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The use of focused ultrasound in oncology: Fundamentals and perspectives (literature review)

Relevance: *The introduction of new non-invasive, safe, and effective methods of treatment of benign and malignant diseases into clinical practice is of high urgency.*

Purpose: *to study literature sources on the experience of using MRI-guided focused ultrasound (MRgFUS) method of thermal ablation for its subsequent implementation and use at the East Kazakhstan Region Multidisciplinary Center of Oncology and Surgery of Ust-Kamenogorsk.*

Results: *The proposed method is based on real-time MRI-guided thermal ablation by focused ultrasound. Numerous studies have shown its clinical and economic efficiency, safety, and convenience for patients with bone metastases, early-stage prostate cancer, and uterine myoma.*

Conclusions: *MRgFUS ablation is a modern non-invasive technique that expands the ways to treat benign and malignant tumors. In certain cases, it can be a good alternative to invasive treatments. MRgFUS ablation can be used in combination with other treatments.*

Keywords: *focused ultrasound, MRI, ablation, cancer, metastases, uterine myoma.*

Introduction:

Expansion of the range of therapeutic options to treat cancer, its metastases, and benign tumors has not lost its importance. This is especially true for non-invasive and the safest methods of treatment that do not require hospitalization and rehabilitation costs for patients. One such technology is focused ultrasound (FUS) ablation under the control of magnetic resonance imaging (MRI). Focused ultrasound has been used in clinical practice for several decades [1].

Fundamentals of MRgFUS

The best-known biological effect of focused ultrasound is thermal ablation. It is known that high-temperature influence on body tissues causes protein denaturation and irreversible damage of both healthy and abnormal cells. Coagulation necrosis occurs, tumor growth stops, and its regression. Simultaneously, the coagulation necrosis development rate differs in different cells due to their morphology, temperature, and exposure time [1-3]. It was found that the degree of thermal tissue damage non-linearly depends on both time and temperature of exposure. [1].

Another effect is the development of occlusion of the vessels feeding the tumor. There are several mechanisms in its pathogenesis. Firstly, the direct thermal closure of microcirculation vessels is important, and their collapse during the destruction of the surrounding tissue with the subsequent development of fibrosis. Secondly, the thrombotic processes are activated due to the vascular endothelium reaction or the vessels' mechanical damage and blood flow stopping under acoustic waves' influence [1, 4].

Besides, focused ultrasound can stimulate the immune response and suppress carcinogenesis in several scenarios: due to the antigenic properties of damaged proteins and tumor cells; due to local inflammatory reactions with the production of effector cells; under the influence of heat shock proteins and increasing the immunogenicity of the tumor, as well as by reducing the level of immunosuppressive cytokines. There is information about the abscopal effect when treating a tumor with FUS. However, to date, these effects may not be strong enough to control tumor growth on their own [5].

Integration with imaging research methods has made FUS the fastest growing therapeutic technology. Focused ultrasound ablation under the control of magnetic resonance imaging (MRgFUS ablation) includes two innovative technologies: a platform to form the focused ultrasound and magnetic resonance imaging with real-time thermography [1, 4, 6]. The advantage of MRI imaging is the possibility of better localization of the target tumor and its edges compared to other methods. Natural tissue contrast provides a high sensitivity of MRI to abnormalities. MRI also supports visualization of the surrounding anatomy and monitoring of temperature changes during therapy, thus arranging a real-time closed-loop system [1, 4, 6, 7].

Some MRI parameters were evaluated to use as temperature indicators. It was found that the resonance frequency of water protons changes due to hydrogen bonds that affect the electronic shadowing of the nucleus that is suitable for thermometry. Simultaneously, the temperature sensitivity does not significantly depend on the tissue type and the thermocoagulation process. These unique features make MR thermometry successful. The main limitations of the method are its sensitivity to movement and inaccuracy in adipose tissue. The ability to perform real-time thermometry has made MRI the most reliable and comprehensive technology for non-invasive FUS ablation monitoring. [1, 4, 6].

ExAblate (InSightec, Israel) is one of the FUS ablation systems approved by the FDA to use in the US [6], Europe, and other countries, and now registered in Kazakhstan. It consists of a control console, an electronic unit, and a portable patient table in several modifications. FUS and MRI 1.5 or 3 Tesla workstations are integrated by the control computer [4, 6]. The ExAblate InSightec system is installed in the East Kazakhstan Region Multidisciplinary Center of Oncology and Surgery of Ust-Kamenogorsk (Figure 1). Treatment is performed in the position of the patient lying on the table inside the MRI scanner.

