The clinical protocol of HIFU treatment of uterine fibroid

In this lecture, we are going to learn about the clinical protocol of HIFU treatment of uterine fibroids. It will include therapeutic principle of HIFU, indications, contraindications and precautions.

I. The Principle of HIFU Ablation

The principle of HIFU ablation is that the transducer of the system concentrates the extracorporeal low intensity ultrasound that penetrates readily through human tissues onto the target lesion inside the body under the imaging guidance, and then converts electrical energy into acoustic energy at the focal point where the targeted tissue undergoes irreversible and instantaneous coagulative necrosis.

During treatment, the patient needs to stay in prone position on the treatment bed of HIFU therapeutic system. The doctor will precisely focus the energy on the targeted lesion through the computer-aided motion system and perform a conformal ablation of the tumor mass via the combination of dot, line, slice and volume treatment planning.

II. Indications and contraindications of HIFU

Technically, fibroids indicated for HIFU treatment must be displayable by the integrated ultrasound scanner and has safe acoustic path. Furthermore, they are normally bigger than 1 cm in diameter.

The clinical indications include: first of all, the patient is diagnosed with confirmed uterine fibroids; second, the integrated ultrasound scanner displays a safe ultrasound pathway, and third, the patient meets one of the following four criteria: 1. presentation of clinical symptoms such as increased menstrual flow, dysmenorrhea, enlarged uterus, frequent urination; 2. symptomatic who cannot tolerate the surgical procedure; 3. asymptomatic who have psychological burden; 4. Patients who meet surgical indications but cannot endure the surgical procedure 5.having the desire for pregnancy.

Patients who do not meet the above criteria for HIFU treatment but with a strong desire for it, may be treated by experienced doctors after sufficient communication. These patients may include: those with chronic pelvic inflammation, pedunculated subserosal or submucosal myoma and other special types of leiomyoma; Patients with longitudinal abdominal surgical scars wider than 15 mm or the width of sound attention displayed on ultrasound image greater than 15 mm; Patients with a history of abdominal liposuction susceptible to risks of skin injury; those who are not suitable for analgesia and sedation; patients with communication difficulties; patients with postmenopausal uterine fibroids or fibroids that do not shrink after menopause.

The contraindications for HIFU ablation

- ✓ Patients with severe underlying diseases, such as cardio-cerebrovascular
- ✓ Patients with collagen diseases or a history of radiotherapy on the lower abdomen.
- ✓ Patients with acute infections, such as pelvic inflammation, adnexitis and cervicitis, etc.
- ✓ Patients with non-benign cervical, ovarian and other gynecological diseases, including uterine sarcoma, cervical and ovarian cancer, etc.
- ✓ Presence of foreign objects, especially intrauterine device(IUD) in the acoustic pathway. In such case, IUD removal is required prior to HIFU.
- ✓ Patients who cannot lie in prone position for at least 1 hour because of lumbar disc diseases or other causes.
- ✓ Patients with cellular myoma, angioleiomyoma or fibroids suspected of malignancy.

The above are contraindications for HIFU and HIFU is strictly prohibited.

III. Precautions for HIFU ablation

First and foremost, make definitive diagnosis. Uterine sarcoma and special types of fibroids such as cellular myoma and angioleiomyoma must be excluded.

Secondly, evaluate the feasibility of HIFU treatment based on MRI signals of the fibroids and their positioning by the integrated ultrasound scanner.

Cases Discussion

Case 1: This is a case of cellular myoma. The patient was 44-year-old. She was presented with a pelvic mass 4 months after found by palpation. Ultrasonography indicated a mass of 82cm*10.4cm*11.3cm. MRI T1WI signal is iso-hyperintense and T2WI is heterogeneous hyperintense. The margin in part of the region of hyperintense signal was blurred. These MRI features are different from the commonly observed. Due to the irregularity of MRI signals, we could not rule out comorbidities in the patient. So we recommended her to go for laparoscopic surgery. Postoperative paraffin section confirmed the diagnosis of cellular myoma.

The second case showed iso-hyperintense signals on T2WI and a liquefaction area in the middle. The transverse view of MRI indicated a blurred boundary between the fibroid and the myometrium, showing the irregularity of the fibroid. The subsequent surgery confirmed the diagnosis of the fibroid of suspected malignant potential.

Case 3: The MRI of the third patient displayed unclear border between the fibroid and the normal endometrium. Laparoscopic surgery was performed due to MRI irregularity. Pathological findings confirmed the diagnosis of angioleiomyoma.

