CEOG Clinical and Experimental Obstetrics & Gynecology

Feasibility of magnetic resonance-guided focus ultrasound surgery (MRgFUS) in the uterine fibroid treatment: evaluation of the treatment radicalization in single and multiple fibroids correlated to clinical outcome

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Summary

Objective: To demonstrate the efficacy of magnetic resonance-guided focused ultrasound (MRgFUS) in uterine fibroid treatment in terms of extension of non-perfused volume and improvement of the symptoms above all in fertile women. This method is a valid alternative to hysterectomy. *Materials and Methods:* From October 2011 to September 2015, 78 patients, aged between 23 and 51 years, affected by uterine fibroids, were treated with MRgFUS in the present department. The authors included 47 patients affected only by uterine fibroids (size range 2- 14 cm) and 31 affected by multiple fibroids. Symptoms were dysmenorrhea, menorrhagia, and infertility. Symptomatology was assessed through the symptoms severity score questionnaire. The authors evaluated the radicalization of the treatment measuring the non-perfused volume (NPV) on the c.e. T1–weighed sequences immediately after the treatment and compared these results with the pre-treatment volume of the fibroids. A dedicated informatics measurement system was used. *Results:* The present results showed a mean of non-perfused volume of 78%, with a good radicalization of the treatment. Patients presented a marked reduction of symptoms (90%) when compared to pre-treatment. *Conclusion:* The treatment of uterine fibroids using MRgFUS is a valid alternative to surgery. A good extension of the necrotic area is obtained in women affected by multiple and single fibroids, maintaining the integrity of the uterus.

Key words: Uterine fibroids; MRgFUS; Ultrasound surgery; Single and multiple fibroids; Non-perfused volume.

Introduction

Fibroids are benign tumours growing in the uterus, which are symptomatic in up to 25% of women in childbearing age [1]. They are monoclonal tumours of the uterine smooth muscle cells and consist of large amounts of extracellular matrix containing collagen, fibronectin, and proteoglycan [2, 3]. Although their pathogenesis is still unknown, there is considerable evidence that estrogens and progestogens proliferate tumour growth [4, 5] as the fibroids rarely appear before menarche [6] and regress after menopause [7]. They are classified depending on their location with regards to the layers of the uterus as sub-serous, intramural, or sub-mucous and can be single or multiple. They are often asymptomatic, but can cause multiple symptoms such as heavy and prolonged menstrual bleeding, severe pain, bloating, constipation, feeling of pelvic pressure, urinary incontinence or retention, or pain. They may also be associated with reproductive problems such as infertility and miscarriage [8].

Ultrasonography is the standard confirmatory test because it can easily and inexpensively differentiate a fibroid from other pathologies. Magnetic resonance imaging (MRI) with infusion of contrast can provide information about vascularization of the fibroids and the relation of the fibroids with respect to the endometrial and serosal surfaces. This relation influences the choice among uterine-sparing treatment options. Hysterectomy is the most common treatment for uterine fibroids and may be associated with lengthy hospitalization and complications [9, 10], which have resulted in a demand for less invasive treatment modalities. Various myomectomy procedures, uterine artery embolization, and magnetic resonance-guided focused ultrasound surgery (MRgFUS) are viable treatment options for uterine fibroids. The advantages of the conservative modalities over open surgical procedures are lower morbidity and shorter recovery times compared with hysterectomy [11, 12]. MRgFUS offers several advantages for treating uterine fibroids because it is a completely non-invasive, outpatient procedure that requires minimal sedation, and allows for a speedy recovery. Patients undergoing MRgFUS typically return to work within 24 hours, compared with ten days after uterine artery embolization (UAE) and six weeks after my-

Revised manuscript accepted for publication July 19, 2016

omectomy or hysterectomy. The initial FDA recommendation was that only women who have completed their families should be treated with MRgFUS. However, with the advantage of consistently good safety and efficacy results being reported, multi-centre fertility studies were commenced and are ongoing. These studies are recruiting women with symptomatic uterine fibroids, who wish to become pregnant. The non-invasive nature of MRgFUS, whereby only the uterine fibroids undergo thermal ablation with no damage to healthy surrounding tissue, suggests that MRgFUS is a safe approach for women who want to preserve their fertility [13]. Purpose of this study was to demonstrate the efficacy of the uterine multiple fibroid treatment, using MRgFUS as a conservative therapy, in fertile women, with the possibility to save the surrounding healthy uterine wall, without fibrotic scar.