Figure 1 - ExAblate system (InSightec, Israel) integrated with Signa Architect MRI, 3 Tesla, by GE (USA)

Ultrasound focusing is provided by a conversion device (transducer) located inside the patient's table or its modifications. The transducer is moved inside the table by the mechanical positioning unit that also changes the focus depth for aiming. The transducer can take a form of a rectal emitter (for prostate cancer treatment) and a form of a helmet (for treating the brain area).

A transducer allows achieving a focus of 1 mm at a frequency of 1.5 MHz. In this case, the length of the focus is 5–20 times bigger than the diameter. Such focusing allows us to overcome attenuation losses and concentrate energy deep in the body without damaging the surrounding tissues. [3, 6].

When using multiple transducers, focusing is improved by controlling the phase differences to obtain a common focus (electrical focusing). Simultaneous targeting of the electron beam to several focal points by rapid focus scanning, reducing the total treatment time for large tumors [1, 3, 6].

Thanks to technical solutions, the coagulation area (spot) can be from 1 mm to 10 mm in diameter and 2-70 mm in length. The spots are spindle-shaped, and their various combinations allow you to destroy areas of tissue with any contours and sizes.

The process of FUS impulse of energy transfer is called sonication. A single sonication can last from several to 20 seconds: the higher the temperature, the less time is needed for cell death and vice versa.

The configuration of the affected area inside the tissue is set automatically based on preliminary images. The system outlines the thinnest, tenths of a millimeter demarcation line - the border between healthy tissue and the target area. The ExAblate MRI system operator can relocate the spots during the procedure and optimize the treatment plan based on the acquired MRI image. The treated tissues' characteristics shall be taken into account to cover the whole area selected for treatment. During the procedure, the physician can change the FUS parameters in the intervals between pulses [1, 4, 8].

Accurate anatomical focusing of the beam and localization of the tumor in the three-dimensional image is possible because of the high resolution and sensitivity of MRI Images painted in a different color on a black and white background, according to the tissue temperature, and are created every 3 seconds during sonication. MRI temperature mapping provides closed-loop control of energy deposition with 1 °C accuracy, 1 mm spatial resolution, and 3 seconds temporal resolution.

Therapy planning software automatically calculates the type and amount of ultrasound exposure needed to treat a specific treatment area while minimizing overall treatment time. The focus is automatically electronically moved to an adjacent after treatment point, and the process is repeated until the entire volume for treatment is removed [1, 8].

FUS technology ensures remote non-invasive thermal coagulation of tissues in a strictly defined area without damaging the surrounding organs and tissues.

Materials and Methods: For the review, we selected publications of the last decade on the use of MRgFUS in painful bone metastases, uterine myoma, and prostate cancer. Due to a large number of articles on this topic, we selected the sources containing information on patient selection criteria, the pathogenetic basis of technology, the method of MRgFUS ablation, side effects and complications, and the comparative effectiveness of treatment from the authors and medical centers with 10-20 years of experience in this area.

Results and Discussion:

Clinical applications of MRgFUS ablation

Application for prostate cancer

Prostate cancer is one of the most common cancer types among the male population worldwide [9]. MRgFUS ablation with a special transrectal system has been used for many years as a focal therapy [4, 8].

Low-risk prostate cancer treatment is a common clinical dilemma between standard therapy of the whole gland (associated side effects that reduce quality-of-life) and active monitoring. Low-risk prostate cancer focal therapy aims to achieve the best balance between cancer control and QoL maintenance [9].

Only part of the prostate gland is removed with the help of FUS; therefore, the spatial accuracy of the MRI diagnosis is necessary. Recommended use of the same platform for diagnosis (targeted biopsy), targeted treatment (MRgFUS), and subsequent biopsy (registered targeted biopsy) is most effective. The biopsy template obtained with transrectal ultrasound (TRUS) is used during the planning and implementation stages of MRgFUS ablation. [4, 8, 9]. Contrast-enhanced MRI is performed to identify the non-perfused area at the end of the ablation process [4,8].

MRgFUS ablation followed by radical prostatectomy resulted in complete coagulation necrosis in the treatment area, as seen in the prostate tissue samples of operated patients [4]. A series of clinical cases confirms the initial experience that MRgFUS is safe and useful for focal therapy of prostate cancer [8, 9]. The treatment was well tolerated in patients with minimal side effects. Early biopsy data showed a reduction or absence of residual tumor in all patients after six months. [4, 9].