So MRI examination before HIFU ablation is required. MRI findings and medical history of patient are critical to exclude cases such as uterine sarcoma and angioleiomyoma, which are not suitable for HIFU because of poor efficacy and anticipated quick relapse.

What is the timing of HIFU ablation? As a non-surgical and non-invasive treatment, HIFU ablation can be performed at any time outside the menstrual cycle and gestation period. For patients with acute pelvic inflammation, treatment can be performed at least 3 months after the symptom relief. For patients with a history of induced abortion or uterine curettage, treatment can be performed after at least one cycle of normal menstruation. For patients with IUD removal, treatment can be performed after the absence of abdominal pain and vaginal bleeding. For patients with a history of lower

abdominal surgery, treatment can be performed at least 3 months after the surgery when the scar is softened.

Process of HIFU Ablation

The process of HIFU treatment involves pre-operation, intra-operation and post-operation.

Pre-operation involves the preparation of bowel, ultrasound coupling balloon and the bladder. For the bowel preparation, fasting and having liquid diet for 1 or 2 days are required based on the patient's bowel movement habit. Patient will take laxatives on the day before operation and undergo enema on the operation day to get rid of gas and food residue in intestines thus to avoid the risk of intestinal injury during HIFU.

Preparation of ultrasound coupling balloon involves keeping the coupling water inside the balloon at a proper temperature, adjusting the size of balloon and getting rid of air bubbles. Most important of all, the balloon must be absolutely bubble-free in order to avoid the risk of skin injury.

Bladder preparation is intended to train the patient to control the size and shape of their bladder. For patients with the lesion in the posterior uterine wall, 1 or 2 weeks of bladder practice on holding the urine is necessary to allow a better and safe acoustic pathway.

Before HIFU ablation, patients will undergo treatment simulation, i.e., positioning of fibroids, to determine the feasibility and extent of treatment, the safety of the acoustic pathway and the extent of sound attenuation in the abdominal scars. Meanwhile, doctors will consider the treatment plan and adjust the angle of the transducer to have a sufficient and safe acoustic pathway for the treatment, getting ready for the next day's operation.

Take a look at this image. The sound attenuation caused by abdominal scars blurs the image. The presence of sound attenuation in the acoustic pathway is dangerous for treatment, as it may cause the doctor to fail to see the presence of intestines in the acoustic pathway. Therefore, HIFU ablation is not recommended for such patients in whom sound attenuation wider than 15 mm occurs in the acoustic pathway.

HIFU ablation of uterine fibroids needs to follow some principles in clinical practice. The integrated ultrasound scanner shows the sagittal view of the patient. According to the transverse diameter of the fibroid, the HIFU system virtually slices the tumor with a 5-6mm inter-distance. The inter-distance changes into 10 mm if the diameter of the tumor exceeds 10 cm. HIFU ablation normally starts with the region of interest, which is most tolerant of and sensitive to ultrasound ablation. It is usually an area of calcification or poor blood supply, which is favorable for ultrasound energy deposition, leading to better efficacy. In the absence of such an area, the safest is to start ablation with the center of the largest slice of the fibroid.

Intratumoral ablation is mandatory in order to protect the uterine serosa and endometrium. The distance from the ultrasound focal point to the head side, the foot side, the right side, and the left side tumor margin, respectively should be between 5 to 10mm. The distance from the ultrasound focal point to endometrium should be 15mm and beyond. And the distance from the ultrasound focal point to the upper tumor margin and the deep tumor margin, respectively should be kept between 10 and15mm.

Dose adjustment should be based on the patients' response to the treatment. If the patient's tolerance permits, we can increase the treatment intensity to achieve the desirable ablation result in a relatively short treatment time. If the patient's tolerance level is low, we need to lower the dose or treatment intensity correspondingly. In addition, adjustment of ultrasound dose should be based on the real-time grayscale change in the targeted region.

In what order does HIFU ablation proceed? The treatment will be performed slice by slice before the appearance of grayscale change. For the region of non-diffusing lumped grayscale change, ablation follows the slice by slice plan. For the region where lumped grayscale changes diffuse to only one slice, ablation continues on the adjacent slice where the grayscale change begins. For the region where lumped grayscale change diffuses to multiple slices, ablation continues on the slice adjacent to the lumped grayscale change area.

Precautions during the treatment: First, observe the fullness of the bladder and regularly discharge the urine to reduce the tension of bladder. If the patient has a big

bladder full of urine with the therapeutic transducer closely against her abdomen, regular discharge of part of urine can help to avoid post-treatment urine retention caused by over-fullness of bladder during treatment.