Materials and Methods

From October 2011 to September 2015, 78 patients aged between 23 and 51 years (mean age 37) affected by uterine fibroids, were treated with MRgFUS in the present department. Fibroids measured between two and 14 cm. Thirty-one patients out of 78 had multiple uterine fibroids and 47 out of 78 presented with a single fibroid (total fibroids treated 85). This study was carried out by a team of three interventional radiologists, three residents in radiology, one gynaecologist, and one resident in gynaecology.

The fibroids, sizing between two and 14 cm, were mainly located in the anterior wall (24) and close to the uterine fundus (30). All patients presented dysmenorrhea, menorrhagia, diffuse uterine enlargement, and chronic pelvic pain. Seven patients had difficulties in conceiving. None of the patients had been submitted to surgical treatment nor drug therapy, except one who had undergone myomectomy eight years before and subsequently relapsed.

After clinic evaluation, patient filled in the UFS-QOL questionnaire, consisting in eight questions about symptom severity and 29 questions about quality of life in terms of concerns, activity, energy, mood, control, self-awareness. and sexual function.

The eight symptom questions of the Severity Symptoms Score (SSS) was evaluated using a Likert scale, assigning five points to every question. The authors considered in this study only the first eight questions about symptom severity, with the final score ranging from 8 to 40 [14].

Inclusion criteria of patients were defined in accordance with the Exablate guidelines for treatments, listed in Table 1.

The authors excluded patients who had standard contraindications to MRI (Table 1), including non-MRI compatible implanted metallic devices, obesity (weight > 110 kg), intolerance to prolonged stationary prone position in the MRI scanner during the treatment, and women with hyper-sensitivity to contrast media. They also ruled out patients unable to understand instructions or communicate sensations during the treatment, to guarantee a safe procedure. Patients were required to refer to the operator any form of symptomatology in terms of back and leg pain and skin burning. Another exclusion parameter was the severe impairment of clinical conditions such as unstable heart disease, cerebrovascular diseases, hemolytic anemia, anticoagulant therapy or disorders of haemostasis. The authors also excluded women affected by such uterine pathologies as ectopic pelvic masses and pelvic inflammatory diseases.

Table 1. — *Exclusion criteria of MRgFUS treatment.*

Exclusion Criteria
1. Hemoglobin <10
2. Patient has hemolytic anemia
3. Patient has unstable cardiac status including:
_ Unstable angina pectoris on medication
_ Documented myocardial infarction within six months of protocol entry
_ Congestive heart failure requiring medication (other than diuretic)
_ Currently taking anti-arrhythmic drugs
_ Severe hypertension (diastolic BP > 100 on medication)
_ Presence of cardiac pacemaker
4. Patient has severe cerebrovascular disease (multiple CVA or CVA within six months)
5. Patient is on anti-coagulation therapy or has an underlying bleeding disorder
6. Evidence of uterine pathology other than leiomyoma
7. Patient has an active pelvic infection
8. Patient has an undiagnosed pelvic mass outside the uterus.
9. Patient weight >110 kg
10. Patient with extensive longitudinal abdominal scarring in an area of the abdomen directly anterior to the treatment area.
11. Patient with standard contra-indications for MR imaging such as non-MRI compatible implanted metallic devices.
12. Individuals who are not able or willing to tolerate the required prolonged stationary prone position during treatment (approximately 3 h.)

All patients were submitted to a preliminary pelvic MRI study to show the lesions. This was performed in the prone position in order to assess the site of the lesion with respect to bowel, bladder, and bone. The authors acquired T2-weighted, T1-weighted, and T1-weighted fat sat sequences on the three planes (to exclude concomitant adenomyosis) without and with injection of contrast medium.

