards.

In our study population, QOL scores have been markedly improved (48.2±27.6 points) after UAE. Similarly, Spies et al described that UAE significantly reduced symptoms ($p < 0.001$) and improved QOL ($p < 0.001$) (Spies et al, 2005). Silva et al reproduced these results in their study in 2020, where they collected retrospective data from 60 patients before, and after uterine artery embolization using „The Uterine Fibroid Symptom – Quality of Life (UFS-QoL)" questionnaire. They found significant improvement ($p<0.001$) between pre- and post-embolization in all scores of UFS-QoL, both for symptom severity and quality of life subscales; total score improved from 41.4 to 92.2 (actual raw score – lowest possbile raw score)/possible raw score range *100; maximum value is 100) (Silva et al, 2020; Spies et al, 2002).

Submucosally located fibroids showed a greater degree of volume reduction after UAE than intramural (difference: 32.7%) or subserosal (difference: 39.1%) fibroids did. Jha et al previously reported this difference, as submucosal fibroids showed a 30-40% greater volume reduction than intramural or subserosal ones did ($p<0.001$) (Jha et al, 2000). Spies et al (15) also indicated that volume reduction of submucosally located fibroids was superior to the volume reduction of subserosal fibroids by 14% at 3 months ($p = 0.02$) (Spies et al, 2002).

Zlotnik et al followed 50 symptomatic premenopausal women with uterine leiomyomas who underwent uterine artery embolization in their prospective longitudinal study in 2014. They found that the average decrease in uterus volume and the leimyomas was 38.9% and 55.2%, respectively (Zlotnik et al, 2014).

In contrast, Firouznia et al reported no difference in volume changes between submucosal fibroids and nonsubmucosal fibroids 12 months after UAE (Firouznia et al, 2008). Sipola et al concluded that the location of the dominant leiomyoma had no significant effect on size reductions of the uterus or dominant leiomyoma. Although they point out, that 81% of leiomyomas in their study were intramural, thus, the statistical power of their study may be insufficient to reach firm conclusions regarding this topic. (Sipola et al, 2010).

The greater degree of volume reduction of submucosal fibroids in response to UAE may be related to the distribution of the embolization particles within the uterine vascular system. The main branches of the intramural uterine artery, called the arcuate arteries terminate in peripheral and radial arteries, the radial arteries are larger and more numerous, and they feed the central two-thirds of the myometrium as well as the endometrium. These arteries may, therefore, provide greater flow of embolic material to the central submucosal branches, as compared with the flow to a subserous fibroid that is fed by a peripheral branch. The central two-thirds of myometrium receives more abundant blood supply via the radial arteries than the outer myometrium, hence the embolic particles can reach submucosal fibroids to the greatest amount (Harman et al, 2006). Furthermore, Aziz et al demonstrated that after embolization of the distal part of the uterine artery, only a few arteries contained the injected embolic particles at the outer parts of the myometrium on histological examination of the hysterectomy specimens (Aziz et al, 1998).

We report that smaller baseline fibroid size (<50 cm^3) was related to a greater volume reduction compared to larger fibroids. This finding is consistent with the results of Spies et al who demonstrated that larger initial dominant fibroid volume predicted less volume reduction at both 3 and 12 months after embolization (Spies et al, 2002). A hypothesis by Burn based on the model of oxygen supply and demand suggested that a large fibroid would be more responsive to embolization of its nutritive vessels than small fibroids would be (Burn et al, 2000). In contrast, deSouza and Williams reported that initial fibroid

size (≥ 50 cm^3 vs. <50 cm^3) was not related to the volume reduction at 4 months after UAE (deSouza et al, 2002). Similarly, Sipola et al, Zlotnik et al, Duvnjak et al. found no association between leiomyoma size and size reduction rate (Sipola et al, 2010).

