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HIGH-INTENSITY FOCUSED ULTRASOUND ABLATION (HIFU) IN THE TREATMENT OF CANCER PATIENTS

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High-intensity Focused Ultrasound Therapy (HIFU) is a rapidly developing technology that combines the latest developments in medical imaging and high-tech treatment. HIFU therapy is distinguished by a wide range of applications in medicine, high treatment efficiency, minimal number of complications, non-invasiveness, short recovery time. This review provides literature data on the use of ultrasound ablation in the treatment of cancer patients.

Keywords high-intensity focused ultrasound ablation, oncological care.

High-intensity focused ultrasound ablation (HIFU) is a rapidly developing technology that includes modern developments in medical imaging and minimally invasive therapy under visual control. HIFU therapy has high treatment efficiency and accuracy, the absence of ionizing radiation, the possibility of treating cancer at all stages (radical in the early stages, palliative in the advanced ones), the absence of anesthesia, a short rehabilitation period, the possibility of treating cancer of many localizations - prostate, pancreas, liver, kidneys, bones, soft tissues, bladder, retroperitoneal space, mammary and thyroid glands, uterus. The method is not limited only to ultrasound ablation of neoplasms, and is also widely used for palliative purposes to relieve pain of tumor genesis.

The first scientific work devoted to HIFU was published in the 20s of the XX century, in which American researchers Wood and Loomis described the effects of focused ultrasound on unicellular organisms and tissue samples of fish [41]. In 1956, Professor A.K. Burov first proposed the idea of using focused high-frequency sound waves in the treatment of malignant tumors [42]. A group of researchers from the Illinois Institute of Technology, USA, in 1957 described in detail the effects of focused ultrasound on animal tissues, thereby laying the theoretical foundations for the introduction of HIFU into clinical practice. The observations published in 1960 by Soviet scientists L. D. Rosenberg and M. G. Sirotyuk on the emission of sound into a liquid in the presence of cavitation, as well as the development of devices for measuring ultrasonic fields in media in the presence of cavitation, made it possible to make a big step in the development of the method and a general understanding of the physics of ultrasound effects on tissues [52]. The appearance of imaging methods in the doctor's arsenal made it possible to monitor changes in tissues exposed to HIFU and evaluate the therapeutic effect in real time. The clinical experience accumulated over many years demonstrates the possibility of using high-intensity focused ultrasound ablation in oncological practice, allowed us to evaluate the effectiveness of the technology and side effects, as well as morphological changes in tissues. The

principle of HIFU therapy is based on the effect of high-frequency sound waves concentrated in a given focus, generated by a piezoelectric element [40]. Ultrasound waves have a pronounced ability to have a focal effect on tissues, unlike scattered waves used, for example, in ultrasound diagnostics. The cytolytic effect is achieved due to a cascade of processes caused by mechanical and thermal effects of ultrasound. Due to the absorption of acoustic energy by tissues, their local heating occurs up to 850C, and as a result, coagulation necrosis occurs. The most important mechanical factor of the impact is the effect of cavitation – the appearance of microscopic gas cavities, microbubbles in the tissues, during the collapse of which a shock wave is formed, developing a pressure in the microenvironment up to 30,000 Bar, which ensures the physical destruction of cells [43, 44]. The great advantage of HIFU therapy is the ability to monitor the ablation zone using diagnostic ultrasound in real time. In addition to ultrasound navigation, MRI control is also used, which provides better visualization, but has the traditional disadvantages of nuclear magnetic resonance: the high cost of the method and spatial limitations [45, 46].

Therapy of pain syndrome of cancer patients

Pain syndrome is noted in 80% of cancer patients, it is often severe and requires treatment with analgesics [19]. Despite the progress made in the treatment of pain in such patients, modern therapies have limited effectiveness, which significantly worsens the quality of life of patients [18, 19].

Different pain management strategies can be implemented depending on the type and stage of cancer. In general, currently, the standard of pain treatment in cancer patients is treatment with nonsteroidal anti-inflammatory drugs and opioids in accordance with the three-step pain scale of the World Health Organization (WHO) [32]. Morphine is the most commonly used opioid; however, its effectiveness is limited by side effects such as sedation, nausea, constipation and respiratory depression; variability in patient response [22]. In addition, the use and effectiveness of opioids is limited by hyperalgesia caused by them, stimulation of tumor growth and neoangiogenesis and the development of opioid dependence [9, 19, 22, 28].

In the case of insufficient analgesic effect, interventional techniques such as regional anesthesia, nerve blockade and neuroaxial neurolysis, as well as implantable drug delivery systems, can be used in drug treatment. Repeated treatment sessions are often necessary [3]. In some cases, neurosurgical operations are performed to modulate or destroy structures involved in the transmission and perception of pain [29].

