

New Surgical Approach to Treat Fibroids and Solid Tumors – Thermal and Nonthermal Ablation

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Abstract

There is a trend toward more minimally invasive treatment for symptomatic uterine fibroids. They are image-guided ablation surgery with focused ultrasound, microwave, and radiofrequency ablations that are becoming tested and used in some medical centers or hospitals. Nevertheless, these image-guided ablation surgeries involve thermal ablation to the fibroids, which might lead to thermal injury to the surrounding tissues, for example, nerve injury, vessel injury, and skin burn due to heat diffusion. A new technology – irreversible electroporation (IRE) – is a new paradigm for treating solid tumors. This nonthermal ablation process does not induce high temperatures when treating cancers or solid tumors. The IRE treatment may soon be used for treating fibroids or other solid tumors. In a few clinical trials, IRE is currently used in experimental studies for treating gynecological cancers. This paper will present the minimally invasive thermal ablation treatments for fibroids, introduce this new nonthermal IRE ablation in treating gynecological cancer, and propose its future uses in uterine fibroids.

Keywords: Fibroids, focused ultrasound ablation, irreversible electroporation, microwave ablation, minimally invasive surgery, radiofrequency ablation

INTRODUCTION

The present management of symptomatic fibroids is mainly surgical, with the laparoscopic or open or vaginal approach most commonly for myomectomy or hysterectomy. Both laparoscopic myomectomy and hysterectomy for treating fibroids could be difficult, with prolonged timing, suturing, or excessive bleeding. Even if these surgical procedures are successful, they are skill dependent and require a long learning curve in practice. Postoperative pain, infection, bleeding, and unintentional organ injury sometimes happen and are not uncommon.

There is a trend toward more minimally invasive treatment for symptomatic uterine fibroids in some medical centers. They are thermal ablation under image guided using magnetic resonance imaging (MRI), computed tomography (CT), or ultrasound (US). It offers an alternative modality to achieve

local thermal fibroid ablation or solid tumors without complications associated with open or laparoscopic surgery or systemic risks. This image-guided ablation is performed using thermal ablation such as focused US ablation, radiofrequency ablation (RFA) or microwave ablation (MWA), and nonthermal irreversible electroporation (IRE).^[1] All thermal ablation induces temperatures $>60^{\circ}\text{C}$ are considered instantly lethal to tissue cells. However, these temperatures generally rose higher and spread in many directions. Thus, the heat diffusion may cause damage to the surrounding tissues, leading to skin burn, bowel injury, or other complications.

Thermal ablation for fibroids

High-intensity focused ultrasound ablation

US-guided high-intensity-focused ultrasound (HIFU) and magnetic resonance-guided HIFU ablation treatment are now

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a new noninvasive surgical procedure that developed rapidly, with vast clinical experience accumulating in treating uterine fibroids, adenomyosis, and other gynecological diseases. HIFU ablation fibroid treatment is to focus US energy on a target point inside the fibroid; the energy can generate thermal heat up to 65°C–85°C and lead to coagulative necrosis without a cut wound.^[2] This minimally invasive fibroid treatment has a high success rate of 90% in reducing the sizes and symptoms of fibroids. Vast clinical experience has been accumulated in treating uterine fibroids.^[3] Unlike traditional surgery, in which wounds are made, with bleeding occurring and possible complications arising. The complications of the HIFU ablation procedure are mild, and the surrounding tissues and organs will often not be seriously damaged or injured. However, thermal injury to its surrounding organs has been reported,^[4-6] though they are few if properly performed by well-trained, experienced doctors. As HIFU is a new treatment modality, accreditation and training programs have been proposed and developed to ensure its operation with high effectiveness and safety.^[7,8]

Radiofrequency ablation

RFA uses a high-frequency alternating electric current to induce focal ionic agitation around the probe tips with resultant rapid heat generation in the target tissues. The RFA procedure involves two approaches for treating fibroids: (1) using transvaginal US to locate the fibroids, an insulated RFA electrode is inserted through a very small abdominal incision to penetrate deep within the fibroid without harming surrounding tissue and (2) using transabdominal US to monitor the transcervical, intrauterine insertion of the insulated RFA shaft into the fibroid. This procedure uses high heat to ablate fibroid tissue in a controlled thermal zone. Bradley *et al.* reviewed 32 articles of 1283 patients treated with laparoscopic and transvaginal RFA;^[9] they concluded that RFA of uterine fibroids significantly reduced fibroid volume (66%), improved quality of life (QOL), and was associated with favorable reintervention rates (4.2%–11.5% in 3-year follow-up). RFA fibroids treatment has proven safe, easy to apply, and effective in reducing symptoms of uterine fibroids.