Side effects of FUS include urinary retention, stress urinary incontinence, bladder outlet obstruction, urinary tract infection, and urethrorectal fistula [8]. These side effect rates reflect the results of early ultrasound-guided tests rather than MRI. MRgFUS has minimal impact on the control of urination, erectile function, pain, and disease [9]. The MRI physician must fully control the focal spot size and location to avoid heat entering critical areas for safe and effective treatment.

Focal therapy is now seen as an alternative to active surveillance for low-risk PCa treatment without life expectancy damage. This approach to saving the neurovascular bundle leads to a low incidence of side effects (single cases) from the genitourinary system compared to alternative treatments of the entire gland [4, 8, 9].

Application for bone metastases

The problem of painful bone metastases remains relevant, despite progress in cancer treatment and pain relief. From 50% to 70% of patients with metastatic bone lesions have severe pain syndrome. External beam radiation therapy in 20-30% of patients does not achieve the goals, and the need for re-treatment reaches 25% [3].

According to the research, MRgFUS ablation is an effective and safe treatment option for patients with painful bone metastases, especially for those who cannot get adequate pain relief with other therapies or are contraindicated due to their physical and functional condition. The procedure is effective even with a single application. However, according to the fact that it does not have a significant general effect on the body, it can be repeated several times if necessary. FUS is also used to treat primary bone tumors [3, 10-13].

A CT scan is done in addition to an MRI scan when planning treatment. CT is usually done without a contrast agent injection to evaluate only the mineralized component of the lesion (osteoblastic or osteolytic metastases) and the integrity or infiltration of the adjacent cortical bone [3].

The mechanism of action of focused ultrasound is based on periosteal denervation of the periosteum. The second effect is related to thermal ablation of the tumor and a decrease in its mass. Due to the high absorption capacity of the bone, ultrasonic energy is only 30% of the soft tissue requirement [3, 10, 11, and 13].

Evidence of new bone formation in patients with osteolysis associated with metastases exposed to FUS is confirmed in addition to earlier studies [3, 13].

A multicenter study using ExAblate showed a significant reduction in pain on a visual analog scale in 72% of patients three months after treatment. There was a 67% reduction in opioid use [3, 10, 11]. The method has shown its effectiveness and the stability of the effect for more than one year. Rare, isolated side effects mainly manifested as mild skin burns that did not require additional treatment and disappeared spontaneously within a week, as well as short-term minor pain [3].

The possibility to repeat the treatment at a safe level makes MRgFUS more effective and applicable than local radiation therapy that is currently standard in patients with pain syndrome with metastatic bone lesions. MRgFUS is a potential treatment option for long-term local tumor control in addition to pain relief [13].

Application for uterine myoma

Uterine myoma is one of the most common diseases in women. Up to 70% of patients with uterine myoma undergo surgical treatment [14].

The studies' data indicate the reliable efficiency and high safety of the MRgFUS method for uterine myoma and adenomyosis. When used optimally, ablation is clinically effective in 85-90% of long-term remission cases [14].

On 09.12.2020, MRgFUS ablation of the uterine myoma was performed under the conditions of the [1]MSE on REM East Kazakhstan Region Multidisciplinary Center of Oncology and Surgery, Ust-Kamenogorsk, the Republic of Kazakhstan. The picture before treatment (Figure 2) shows the myoma location, size, and anatomical structures.

During treatment, the positioning of the spots was optimized (Figure 3).