Our study showed that fibroids that were isointense or hyperintense to the myometrium on CE images elicited 13.7% greater mean volume reduction than fibroids with hypointense signal. Similarly to our results, Harman et al reported that fibroids with a hyperintense signal on CE images showed 28.7% greater volume reduction than fibroids of contrast-enhancement equal to or lower than that of myometrium at 6 months after UAE (Harman et al, 2006). On contrast-enhanced images, cellular fibroids show homogeneous enhancement, whereas fibroids with degenerative process or necrosis have a heterogeneous or hypointense signal compared to the normal myometrium (Cura et al, 2006; Cao et al, 2014). In contrast, Burn et al and deSouza and Williams have found no correlation between the degree of gadolinium-enhancement and volume reduction after UAE (Burn et al, 2000; deSouza et al, 2002). In the study of Sipola et al, the value of contrast enhancement was controversial (Sipola et al, 2010). In Spearman rank correlation analysis, contrast enhancement was not associated with leiomyoma size reduction. However, contrast enhancement was useful in identifying patients with 50% uterus size reductions and 75% dominant leiomyoma size reductions. They concluded that contrast enhancement could possibly be useful in fibroids that are hyperintense on T2 images due to degeneration but show no perfusion after intravenous contrast due to necrosis and as a result do not respond to further treatment with UAE (Sipola et al, 2010). In the study of Zlotnik et al, perfusion pattern was evaluated in the T1 images using the PP ratio. The peak high-contrast phase (HCP) and precontrast phase (PCP) are parameters for this relationship, and the PP ratio = [(HCP fibroid-PCP fibroid)/PCP fibroid]x100. They found that this ratio was not associated with a reduced leiomyoma volume (Zlotnik et al, 2014). The study by Duvnjak et al. have not shown a significant correlation between the post-contrast T1-weighted SI ratio and the volume reduction in the dominant fibroid. As a possible explanation they added that different MRI scanners and different delay times between scanning and contrast administration could explain these results (Duvnjak et al, 2017).

In our study, fibroids with isointense or hyperintense T2 signal compared to myometrium showed a 15.1% greater mean volume reduction than fibroids with T2 SI lower than that

of myometrium (Kalina et al, 2018). This finding is consistent with the results of deSouza and Williams (deSouza et al, 2002) who found that isointense or hyperintense fibroids on T2-weighted images showed 23.3% greater volume reduction than fibroids with hypointense signal compared to myometrium at 4 months after UAE. Burn et al. and Chang et al. also demonstrated the association between high T2 SI and greater volume reduction, which may be due to the higher fibroid cellularity and vascularity (Burn et al, 2000; Chang et al, 2012).

The idea of prospectively testing the hypothesis that quantitative MRI parameters obtained by calculating T1 time, T2 time, leiomyoma-to-skeletal muscle T2 SI-ratio can predict uterus and leiomyoma size reductions after UAE comes from Sipola et al in 2010. In their single-center, prospective clinical trial of 52 patients, leiomyoma size reductions were accurately predicted with leiomyoma-to-skeletal muscle T2 SI-ratio (ROC curve A_z=0.930; 95% confidence interval [CI]: 0.853, 1.000) (Sipola et al 2010). Leiomyoma size reductions ≥75% were predicted by leiomyoma-to-skeletal muscle T2 SI-ratio 3.5 and T1-time 750 msec with 100% and 86% sensitivities and 67% and 72% specificities, respectively. Uterus size reduction ≥50% were identified by dominant leiomyoma-to-skeletal muscle T2 SI-ratio 2.5 (Sipola et al, 2010).

Similar results were found by Duvnjak et al in their prospective study of 52 patients. In their study they calculated fibroid-to-iliac muscle signal intensity ratio as SI of the dominant fibroid/SI of the iliac muscle on T1-, T2-, and T1 post-contrast-weighted sequences. Statistically significant correlation between SI fibroid-to-muscle ratio and imaging volume reduction outcome was only found ratio at the T2-weighted sequence. They concluded that a high SI fibroid-to-muscle ratio on T2 sequence can predict a volume reduction outcome of UFE; The correlation between SI fibroid-to-muscle ratio at the T2-weighted sequence and imaging volume reduction outcome was statistically significant ($p<0.002$). Spearman's rank showed positive correlation ($r = 0.439$, $p<0.003$) between the fibroid-to-muscle SI ratio on T2-weighted sequence; these information may be used for better patient selection. The authors have not compared volume reduction with the T2 values of the myometrium (Duvnjak et al, 2017).

Zlotnik et al reached similar conclusion in 2014 in their prospective longitudinal study of 50 patients with 179 examined leiomyoma. They concluded that symptomatic uterine

leiomyomas in patients undergoing UFE show volume reductions greater than 50% by magnetic resonance imaging when the leiomyomas are submucosal and/or had a high fibroid-to-muscle ratio in the T2 images (Zlotnik et al, 2014).

Cakir et al reproduced these results in 2021 in their retrospective study of 30 patients. SI ratio (fiborid/iliac muscle) assessed from pre-procedure T2W MR images was found to be a significant determinant of ≥50% volumetric regression in the fibroid after UFE ($p = 0.017$) (Cakir et al, 2021).

On the contrary, Jain et al and Hecht et al did not find association between T2 SI and volume reduction after UAE (Jain et al, 2007; Hecht et al, 2011).