Treatments such as radiation therapy, chemotherapy, and surgery can eliminate pain, but they can also make it worse. In addition, neuropathy caused by chemotherapy is observed in 30-70% of patients and often leads to a reduction in the dose of the drug to a suboptimal level and, as a consequence, to inadequate treatment [19].

HIFU therapy of bone metastases

Bone metastases are one of the most common causes of pain in cancer patients [21]. Regardless of the cause - mechanical or biochemical - the pain can be severe and difficult to control.

Currently, the standard of treatment for metastatic bone pain is radiation therapy. However, this method is not effective enough in many cases. It is reported that 20-30% of patients do not experience adequate anesthesia, and a significant number of them have recurrent pain. At the same time, there is a limitation of repeated treatment due to the significant toxic effects of radiation [30]. In most cases, radiation therapy has a long latency period, up to 4 weeks, necessary to achieve a palliative effect in patients with severe pain syndrome [13, 17].

In the last decade, HIFU therapy has been approved for the treatment of bone metastases in the USA, Europe, Asia, Canada, Israel and Russia. In 2015, a consensus was reached by recognized international experts on the effectiveness of the treatment of painful bone metastases by HIFU therapy [12]. There are several mechanisms for pain relief achieved with HIFU. Periosteal denervation caused by heating has the greatest effect on pain relief [4]. Coagulation necrosis of the tumor can lead to a decrease in pain due to a decrease in the size of the tumor [4]. Moreover, the removal of tumor cells reduces the local release of chemical mediators and the degree of osteolysis caused by osteoclasts [37]. Also, HIFU therapy causes bone remodeling with rapid recovery of thermal damage and accelerated sclerosis in osteolytic metastases [2, 5, 8, 14,15, 24,].

Clinical studies of HIFU therapy were conducted under the control of ultrasound [16] and MRI [4, 5, 8, 11, 14, 17, 24], which have demonstrated the high effectiveness of the method for relieving pain syndrome in patients with bone metastases.

Currently, HIFU is recommended as a second-line treatment after radiation therapy to relieve pain associated with bone metastases other than the bones of the skull and spine. HIFU can be used to treat metastases of the ribs, sternum, pelvic bones, shoulder girdle, back of the lumbar and sacral vertebrae and limbs [12].

HIFU can be used as a first-line treatment when radiation therapy is contraindicated or the patient refuses to receive it. The main goal of treatment is analgesia, although local control of the tumor can be assessed as a secondary goal [11]. In 2013, a randomized placebo-controlled blind multicenter HIFU study was conducted with 147 patients. Pain reduction was achieved in 64.3% of patients, and about 20% of them achieved complete anesthesia. In two thirds of patients, the response was achieved within 3 days [13]. In the study Bertrand et al. [1] it is reported that all patients had a significant reduction in pain a week after HIFU. In addition, the study noted that a complete tumor response was achieved in 37.5% of patients, a partial response in 50%. In another study, the authors show that in 53% of patients with bone metastases, pain relief occurred within 30 days after treatment [10].

HIFU has advantages for relieving pain syndrome in patients with bone metastases. There are no restrictions based on the type of bone injury (osteolytic or osteoblastic) associated with previous radiation therapy or chemotherapy. In addition, the number of sessions that a patient can undergo in cases of relapse of pain is not limited [4, 13, 17]. Moreover, HIFU can be performed simultaneously

with chemotherapy [23]. Pain syndrome is stopped in 60-100% of patients, is achieved within 3 days and lasts more than 3 months [4, 8, 13, 17, 24].

HIFU Pancreatic Cancer Therapy

Pancreatic adenocarcinoma accounts for more than 95% of all pancreatic cancers and is currently the fourth leading cause of cancer death. Pancreatic cancer is most often detected at an inoperable stage, and only 20% of patients are operable at diagnosis [7]. In addition, after surgery, the frequency of local-regional relapses is high, which explains the high mortality rate. 60-90 % of patients with pancreatic cancer have a pronounced pain syndrome [49].

In a recent meta-analysis, it was shown that the use of HIFU relieves pain syndrome in most patients with pancreatic adenocarcinoma. The mechanisms of action are not fully understood, but they can be based on thermal damage to the nerve endings of the tumor, inactivation of the fibers of the abdominal plexus and a decrease in the volume of the tumor, which leads to a decrease in mechanical pressure on nerve structures. It is noted that HIFU therapy is effective in relieving pain syndrome in 80-100% of patients with pancreatic cancer [7]. The immediate analgesic effect is significant, since most patients can stop taking opioid medications. In another study, the analgesic effect of HIFU therapy was noted for a longer period - up to 17 months [34]. In the study Marinova et al. [20] it is reported that 85% of patients after HIFU achieved long-term relief of pain syndrome, while 50% of patients after treatment did not need any additional analgesics.