Patients were considered technically treatable with MRgFUS when the fibroids could be reached by the ultrasound beam. The authors studied the distance of the fibroid from the skin and established a limit of 14 cm as appropriate for the ultrasound beam focalization. Patients presenting bowel interposition in the path of the ultrasound beam were excluded to avoid damages in the bowel wall. In fact, air bubbles or hard particles inside the bowel can reflect or absorb the ultrasound energy. Other exclusion criteria were as follows: pedunculated fibroids that could be dislodged inside the peritoneal cavity after treatment, calcified fibroids that do not allow beam penetration, fibroids with vascularized structure and MRI dishomogeneous signal, that do not allow to reach therapeutic temperatures, and women with extensive abdominal scars that were likely to divert and absorb ultrasound energy causing pain and burns.

The fibroids measured between two and 14 cm. Thirty-one patients out of 78 had multiple uterine fibroids and 47 out of 78 presented a single fibroid.

The pre-treatment volume of the fibroid was measured on the T2-weighted sequences acquired prior to the treatment in order to evaluate the target area. The authors also considered the non-perfused volume (NPV), measured immediately after treatments by c.e. T1 weighted fat sat sequences, representing the treated area, and repre-

senting an index of radicalization. This value was the volume of the lesion submitted to treatment and is correlated to the efficacy of the treatment itself.

All measurements were taken using an informatics method called "Lesion Management on Carestream Health", (Vue PACS, version u.11.3.2.4051) that allowed a semiautomatic measure of the target area.

Results

The treatment efficacy was evaluated in terms of images and clinical response. The mean value of the pre-treatment volume for the uterine fibroids was 39.5 cc (maximum 214 cc and minimum 1.2 cc). The treatment showed a mean value of NPV of 30.5 (maximum value 202.8 cc and minimum value of 0.4 cc), with a mean percentage value of 78%.

The clinical follow-up of was carried out immediately after treatment, after six months, and after one year.

The UFS-QOL showed an important score reduction passing from a mean pre-treatment score of 27.8 to a 13.7 after six months (reduction of 50.08%) and to 9.1 after one year post-treatment (reduction of 67.3%). Five patients showed a partial regression of the symptoms with a reduction in the UFS-QOL of only 6-9 points after six months (Figure 1).

After ten days from the treatment, the authors appreciated the disappearance of abdominal pain, dyspareunia, and inter-menstrual vaginal bleeding most of all in the women affected by intra-mucosal fibroids. After six weeks, patients referred a regularization of the menstrual cycle with a reduction of menorrhagia and dysmenorrhea. No one complained of skin burns or back and leg pain deriving from a possible injury of the sciatic nerve (Figure 2).