Opposing other results (Jha et al, 2000; Burn et al, 2000; Sipola et al, 2010) that reported that high fibroid T1 SI was predictive of a poor response to embolization, we did not find relationship between T1 SI and UAE outcome. Most fibroids are isointense to the sorrounding myometrium on T1-weighted images (Kirby et al, 2011). Hyperintensity of fibroids on T1 weighted images may be the consequence of the presence of either blood or fat, indicating that the fibroid had undergone haemorhagic necrosis or it is the rarely occuring lipoleiomyoma (Cao et al, 2014). A fibroid that has outgrown its vascular supply and consequently has undergone hemorrhagic degeneration is expected to show a poor response to UAE (Burn et al, 2000).

Limitation of this study is that MR studies were done in 3 different MR units, however, all images were uploaded to our PACS system; however, all images were uploaded to the PACS system, and the images were evaluated by same radiologist with 20 years of MRI experience.

In conclusion, submucosal localization, volume of less than 50 cm^3, high vascularity and high T2 SI on pre-treatment images were associated with post-treatment volume changes; these findings may help in the treatment decision.

4.2. Safety and effectiveness of UFE in fibroids larger than 10 cm

From the very beginning of the acceptance of UAE as an alternative treatment for hysterectomy, many centers tried to investigate risk factors for complications. Early publications suggested that the size of the fibroid, the total uterine size, and the amount

of applied PVA particles represent higher risk. Recent publications debated these suggestions (Parthipun et al, 2010).

Pelage et al. published their data about 80 patients with UAE (Pelage et al 2000). Although the size of the fibroid was not given, they reported one case when acute hysterectomy was needed 17 days following UAE due to necrosis and infection of a large subserosal fibroid. In their discussion, the authors referred to another group who reported two cases of emergent hysterectomy related to fibroid infection following large uterine fibroid (Goodwin et al, 1997; Worthington-Kirsch et al, 1998).

Katsumori et al. published their study with the involvement of 152 patients (Katsumori et al, 2003). The authors specially focused on risks of UAE in groups with fibroid smaller or larger than 10 cm (Spies et al, 2002). Based on their experience, there was no statistically significant difference in septic complications between the two groups ($p = 0.172$) (Spies et al 2002). In 2008, Firouzina et al. studied cases of 101 patients whether size, position, and the number of fibroids influence the effectiveness or complication rate of UAE. No correlation was found between the number of complications and the size of the fibroid (Firouznia et al, 2008).

From 2010, two further groups published that large uterine fibroid would not mean contraindication for UAE. Smeets et al. investigated long-term follow-up data of 71 patients with large uterine fibroids. One patient appeared 7 weeks later with vaginal discharge and fever, thus hysterectomy was performed (Smeets et al, 2010). The role of the fibroids larger than 10 cm was worked out on 121 cases in a study from Parthipun et al. (Parthipun et al, 2010). Out of 30 patients with large fibroid, only one septic complication was reported but there was no necessity of hysterectomy. From the group having fibroid smaller than 10 cm in size, one emergent hysterectomy was reported. Extensive statistical analysis of this study revealed no significant correlation between large uterine fibroid and septic hysterectomy (Parthipun et al, 2010).

A throrough systematic review and meta-analysis conducted by Llewellyin et al. identified four observational studies with a total of 839 patients (giant = 163, non-giant = 676) - out of the 839 patients, 303 were from our study - reported an insignificantly longer operation time and hospital stay in the giant fibroid group and no difference in the rate of total complications. Using the SIR classification system to categorise

complications they found no difference in the rate of minor complications, however, a greater prevalence of major complications and reinterventions was identified in the giant fibroid group. As they conclude, current evidence shows UAE is a safe and effective option to treat giant fibroids. However, the limited available data indicates a relatively higher risk of complications and reinterventions when compared with non-giant fibroids. (Llewellyin et al, 2019).

Based on our experience as one of the largest series for such an analysis (303 patients) and recent results from the literature, UAE can be considered as a safe and effective procedure for treatment of fibroids larger than 10 cm of the largest diameter. Since there was no significant difference in complications between patients having fibroids smaller or larger than 10 cm, UAE can be offered for women having large uterine fibroid.

5. Conclusion

5.1. Pre-embolization MRI parameters of fibroids as prognostic values for the effectiveness of UFE

- Fibroid location, T2 SI compared to myometrium, contrast enhancement (CE), and size showed significant association with the degree of VR after uterine artery embolisation.

- The mean volume reduction (VR) of submucosal fibroids was 82.1±18.5%, which was significantly greater than the VR of intramural (49.4±30.7%) and subserosal (43±28.3%) fibroids ($p<0.01$ for both). The VR of intramural and subserosal fibroids did not differ significantly ($p=0.79$).

