VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2024, vol. 95, no. 3, 212–217
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ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/GP.a2023.0065

Current status and outlook of minimally invasive treatment for leiomyomas

Bin Meng, Ning Liu, Xiaotao Wang, Zhe Geng, Qian Li, Mingmin Xu

Department of Ultrasound, Zhejiang Rongjun Hospital, Jiaxing, China

ABSTRACT

Objectives: Leiomyomas are benign, highly prevalent gynecologic conditions that can cause abnormal uterine bleeding, pelvic pain, urinary difficulties, and/or bladder or rectal obstruction. With advances in medical technology, women are increasingly interested in treatments that avoid surgery and/or preserve the uterus, which has undoubtedly contributed to the development of minimally invasive approaches. This article reviews the literature and evaluates the effectiveness and safety of minimally invasive approaches for the treatment of leiomyomas and describes the current state of development of minimally invasive treatment modalities for leiomyomas.

Material and methods: Web of Science and PubMed were systematically evaluated using the following keywords: uterine artery embolization, high-intensity focused ultrasound, microwave ablation, radiofrequency ablation, myomectomy, hysterectomy, leiomyomas, fertility. English abstracts relevant to the topic were selected and full-text articles were carefully analyzed.

Results: Uterine artery embolization is an effective treatment modality that has been widely validated, and the remaining means each have their distinct advantages in clinical practice, but more practical and comparative studies are needed. Minimally invasive myomectomy and minimally invasive hysterectomy are technically advanced compared to classical open surgery and are widely used due to the completion of practical experience, but a continuous interest in non-invasive minimally invasive treatment modalities is retained.

Conclusions: Minimally invasive treatment modalities for leiomyomas have emerged as an important treatment option when considering patient requirements, and further research and practice are needed to support their development into a mainstream modality for the treatment of leiomyomas.

Keywords: leiomyomas; minimally invasive surgical procedures; treatment outcome; fertility

Ginekologia Polska 2024; 95, 3: 212–217

INTRODUCTION

Leiomyomas are benign lesions or tumors of the uterus, consisting of smooth muscle cells and fibroblasts enriched with extracellular matrix (ECM). Leiomyomas appear to develop and regulate gene expression in response to the menstrual cyclicity of gonadal steroids (mainly estrogen and progesterone), developing between menarche and menopause. Leiomyomas are common, occurring in more than 70% of women. However, leiomyomas can be asymptomatic, with 25–50% of women having clinical symptoms. Common symptoms include menstrual bleeding, urinary or pelvic discomfort, dysmenorrhea, painful disorders, infertility, and recurrent miscarriages, severely affecting the quality of life of the patient. The main risk factors for leiomyosarcoma include age and race, it can begin to develop during adolescence, and black women are two to three times more likely to develop the disease than white women [1].

After years of exploration, the treatment options for leiomyomas have become very mature and diversified. The classic treatment options are abdominal myomectomy or hysterectomy, but due to the long recovery time, scarring, and greater harm of these approaches, women's strong need to avoid surgery and to preserve the uterus and fertility has also strongly promoted the development of minimally invasive treatment for leiomyomas [2]. Minimally invasive treatment options are less invasive and less harmful. The advantages of minimally invasive treatment options are undeniable, as they are less invasive and have a faster recovery after surgery. At the same time, however, a significant number of treatment options are still at a stage where their

Corresponding author:
Bin Meng
Department of Ultrasound, Rongjun Hospital of Zhejiang Province, No.309 Shuangyuan Road, Jiaxing, 314000, Zhejiang Province, China
e-mail: mb521520@163.com

Received: 9.02.2023 Accepted: 1.06.2023 Early publication date: 21.07.2023
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safety and efficacy need to be monitored and larger-scale practice is needed to confirm their effectiveness or optimize their procedures.

UTERINE ARTERY EMBOLIZATION (UAE)

This technique achieves reduction of leiomyomas by injecting microspheres into the uterine artery. Routine preoperative preparation of the patient includes fasting for at least six hours, premedication for documented history of allergy to contrast agents, and laboratory assessment of coagulation parameters and renal function. New techniques for uterine artery embolization are flourishing with the development of medical treatments, such as the injection of lidocaine with embolic pellets [3], the development of unilateral trans-radial access, *etc.* [4]. Compared to conventional myomectomy, although it may require additional surgical intervention, its advantages such as short hospital stay, minimally invasive, rapid postoperative recovery, local anesthesia only, and reproducibility are evident, which is why its acceptance by patients and the percentage of procedures is increasing year by year [5]. This is why its acceptance by patients and the percentage of surgical procedures are increasing year by year.