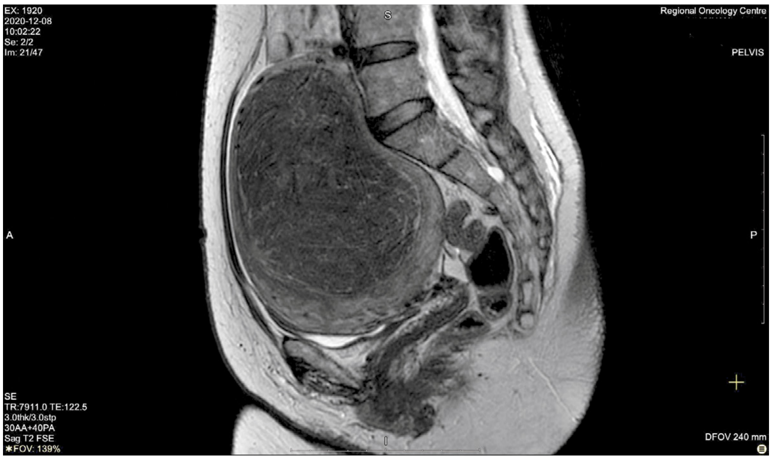

Figure 2 – Myoma uteri before treatment without contrast enhancement

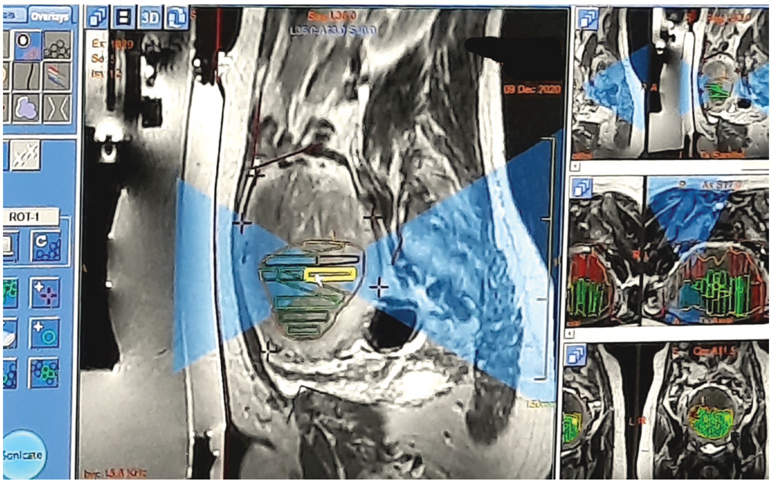

Figure 3 - Image of the treatment process on the display

A two-stage treatment is planned due to the large size of the tumor. According to the results of the first stage of ablation, the non-perfused volume of myoma was more than 90% of the volume of the affected area (Figure 4). The procedure was performed on an outpatient basis, without any complications. The patient returned to work the day after the ablation.

The effect is assessed by measuring the non-perfused volume of fibroid tissue on T1-weighted images with gadolinium contrast at the end of the treatment. Higher nonperfused volume ratios are associated with a lower likelihood of recurrence due to myoma regrowth and reduced need for additional procedures [6, 14, 15].

The results of a study in which elective hysterectomy was performed for one month after ablation showed that MRgFUS could successfully induce thermal coagulation and necrosis of uterine myoma [14].

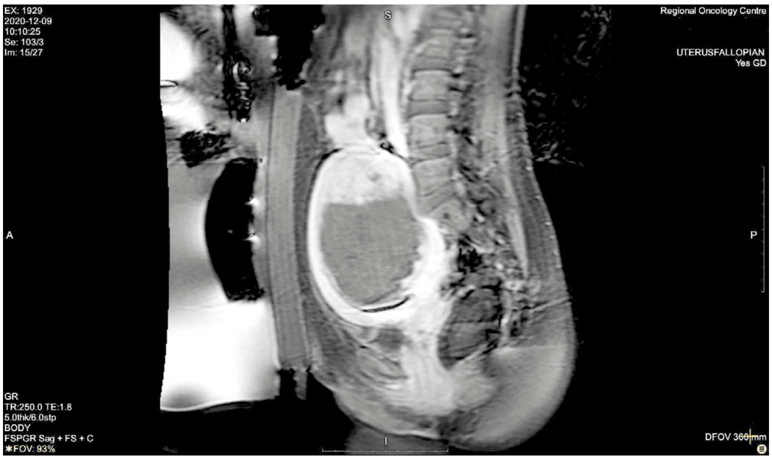

Figure 4 - Uterine myoma after treatment with MRgFUS with contrast enhancement (dark part - non-perfused myoma volume)

Studies have shown that MRgFUS as a first-line treatment for symptomatic myoma is preferable to other methods, including UAE, myomectomy, and hysterectomy, in terms of cost-effectiveness [6, 14-16].

In 2004, the ExAblate 2000 system indication allowed treatment of a maximum of 33% of myoma volume due to concerns about damage to normal uterine tissue. In 2009, the FDA allowed the treatment of 100% of the myoma volume, provided that the treatment focus should be at least 10 mm away from the serous surface of the uterus [6].

In a 2008 study with the ExAblate system, the number of ultrasound treatments performed for a typical ablation ranged from six to 31 per case. A retrospective study of 115 patients in 2013 had an average of 74 sonicators during a treatment session [6].

Side effects of FUS ablation include fatty swelling of the anterior abdominal wall, minor burns, pain in the pelvic area, nausea, vomiting that does not require special treatment and run its course. There were cases of severe skin burns, one case of bone destruction with subsequent successful conservative treatment, and the expulsion of necrotic masses and a node into the uterine cavity. The frequency of side effects on average varies from 0.003% to 0.088% of treated cases. One case of intestinal injury followed by anastomosis and three acute renal failure cases due to lysis of necrotic tumor masses were described [6, 15, 17].