Second, pay attention to the intra-operative pain. The doctor needs to identify the cause of the pain, whether by the drugs or by the stimulation of endometrium or nerve. The operator needs to ensure the clearance of the acoustic pathway, i.e., no intestines in the acoustic pathway, and avert the injury of endometrium before continuing the treatment.

The operator should change to a new site before continuing the treatment if the patient has radiating pain during treatment. Prolonged treatment of the same site should be avoided otherwise it may cause neurological injury.

Pay attention to intra-operative sensation of heat and searing. The operator should stop treatment, lower down the therapeutic transducer and leave the abdominal skin cooled down by degassed water if the patient feels boiling or searing heat of skin.

It is critical to control the rate and direction of the diffusion of lumped grayscale change during treatment. If the grayscale change diffuses too quickly, it may invade the uterine serosa or endometrium adjacent to other organs, consequently causing secondary thermal injury to the organs.

Then, what is the criteria for termination of the procedure? Appearance of diffusing lumped grayscale change over the whole targeted region is the benchmark for termination.

If there is no obvious lumped grayscale change, the following principal should be followed for treatment termination: 1. with 400W of sound power, the total sonication time for a fibroid should not exceed 700s/h. 2. For the fibroid located on the anterior uterine wall, the sonication time should not exceed 250s/cm. 3. For the fibroid located on the posterior uterine wall, the sonication time should not exceed 350s/cm. This principle does not apply to the fibroids visualized on T2WI as hypo-intense signals and as inconspicuous enhancement on T1WI. Color ultrasound and ultrasound contrast can be the primary evaluation of treatment efficacy.

Evaluation of treatment efficacy immediately after HIFU can be done with color ultrasound. Color ultrasound can be used to assess the treatment outcome if satisfactory diffusing grayscale change appears or distribution of sonication points is completed. The image before HIFU showing rich vascularity is totally different from that after HIFU showing absence of blood flow signals, indicating the occurrence of irreversible and instantaneous coagulative necrosis of tissue. It should be stressed that parameters for the color ultrasound imaging must be set the same before and after HIFU to make the comparison.

If the color ultrasound displays desirable treatment outcome, ultrasound contrast can be used for further assessment. Pre-operative contrast-enhanced ultrasound shows that the whole lesion is perfused with contrast agent, whereas post-operative contrast-enhanced ultrasound shows the lesion has changed into a non-perfused area, like a black hole. This black hole represents the volume ablated, a very precise volume of ablation.

When treatment ends, the operator should examine the patient' skin and observe if there is any redness, blisters and ulcers, and check the motion and sensation function of the lower limbs and fill the bladder with 4-10℃ saline to cool down it. For patients with a large myoma or the mass located on the posterior uterine wall, they are required to remain in prone position for 2 hours immediately after HIFU to avoid secondary sacral nerve irritation. Patients are advised not to have food for 2 hours immediately after HIFU and to restore food intake with fluid diet. If treatment has been completed in a short time, and the bladder has not been filled big during treatment, the Foley catheter can be removed immediately after treatment. Otherwise, the catheter should be remained in the bladder for 4-6 hours t.

MRI examination immediately after HIFU confirmed the precise ablation of the targeted region as displayed by color ultrasound and ultrasound contrast.

A two-year follow-up is recommended after the HIFU procedure at intervals of one month, three months, 6 months, 12 months, and 24 months, respectively. Follow-up check include improvements in clinical symptoms such as decrease of menstrual blood,

improvement of uterine pressure and the shrinkage of lesion volume. B-mode ultrasound or MRI is used to measure the fibroid shrinkage.

Generally, after HIFU ablation, the volume of the ablated fibroid shrinks by 45% at 3 months and by 60% at 6 months. MRI can be used to better distinguish the ablation rate and necrosis volume.

A 2-year follow-up table is required to collect the information that includes menstrual blood before and after HIFU, dysmenorrhea, the size of uterus and fibroids, number of fibroids, and anemia, etc.

This is the follow-up of a case with the fibroid located on the posterior uterine wall. Contrast-enhanced MRI showed that the lesion infused with contrast agent changed into a clear, smooth, non-perfused area, indicating complete ablation of the fibroid. 6 months after HIFU, the fibroid shrank significantly and shrank more after a year. The fibroid almost disappeared after 2 years with the uterus restoring normal size.

From the above analysis, we can see that screening indications before HIFU ensures the desirable ablation volume and efficacy of ablation and satisfactory outcome.