HIGH INTENSITY FOCUSED ULTRASOUND (HIFU)

High-intensity focused ultrasound is a technique that concentrates an ultrasound beam to a point so that the energy at that point is maximized. Its treatment principle is to heat, cavitate, and damage blood vessels by concentrating energy on the target location causing blood supply disruption. Magnetic resonance imaging guided high intensity focused ultrasound (MRgFUS) is one of the most effective methods of treatment, using focused high-energy ultrasound waves guided by magnetic resonance imaging to instantaneously destroy tissue. The high-energy ultrasound heated the target site to 55°C to 85°C, resulting in coagulation necrosis and cell death. MRI images' high contrast, spatial resolution, and multidimensional capabilities provide optimal tissue localization, and MRI thermometry provides real-time thermal imaging of the ablated area [6]. The MRgFUS is also capable of providing real-time thermal imaging of the ablated area. A series of tests, such as evaluation of symptoms and examination of standard contraindications to MRI, is required before deciding whether to use MRgFUS. The best results have been obtained with less than 4 fibroids or less than 50 mL fibroids, with a higher safety profile for fibroids located in the submucosa [7]. It is safer to treat myomas located in the submucosa. To achieve a complete treatment, the distance of the myoma from the anterior abdominal wall must be less than 12 cm.

In general, the patient's symptoms improve significantly after surgery and are accompanied by a reduction in the size of the uterus [8]. Tracking the proportion of patients requiring re-intervention at different time points after surgery shows that the proportion increases with time from 12–48 months and also indicates that older age at treatment tends to mean a lower risk of re-intervention [9]. The study also noted that older treatment age tended to mean a lower risk of reintervention. Compared to uterine artery embolization (UAE), the effectiveness of treatment and post-treatment effects on fertility are similar, but patients receiving MRgFUS after a longer period (60 months) have a poorer quality of life and require less re-intervention than those receiving UAE, with longer recovery times and more medications, and require additional attention to the potential for high-energy sound waves to cause burns and intestinal damage. The MRg is a very good candidate for the UAE. Due to these limitations, MRgFUS is still not a widely used treatment for leiomyomas, but it still offers an effective and reliable option for the non-invasive treatment of fibroids and has great potential for development [10].

Another more widely used treatment is ultrasound-mediated high-energy focused ultrasound (USgHIFU), which, as the name implies, is guided by ultrasound images. After 918 patients were treated, the fibroids were significantly reduced in size, with only 4.6% experiencing symptomatic recurrence [11]. A survey of the fertility status of patients treated with USgHIFU showed that the mean time to pregnancy after HIFU treatment was 5.6 ± 2.7 months, with 88.75% of patients having normal deliveries (including cesarean section). All patients had well-developed fetuses during pregnancy and childbirth without uterine rupture or perinatal and postpartum complications [12]. Thus, USgHIFU is a very friendly treatment option for patients with leiomyomas who wish to have children and can significantly shorten the postoperative period of pregnancy preparation.

Patients who have undergone USgHIFU treatment tend to have a better quality of life and health than laparoscopic myomectomy, mainly because of its non-invasive, minimally invasive advantages. Compared to MRI-guided high-energy focused ultrasound treatment, it is also able to detect and fully ablate myomas up to one centimeter in diameter, despite its slightly less accurate imaging, in addition to the advantages of shorter imaging time, higher treatment efficiency, higher ablation rate, and shorter treatment time. Years of application have also made the technique more stable and mature.

RADIOFREQUENCY ABLATION (RFA)

Radiofrequency ablation (RFA) is a type of hyperthermic ablation, similar to high-energy focused ultrasound, which also causes tissue destruction through high temperatures, although the method of generating high temperatures is slightly different, as the energy is generated in the radio

frequency range (between 3 kHz and 300 GHz) in the form of alternating current (AC) [13]. The coagulation necrosis caused by RF energy results in a reduction in the size of the myoma and enhances the patient's quality of life. the RFA system includes a multi-needle electrode array with thermocouple technology that allows real-time temperature feedback to maximize ablation volume while minimizing needle puncture points. The addition of paired real-time ultrasound to the RFA allows for more precise localization of fibroids [14].

Trans-laparoscopic radiofrequency ablation is effective in small and non-irritating symptomatic leiomyomas. After treatment, the patient's symptoms will remain improved for a long time with a significant improvement in quality of life (including reduction in fibroid size, menstrual bleeding, *etc.*) and a low rate of re-intervention [15]. Transcervical radiofrequency ablation, performed under local anesthesia only, with short operative time and rapid postoperative recovery, is indicated for the treatment of small, solitary or superficial leiomyomas. It offers less surgical trauma and lower surgical risk than trans-laparoscopic radiofrequency ablation, but its treatment outcome may be inferior to that of trans-laparoscopic radiofrequency ablation. The new staging method for leiomyomas developed by the International Federation of Obstetrics and Gynecology provides an important basis for choosing laparoscopy or hysteroscopy in clinical practice (FIGO types 2–5, and 6 are suitable for laparoscopic procedures, FIGO types 1–5, and 6 are suitable for hysteroscopic procedures, and FIGO types 7 and 8 are not suitable due to their anatomical location and risk of producing thermal injury (using these two therapies) [14] and can make an assessment of the difficulty of the procedure.