- Eighteen fibroids (16.5%) that were isointense or hyperintense to myometrium on pretreatment T2-weighted images showed a mean VR of 63.7±25.8%, whereas the other 91 fibroids (83.5%) that were hypointense to myometrium showed a VR of 48.6±31.3% ($p=0.041$).

- Twenty-nine fibroids (27.4%) with isointense or hyperintense signal compared to myometrium on contrast-enhanced images showed a volume reduction of 61.3±27.4% which was significantly greater then the volume reduction of 47.6±31.6% showed by the 77 fibroids (72.6%) with hypointense signal compared to myometrium ($p = 0.035$).

- Fibroids with a baseline volume of <50 cm^3 (n=59; 54,1%) showed a VR of 54.9±37.1% (range, -112.1–99%), which was significantly greater than the degree of VR showed by fibroids ≥ 50 cm^3 (n=50; 45,9%; 46.7±20.6%; range, 5.1–90.3%; $p=0.021$).

- No statistically significant associations were found between fibroid T2 SI compared to skeletal muscle ($p=0.421$), T1 SI compared to myometrium ($p=0.270$) and skeletal muscle ($p=0.14$) and volume reduction following uterine artery embolisation.

- Mean QOL) score before UAE was 38.5±24.3 points, which improved by 48.2±27.6 points to 86.7±15.9 points at 36.0±11.5 months after the procedure ($p< 0.001$).

- UAE was completed in all patients without any major complications.

- These findings may help with treatment decisions for patients requiring uterine fibroid embolisation in selected cases.

5.2. Safety and effectiveness of UFE in fibroids larger than 10 cm

- Quality-of-life score was 33.3 ± 23.5 and 33.5 ± 24.1 before, whereas 85.6 ± 16.0 and 81.5 ± 23.5 after UAE in Group 1 (≤10 cm fibroids) and Group 2 (>10 cm fibroids), respectively. Thus, there was no significant difference in the clinical effectiveness between fibroids with ≤10 cm largest diameter compared to those >10 cm.

- There were 4 myoma expulsions, 1 acute myomectomy, and 2 acute hysterectomies reported from Group 1, meanwhile 1 myoma expulsion, 1 acute myomectomy, and 2 acute hysterectomies were documented from Group 2 ($p>0.05$ in all cases). Thus, there was no significant difference in the number of minor and major complications between fibroids with ≤10 cm largest diameter compared to those >10 cm.

- Since there was no significant difference in complications between patients having fibroids smaller or larger than 10 cm, UAE can be offered for women having large uterine fibroid.

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6. Summary

MRI characteristics of 109 fibroids (≥3 cm) in 70 patients were analysed retrospectively. Imaging was performed 1.8±1.3 (SD) months before and 6.6±1.8 months after UAE. The mean fibroid volume decreased by 51.1±30.8% during the 6.6±1.8 months ($p<0.001$). Mean quality-of-life score improved by 48.2±27.6 points ($p<0.001$). The mean VR of submucosal fibroids was greater than that of intramural and subserosal fibroids. Fibroids that were isointense/hyperintense to myometrium on T2-weighted images showed a better response than hypointense fibroids. On contrast-enhanced images, isointense/hyperintense fibroids showed a better VR than hypointense fibroids. Baseline fibroid volume of < 50 cm^3 was also associated with favourable imaging outcome. T2 SI compared to skeletal muscle and T1 SI compared to myometrium or skeletal muscle did not show association with VR.

From 28 April 2008 until 31 December 2012, 303 patients had uterine artery embolization (UAE). 262 patients had small (largest diameter ≤10 cm [Group 1]), 41 patients had large (largest diameter >10 cm [Group 2]) fibroid. During the mean follow-up time (7.79 ± 5.16 [SD] month), data on 275 patients (275/303 = 90.8 %) were available. Quality-of-life score was 33.3 ± 23.5 and 33.5 ± 24.1 before, whereas 85.6 ± 16.0 and 81.5 ± 23.5 after UAE in Group 1 and Group 2, respectively. There were 4 myoma expulsions, 1 acute myomectomy, and 2 acute hysterectomies reported from Group 1, meanwhile 1 myoma expulsion, 1 acute myomectomy, and 2 acute hysterectomies were documented from Group 2 (NS differences).

The major finding of our results are that localisation, T2 SI, contrast enhancement, and <50 cm^3 fibroid volume were associated with better volume reduction, these data may help in patient selection, and with treatment decisions; there was no significant difference in the effectiveness and in the number of minor and major complications between fibroids with ≤10 cm largest diameter compared to those >10 cm, thus, uterine artery embolisation can also be offered to patients with fibrois with >10 cm.

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DOI:10.14753/SE.2022.2678

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