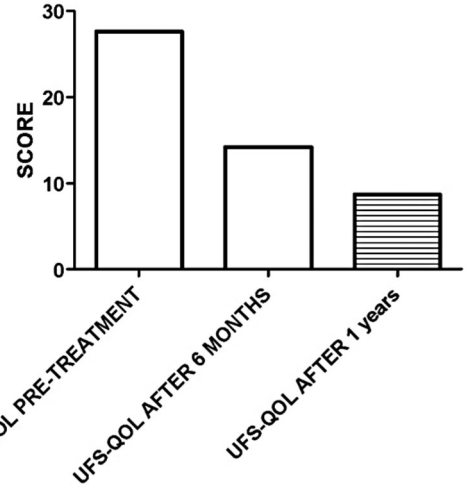

Figure 1. — *SSS pre-and post-treatment.*

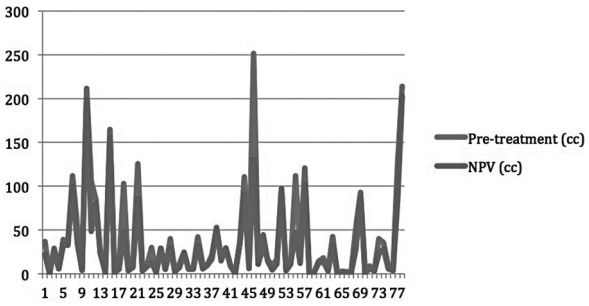

Figure 2. — *Evaluation of NPV value.*

Discussion

Uterine fibroids are benign tumours with high incidence in women. They are the third leading cause of hysterectomy with several consequences on the healthcare expenses. Hysterectomy is a leading surgical option for relief from symptomatic leiomyoma. It includes laparoscopy, laparotomy, and transvaginal procedures. Factors such as severity of symptoms and desire for future childbearing must be considered before this therapy is selected [15, 16]. In a comparative study of symptom relief after hysterectomy, uterine artery embolization, and myomectomy, all three modalities showed substantial symptom relief, but women who underwent hysterectomy had the greatest symptom improvement [17]. Disadvantages of hysterectomy include permanent infertility and operative-related morbidities such as anaesthesia complications, blood loss, and bowel and urinary tract injuries. Myomectomy is a uterus-preserving surgical option performed either through laparotomy, laparoscopy, or transvaginal approach where leiomyoma alone are removed. A major drawback of the transvaginal technique is the risk of needing to proceed to a laparotomy during the procedure, with weight of the leiomyoma and location within the fundus being the most frequently documented risk factors [18]. Mini-laparotomy myomectomy is a feasible option for women desiring an outpatient procedure. This cost-effective technique uses a smaller incision, and removal of leiomyoma is aided by a laparoscope. It can be accomplished with minimal analgesia, minimal blood loss, a mean recovery time of 3.5 hours, and a low complication rate that allows for same-day discharge. There is an increased, albeit rare, risk of uterine rupture in pregnancies following laparotomy and laparoscopic myomectomy involving uterine entry. A more common risk following myomectomy is an increased risk of cesarean delivery, with rates as high as 50% following laparotomy myomectomy [19]. Myomectomy is a mini-invasive therapy that can be used just for specific dimension and position of uterine fibroids. UAE [20] is an increasingly popular choice among women with symptomatic leiomyoma as a mini-

mally invasive alternative to hysterectomy and myomectomy. UAE has a high technical success rate (95–98%), rapid recovery, and low perioperative complication rate (1–5%), with sustained patient satisfaction and improvement of symptoms in the majority of women. There is evidence showing that clinical success of UAE among women with bulk-related symptoms relates to leiomyoma volumetric reduction [21]. Nonetheless, while criteria are established to determine if patients are appropriate candidates for UAE, there is no preoperative clinical observation or imaging feature that can predict the degree to which individual patient's leiomyoma will respond to embolization. Stating the UAE as a valid procedure in the treatment of highly vascularized fibroids, it has nonetheless proved to be unsuitable for young patients, notably for those who desire to carry out a pregnancy, since the procedure itself modifies the adnexa of uterus vascular systems [22]. From the present authors' results, it can be concluded that, when it is possible, the MRgFUS treatment represents an alternative therapy for single and multiple fibroids, since the application lasts no more than 180 minutes, it does not require general anaesthesia with an hospitalization in day-surgery (only one day). Furthermore, it is a non-invasive technique: no cutaneous or organ incision is made, thus no hematic loss neither blood transfusions appear and patients after MRgFUS treatment who would bear a pregnancy would not be candidates for cesarean sections; no relapse on the treated section is observed. Clinical symptomatology disappears or is strongly reduced with a reduction of the treated mass from 70% to 100 %. The procedure can be repeated even at short-term, due to the preservation of the organ.

References

[1] Ryan G.L., Syrop C.H., Van Voorhis B.J.: "Role, epidemiology, and natural history of benign uterine mass lesions". *Clin. Obstet. Gynecol.*, 2005, *48*, 312.

[2] Sankaran S., Manyonda I.T.: "Medical management of fibroids". *Best Pract. Res. Clin. Obstet. Gynaecol.*, 2008, *22*, 655.

[3] Parker W.H.: "Etiology, symptomatology, and diagnosis of uterine myomas". *Fertil. Steril.*, 2007, *87*, 725.

[4] Rein M.S., Barbieri R.L., Friedman A.J.: "Progesterone: a critical role in the pathogenesis of uterine myomas". *Am. J. Obstet. Gynecol.*, 1995, *172*, 14.

[5] Andersen J.: "Growth factors and cytokines in uterine leiomyomas". *Semin. Reprod. Endocrinol.*, 1996, *14*, 269.