In a comparative study by Melody Taheri et al. [16] on RAF, UAE, and FUS, it was noted that the treatment effect of RFA was striking among these three minimally invasive treatments (70%, 54%, and 32% reduction in myoma volume for the three, respectively). In terms of impact on fertility, from the available data, the majority of patients treated with RFA delivered at full term with no neonatal complications [17]. Therefore, RAF treatment may be a preferable option for those patients who wish to preserve their fertility.

MICROWAVE ABLATION (MWA)

Microwave ablation (MWA) is a treatment method that uses high-frequency microwave heat to destroy tumor tissue. From the treatment data of microwave ablation (344 patients from eight treatment centers in China), the average ablation rate of myoma after (MWA) treatment was 86.6% (54–100%), and no serious complications occurred [18].

Compared to HIFU, both are safe and effective treatment modalities, however, MWA benefits from a different treatment mechanism (energy decay during the propagation of ultrasound, significant cooling due to blood flow during HIFU treatment) and can produce higher instantaneous temperatures and a wider power field. Therefore, MWA is more suitable for the treatment of large and multivessel fibroids, while HIFU is more suitable for small fibroids and less vascular fibroids, but MWA treatment requires hospitalization and general anesthesia, while HIFU therapy does not [19]. There is no significant difference in treatment outcome or improvement in quality of life compared to UAE, but MWA has a lower risk of embolic complications, is better tolerated, and is less costly [20]. However, MWA has a lower risk of embolic complications and is better tolerated and uses fewer medical resources. Overall, MWA, RFA, and HIFU are all thermal ablation therapies, and further high-quality, multicenter, large sample randomized controlled trials are needed for MWA therapy.

UTERINE FIBROID REMOVAL

Minimally invasive myomectomy has been developed in various ways today, such as laparoscopic myomectomy (LM) and hysteroscopic myomectomy (HM). Compared to cesarean surgery, LM has advantages in terms of reduced bleeding, postoperative complications, and hospitalization. However, this does not mean that LM is free from complications and contraindications, and the size of the fibroids may make the procedure more difficult and increase the risk of intraoperative and postoperative complications [21]. Laparoscopic myomectomy is slightly less time-consuming than cesarean surgery, taking about 70 minutes on average, but the risk of bleeding events is significantly higher with cesarean surgery [22]. The former patients had a higher quality of life compared to those treated with HIFU, which may be attributed to the fact that HIFU is a non-invasive treatment modality. In addition, the size of the fibroids may affect the pregnancy rate in patients after laparoscopic myomectomy. The number and type of myomas do not affect postoperative pregnancy rates or pregnancy outcomes. Postoperative pregnancy interval does not affect pregnancy outcome, placental adhesions during pregnancy, and postpartum hemorrhage [23]. Therefore, the pregnancy rate can be improved by shortening it according to the patient's condition.

In recent decades, thanks to advances in equipment, HM has become a highly recognized minimally invasive treatment for leiomyomas. The size of fibroids treated with the HM method is under 4 cm, since the operating instruments are in the operating scope of about 1 cm. For fibroids larger than 4 cm, additional treatment is needed to reduce the size of the fibroids before using HM. Pre-treatment with gonadotropin-releasing analog (GnRH-a) or the HIFU method is commonly used, and the HIFU method of management often brings advantages in terms of operative time and intraoperative bleeding. There was no significant difference in

Table 1. Advantages and disadvantages of minimally invasive treatment modalities for leiomyomas

Treatment modality	Advantages	Disadvantages
UAE	No surgical incision required; reduced postoperative pain and recovery time; preservation of the uterus	Some treatment limitations; may require multiple treatments; some complications may occur
MRgFUS	Non-invasive; preservation of the uterus and fertility; no anesthesia or hospitalization required; high precision	Indication limitations; longer time required; may require multiple treatments; complications from burns and intestinal injuries
USgHIFU	Non-invasive; easy to undergo; reduced complications; preservation of uterus and fertility	Restricted treatment depth; low precision; takes longer time
RFA	Less trauma and bleeding; preservation of the uterus and fertility; less risk of complications	Professional equipment and technology required; may require multiple treatments; requires surgery under anesthesia
MWA	Fast, effective treatment; less risk of complications; for larger fibroids; preservation of uterus and fertility	Requires specialized equipment and techniques; some complications may occur; requires surgery under anesthesia
Myomectomy	Preservation of the uterus; complete removal of the fibroids	Larger bleeding volume and trauma; longer recovery time; possible postoperative complications and scar formation
Hysterectomy	Complete removal of fibroids and uterus	Greater trauma and bleeding; requires general anesthesia and longer recovery time; not suitable for reproductive needs