RFA has sometimes been limited by the lack of accurate monitoring of the ablated tissue zone, the precise location of fibroids by US imaging, and the need for multiple serosal punctures for multiple fibroids, leading to serosal injury, adhesions, and potential myometrial disruption during pregnancy.

Microwave ablation

Microwave is a heat-based ablation method, with cell death after exposure to elevated high temperature through the production of electromagnetic waves with resultant oscillation of water molecules within the target tissue.^[10] MWA has advantages over RFA, with a more rapid and sustained rise in

temperature, good tissue penetration, and minimal heat sink effects when treating fibroids.

During WMA, the electrode antenna is accurately inserted into the fibroid under transabdominal US guidance. The microwave generator emits an electromagnetic wave with a frequency of 2450 MHz causing thermal necrosis. Ierardi *et al.* reviewed six papers using PubMed databases and reported the literature's overall experience of percutaneous MWA. Five hundred and forty-one patients (with 647 fibroids) were treated.^[11] The volume reduction rate of fibroids was from 15.9% to 93.1%, and the QOL improved after treatment. From these studies, US-guided percutaneous MWA is minimally invasive, has a short treatment duration, is easy to perform, and has been broadly used for the treatments of fibroids with favorable effects. There were no major complications requiring further interventions or hospitalization. Minor complications were observed, in particular lower abdominal pain, blood-stained vaginal discharge, and fragments of necrotic tissues from the vagina in some patients. However, given the great variations in fibroid volume reduction, more cohort studies and randomized, prospective clinical trials are still needed to demonstrate the benefits of MWA in managing uterine fibroids.

Nonthermal ablation for solid tumors

Given the risks of thermal injury to other organs after thermal ablation, nonthermal ablation without thermal risks would be desirable. The nonthermal ablation IRE approach, now tested in solid cancer research, would be of interest to apply to the treatment of uterine fibroids.

IRE – It is an innovative surgical technique already used for the nonthermal ablation of cancer and is showing great promise. The principle of this treatment is based on the finding that, when an electric field is applied to a biological cell, transmembrane voltage is induced then structural rearrangement of lipids in the membrane leads to the appearance of hydrophilic pores. Then, the membrane becomes permeable to small or large molecules that cannot pass the cell membrane. IRE occurs after cells are exposed to an electrical field for sufficiently high electric energy; it results in cell apoptosis and death.^[12] Some current research information on IRE is as follows.

IRE electrodes can be applied to a tumor in patients at laparotomy or by percutaneous puncture under CT, MRI, or US-guided scanning. The ablation volume can include the whole tumor using up to 8 needle electrodes. Two electrodes are used for small lesions or at the periphery of the tumor, using 4–8 electrodes for a larger lesion. The electrodes have a 1.5–2.0 cm working tip and are inserted 1.5–2.5 cm apart. Multiple electric pulses with a voltage of 2400–3000 V/cm can be administered between electrodes for 70–90 ms or a shorter pulse duration. The IRE technique is easy to apply. The ablation area can be calculated, and the extent of electroporation can

also be imaged and monitored by real-time US scan or with electrical impedance tomography.^[13]

Research studies show that IRE did not produce a thermal effect that leads to cell membrane breakdown.^[14] This ablation approach damages only the plasma membranes of tumor cells. However, it does not affect the extracellular matrix components that maintain the integrity of its surrounding tissues, such as blood vessels, nerves, lymphatics, and muscles.^[15] These latter tissues have a higher electric tolerance threshold and remain unharmed. The apoptotic or necrotic tumor cells were reabsorbed quicker, tissue healed faster, and organ functions returned earlier because of healthy surrounding tissues. It is interesting to apply it for uterine fibroid ablation when faster reabsorption would be desirable to reduce fibroid symptoms.