[6] Fields K.R., Neinstein L.S.: "Uterine myomas in adolescents: case reports and a review of the literature". *J. Pediatr. Adolesc. Gynecol.*, 1996, *9*, 195.

[7] Cramer S.F., Patel A.: "The frequency of uterine leiomyomas". *Am. J. Clin. Pathol.*, 1990, *94*, 435.

[8] Munro M.G., Critchley H.O., Fraser I.S.: "The FIGO classification of causes of abnormal uterine bleeding in the reproductive years". *Fertil. Steril.*, 2011, *95*, 2204.

[9] Lalinec-Michaud M., Engelsmann F.: "Anxiety, fears and depression related to hysterectomy". *Can. J. Psychiatry*, 1985, *30*, 44.

[10] Lim P.C., Crane J.T., English E.J., Farnam R.W., Garza D.M., Winter M.L., Rozeboom J.L.: "Multicenter analysis comparing robotic, open, laparoscopic, and vaginal hysterectomies performed by high-volume surgeons for benign indications". *Int. J. Gynaecol. Obstet.*, 2016, *133*, 359.

[11] Volkers N.A., Hehenkamp W.J., Birnie E., Ankum W.M., Reekers J.A.: "Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 2 years' outcome from the randomized EMMY trial". *Am. J. Obstet. Gynecol.*, 2007, *196*, 519.e1.

[12] Edwards R.D., Moss J.G., Lumsden M.A., Wu O., Murray L.S., Twaddle S., *et al.*: "Uterine- artery embolization versus surgery for symptomatic uterine fibroids". *N. Engl. J. Med.*, 2007, *356*, 360.

[13] Zaher S., Lyons D., Regan L.: "Uncomplicated term vaginal delivery following magnetic resonance-guided focused ultrasound surgery for uterine fibroids". *Biomed. Imaging Interv. J.*, 2010, *6*, e28

[14] Spies J.B., Coyne K., Guaou Guaou N., Boyle D., Skyrnarz-Murphy K., Gonsalves S.M.: "The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata". *Obstet. Gynecol.*, 2002, *99*, 290.

[15] Practice Committee of American Society for Reproductive Medicine in collaboration with Society of Reproductive Surgeons: "Myomas and reproductive function". *Fertil. Steril.*, 2008, *90*, S125.

[16] Mukhopadhaya N., Pokuah Asante G., Manyonda I.T.: "Uterine fibroids: impact on fertility and pregnancy loss". *Obstet. Gynaecol. Reprod. Med.*, 2007, *17*, 311.

[17] Pies J.B., Bradley L.D., Guido R., Maxwell G.L., Levine B.A., Coyne K.: "Outcomes from leiomyoma therapies: comparison with normal controls". *Obstet. Gynecol.*, 2010, *116*, 641.

[18] Bhave Chittawar P., Franik S., Pouwer A.W., Farquhar C.: "Minimally invasive surgical techniques versus open myomectomy for uterine fibroids". *Cochrane Database Syst Rev.*, 2014, *10*, CD004638.

[19] Sutton C., Standen P., Acton J., Griffin C.: "Spontaneous uterine rupture in a preterm pregnancy following myomectomy". *Case Rep. Obstet. Gynecol.*, 2016, *2016*, 6195621.

[20] Goodwin S.C., Spies J.B., Worthington-Kirsch R., Peterson E., Pron G., Li S., *et al.*: "Uterine artery embolization for treatment of leiomyomata: long-term outcomes from the FIBROID Registry". *Obstet. Gynecol.*, 2008, *111*, 22.

[21] Spies J.B., Myers E.R., Worthington-Kirsch R., Mulgund J., Goodwin S., Mauro M.: "The FIBROID Registry: symptom and quality-of-life status year after therapy". *Obstet. Gynecol.*, 2005, *106*, 1309.

[22] Toor S.S., Tan K.T., Simons M.E., Rajan D.K., Beecroft J.R., Hayeems E., Sniderman K.W.: "Clinical failure after uterine artery embolization: evaluation of patient and MR imaging characteristics". *J. Vasc. Interv. Radiol.*, 2008, *19*, 662.

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