UAE — uterine artery embolization; MRgFUS — intensity focused ultrasound; USgHIFU — ultrasound-mediated high-energy focused ultrasound; RFA — radiofrequency ablation; MWA — microwave ablation

the rate of intraoperative complications and one-time resection of leiomyomas between the two groups ($p > 0.05$) [24].

The complications of HM therapy are difficult to ignore and include uterine perforation, bleeding, adhesions, incomplete resection, infection, intravenous infiltration/hysterectomy with intravascular absorption (OHIA) syndrome, and venous air embolism [25, 26]. These can be very critical and even life-threatening, so other treatment options should be used in cases where the risk of HM is known to be high [26].

HYSTERECTOMY

Hysterectomy includes total hysterectomy, which removes both the uterus and the cervix, and subtotal hysterectomy, which removes only the uterus but leaves the cervix intact, for cases where the cervical examination is normal and the patient requests to keep the cervix or where cervical removal is difficult. With the development of surgical techniques, minimally invasive surgical methods have been developed for hysterectomy: total laparoscopic hysterectomy (TLH), total vaginal hysterectomy (TVH), *etc.* [27], which are essentially variations of laparoscopic hysterectomy and vaginal hysterectomy. In general, removal of the uterus means loss of reproductive function and cessation of menstruation, which may also have some endocrine effects. However, patients will have to resort to hysterectomy when other treatment modalities have serious sequelae or are not effective.

In contrast, the laparoscopic route (TLH) is more popular with patients because of its less pain, less blood loss, and quicker recovery. TVH has the shortest multisite procedure time, but TLH has a lower complication rate, which may explain the increasing popularity of TLH with patients [28]. Women who have a hysterectomy appear to have a greater improvement in health-related quality of life than women who have a myomectomy, but this is limited to those who have a minimally invasive procedure. Such a difference is not surprising given that hysterectomy eliminates the possibility of myoma-specific symptoms and dysfunctional uterine bleeding [29].

The most common complication of benign hysterectomy is urinary tract infection, and the use of minimally invasive means has greatly reduced this possibility. It is also worth mentioning that some ethnic differences were demonstrated among patients who underwent hysterectomy. Due to the large sample taken, the varying levels of hospitals, and the different ages of the patients, body mass index, and other various indicators, there are no strict limits on the criteria for comparison, but the results can still serve as an important reference.

SUMMARY AND OUTLOOK

Table 1 summarizes the minimally invasive treatment modalities for leiomyomas described in this article. Uterine artery embolization is a widely validated treatment modality for the minimally invasive treatment of leiomyomas, while high-energy focused ultrasound, microwave ablation, and radiofrequency ablation require larger randomized controlled trials to confirm their practice results. The development of myomectomy and hysterectomy in the minimally invasive direction is more dependent on the overall technological advances in surgery, and both will be further revolutionized when new techniques become available. In addition to surgical treatments, pharmacological treatments are also evolving, such as selective progesterone receptor modulators (SPRM), gonadotropin-releasing hormone analogs (GnRH).

In addition, it should be noted that some malignant tumors different from fibroids, may also be asymptomatic

at first, and blind use of minimally invasive modalities may cause them to metastasize and spread, therefore, after the tissue biopsy is completed, the appropriate modality should be chosen to address them in the shortest possible time according to the situation. In conclusion, in the current fast-paced life, minimally invasive treatment modalities for leiomyomas with short treatment time and quick postoperative recovery are becoming the first choice for more and more people, and minimally invasive treatment (except hysterectomy) is also a better choice for patients who wish to preserve their uterus while remaining fertile. With the huge demand, minimally invasive treatment needs to be accelerated and developed rapidly.

Article information and declarations

Author contributions

As the first author and corresponding author, (Bin Meng) was responsible for the conceptual design and experimental planning of the study, performed the main experimental work, conducted the data analysis and interpretation, and undertook the main writing and revision of the paper. (Ning Liu) was responsible for the execution and data collection of part of the experiment. (Xiaotao Wang and Zhe Geng) participated in the data analysis. (Mingmin Xu and Qian Li) provided expertise and technical support, participated in research discussions and interpretation of results. All authors participated in the final review and approval of the paper.

Funding

This research was supported by grants of Jiaxing Public Welfare Research Program (2019AY32014).

Conflict of interest

All authors declare no conflict of interest.

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