Due to the well-known nonthermal nature of IRE, adverse thermal injury events such as serious bowel or nerve injury that may occur during thermal ablation are almost eliminated. IRE does not cause injury to blood vessels and nerves and can kill off cells very close to vessels; thus, it might offer more effective treatment to minimize residual tumors.^[16] Compared to local thermal ablation, IRE has fewer side effects such as skin burn and pain, and no serious thermal bowel or nerve injury is reported. Nevertheless, IRE has mild drawbacks, including muscle contractions and potential cardiac arrhythmia upon electric simulations.^[17] For large tumors, IRE may be difficult to achieve a complete tumor ablation, leading to recurrence. Hopefully, the third-generation IRE technology – with nanosecond pulsed ablation (H-FIRE) – can minimize the risks of muscle contraction and cardiac arrhythmia and may achieve a better ablation outcome.^[18]

Evidence suggests that this IRE technique activates the immune system.^[19] The IRE ablation can generate antigens that significantly stimulate the body's immunity to control tumor progression.^[20] In contrast, other thermal ablation might lead to protein denaturation, with associated changes in tumor antigenicity that might mislead the body's immune response.^[21]

IRE has been used in combination with cytotoxic drugs for a technique known as electrochemotherapy. Okino and Mohri introduced this technique in 1987,^[22] and electrochemotherapy has been used in clinical trials for treating superficial primary and recurrent vulvar cancer.^[23] Because IRE does not denature hormonal proteins, it is hopeful that cellular electroporation can complement and potentiate antiestrogen medication for treating uterine fibroid.

DISCUSSION

For over two decades, hyperthermic fibroid ablation, regardless of the thermal energy source, has been used to create large areas of tissue necrosis within fibroids that result in reductions

in fibroid volume and associated symptoms and improve the QOL. While it is apparent that when a portion of the fibroid is left unabated, the surviving fraction of the fibroid can continue to grow, and symptoms can persist. Thermal ablation could not effectively eradicate fibroid cells close to blood vessels due to the “heat-sink” effect. As a result, the recurrence of fibroids next to a vascular area tends to occur. Thermal ablation may also cause thermal damage to the bladder, ureters, skin, and bowels, leading to urinary tract injury, skin burn, or bowel perforation. IRE is a new nonthermal technological breakthrough, applicable to all solid tumors, that can ablate even those tumor cells close to blood vessels, nerves, and other surrounding organs.

Nevertheless, IRE ablation still has insufficient preclinical studies and clinical trials to support its wide applications. Most clinicians are unaware of this technology due to great demands with various competitive local tumor ablation modalities.^[24] With the increasing interest in the studies of electroporation technology, the International Society for Electroporation-Based Technologies and Treatments was formed in Europe in 2016. The society aims to promote advancing the scientific knowledge of pulsed electric and electromagnetic fields, emphasizing electroporation, and facilitating its applications, particularly with chemotherapy. Electrochemotherapy has become a new treatment modality for treating basal cell carcinoma, advanced melanoma, breast cancer, vulvar cancer, and other solid tumors.^[25] Thus, electroporation technology is fast spreading treatment modality throughout Europe and the USA for the treatment of solid tumors. The IRE is already successfully used in different cancer treatments with experimental studies to treat a deep-seated tumor.^[26] Hopefully, its application for fibroid ablation is not far-reaching.

Furthermore, reversible electroporation (RE) with rapid cell recovery can be demonstrated *in vitro* and *in vivo* research with low electric frequency and short electric current exposure. The RE technology is already successfully used in many biomedical applications, including electrochemotherapy, gene electrotransfer, electrofusion, and electroimmunotherapy.^[27]

CONCLUSION

Uterine fibroids are very common in women and often require surgery for symptomatic treatment. Image-guided ablation for treating fibroids can become more popular and acceptable, as described in this paper. They are minimally invasive fibroid treatments that are safe, easy to perform, and without general anesthesia. They can also be performed in the outpatient setting without the risks of open, laparoscopic, or vaginal surgeries. All thermal ablation treatments of fibroids require more comparative or randomized clinical trials to validate their effectiveness and safety. For the new IRE ablation technology,

we may need to wait for the increasing applications of IRE ablation to solid tumors and its long-term results before treating fibroids.

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Conflicts of interest

There are no conflicts of interest.

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