Physicians should strictly follow the procedure and use additional means to reduce the side effects and complications risk to prevent side effects and complications.

Preliminary data suggest that ultrasound ablation is not an obstacle to future pregnancies [14-16]. As MRgFUS continues to evolve and undergo technical improvements, the method will become the first choice therapy for many women and an important tool in the arsenal of personalized therapy for uterine myoma [6, 18].

Prospects to use the MRgFUS ablation

The use of MRgFUS as a treatment for cancer is diverse: from ablation of focal breast cancer to palliative pain relief in focal bone metastases. As technical capabilities evolve, new applications for focused ultrasound are emerging, including for brain tumors, opening the blood-brain barrier with pharmacological treatments for brain cancer, and cancer immunotherapy, as noted at the Focused Ultrasound and Immunotherapy Summit in October 2016, organized by the Cancer Research Center and Focused Ultrasound Foundation (USA).

Conclusions: MRgFUS ablation has been used for many years to treat painful bone metastases, bone tumors, prostate cancer, uterine myoma, and adenomyosis. The method has shown high efficiency and safety with the correct patient selection. Despite the lack of some data on the use of this type of ablation, there has been an expansion of indications for its use over the past decade. MRgFUS ablation can be used as an independent type of treatment and in combination with other methods. The technology is distinguished by non-invasiveness, no need for hospitalization, and subsequent long-term rehabilitation. All this makes us optimistic about the further selection of patients for MRgFUS ablation at the Multidisciplinary Center of Oncology and Surgery in Ust-Kamenogorsk and introducing this method into clinical practice.

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ТҰЖЫРЫМ

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Онкологияда фокусталған ультрадыбысты қолданудың негіздері мен болашағы (әдебиеттке шолу)

Өзектілігі: *Клиникалық практикаға қатерсіз және қатерлі ауруларды емдеудің жаңа инвазивті емес, қауіпсіз және тиімді әдістерін енгізу жоғары өзектілікке ие.*

Мақсаты: *Өскемен қаласының ШҚО көпсалалы «Онкология және хирургия орталығы» ШЖҚ КМК жағдайында ФУЗ-МРТ - абляция технологиясын одан әрі енгізу және қолдану үшін пайдалану туралы жарияланымдарды зерделеу.*

Нәтижелері: *Бұл әдіс фокусталған ультрадыбыстық және нақты уақыт режимінде МРТ бақылауымен термиялық абляцияға негізделген. Көптеген зерттеулер сүйек метастаздары бар, қуық асты қатерлі ісігінің бастанқы сатысы және жатыр миомасы бар науқастар үшін бұл әдістің клиникалық және экономикалық тиімділігін, қауіпсіздігі мен ыңғайлылығын көрсетті.*

Қорытынды: *ФУД-МРТ-абляциясы – бұл қатерсіз және қатерлі ісіктерді емдеудің терапевтік арсеналын кеңейтетін заманауи инвазивті емес технология. Оны белгілі бір жағдайларда қолдану инвазивті емге жақсы балама бола алады. ФУД МРТ абляциясын басқа емдеу әдістерімен бірге қолдануға болады.*

Түйінді сөздер: *фокусталған ультрадыбыстық, МРТ, абляция, қатерлі ісік, метастаздар, жатыр миомасы.*

АННОТАЦИЯ

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Применение фокусированного ультразвука в онкологии: основы и перспективы (обзор литературы)

Актуальность: *Внедрение новых неинвазивных, безопасных и эффективных методов лечения доброкачественных и злокачественных заболеваний в клиническую практику имеет высокую актуальность.*

Цель: *изучить публикации об использовании технологии ФУЗ-МРТ- абляции для последующего внедрения и применения в условиях КГП на ПХВ ВКО Многопрофильный «Центр Онкологии и Хирургии» г. Усть-Каменогорск.*

Результаты: *Данный метод основан на термической абляции под действием фокусированного ультразвука и под контролем МРТ в режиме реального времени. Многочисленные исследования показали клиническую и экономическую эффективность, безопасность и удобство этого метода для пациентов с метастазами в кости, с начальной стадией рака предстательной железы и миомой матки.*

Заключение: *ФУЗ-МРТ-абляция – это современная неинвазивная технология, расширяющая терапевтический арсенал методов лечения доброкачественных и злокачественных опухолей. Его использование в определенных случаях может стать хорошей альтернативой инвазивным методам лечения. ФУЗ-МРТ-абляция может использоваться в комбинации с другими методами лечения.*

Ключевые слова: *фокусированный ультразвук, МРТ, абляция, рак, метастазы, миома матки.*