In addition to the analgesic effect, a number of authors note local tumor control. It was also noted that pain relief occurs even in the absence of a tumor reaction. Xiong and co-authors [35] inform that the analgesic effect was achieved in 88.0% and 76.2% of patients in both the presence and absence of an objective tumor response, respectively. Similar results were obtained by Zhao et al. [39]: pain relief was achieved in 88.2% of patients with a tumor response in 35.0% of patients with stable or progressive disease. In the work of Ning et al. [25] the results of treatment with HIFU therapy in 523 patients with unresectable pancreatic tumors were published. The authors noted that the majority of patients had complete or partial relief of pain syndrome, as well as an increase in patient survival compared with chemotherapy.

In addition to pain relief, HIFU therapy increases patient survival. A significant increase in survival was observed in an uncontrolled series of cases of patients with pancreatic adenocarcinoma of stage III and IV, who underwent HIFU in conjunction with chemotherapy. The maximum survival after treatment was 3.4 years [31].

HIFU Prostate Cancer Therapy

The main advantages of HIFU in the treatment of prostate cancer are the non-invasiveness of the method, the absence of ionizing radiation, the possibility of use in patients with severe concomitant pathology, good medium and long-term oncological results, the possibility of repeated procedures in one patient and a low percentage of perioperative complications [46]. In addition, an important factor of reproducibility of the method is its low cost and short learning curve of the operator. Chiang P. H., Liu Y. Y. presented a large retrospective study involving

492 patients comparing the main surgical methods of prostate cancer treatment - radical prostatectomy, brachytherapy, cryodestruction and HIFU. The average follow-up period was 3 years. The highest frequency of biochemical relapse after treatment (54.7%) was observed in the brachytherapy group, especially in patients of intermediate and high risk according to D'Amico. The HIFU group demonstrated not only good oncological results, but also satisfactory urine retention function (according to the IPSS questionnaire), and the absence of erectile dysfunction in 65.5% of patients a year after treatment [47]. In 2015, Stephanie Guillaumier and co-authors presented a multicenter study of 5-year results after focal HIFU therapy for localized prostate cancer. The analysis included 625 patients who underwent HIFU therapy, and their rates of relapse-free, metastatic, cancer-specific, and overall survival were 88%, 98%, 100% and 99%. In the same year 2015, a group of British and American researchers led by Mark Emberton published data from a multicenter study involving 754 patients. The average follow-up period was 46 months, while 70% of patients had no biochemical relapse [48]. Mutsuo Hayashi et al. A study of 224 patients with localized prostate cancer was published. There were no prostate cancer deaths among the studied patients. 7-year relapse-free survival among all patients was 75%, and five-year relapse-free survival for patients of low, intermediate and high risk groups was 98%, 84% and 59%, respectively [49]. In 2013, German scientists Ganzer R., Fritsche H. M. described their fourteen-year experience of using HIFU therapy in the treatment of localized prostate cancer. 538 patients were examined, and the average follow-up period was 8.1 years. Overall survival after 5 years was 81%, after 10 years - 61%, cancer-specific survival was 96.7% (death from prostate cancer in 18 patients) [50]. Samara scientists in 2015 presented 7-year results of the use of HIFU in 976 patients with localized prostate cancer. The Kaplan-Meyer relapse-free survival in the entire group of patients was 79.2%, in the low– and medium-risk groups according to D'Amico - 93.9% and 91.8%, respectively [50].

HIFU therapy for other cancers that cause pain syndrome

The possibility of using HIFU therapy to relieve pain in patients with other malignant neoplasms was analyzed. These studies should be taken into account and considered as an option for conducting therapy for pain relief.

Neuroendocrine tumors of the pancreas (NPJ) were effectively treated with HIFU under ultrasound control [6, 26, 27]. Although NTTP are not as aggressive as pancreatic adenocarcinoma, they are often diagnosed late, when most patients have abdominal pain, dyspepsia and insomnia due to pain. The majority of patients noted the disappearance of pain after therapy.

A study was published evaluating HIFU therapy under ultrasound control for the treatment of inoperable hepatocellular carcinoma in 145 patients. Relief of pain syndrome was achieved in 84.8% of patients. In addition, appetite improved in 76.3% of patients and the general well-being of patients. At the same time, survival was higher in patients in the group where HIFU treatment was carried out for the entire volume of the tumor [36].

A group of 83 patients with gastric cancer metastases to abdominal lymph nodes who received chemotherapy in combination with HIFU was compared with 102 patients who were treated with chemotherapy alone. 56 out of 83 patients in

the chemotherapy and HIFU group and 64 out of 102 patients in the chemotherapy-only group experienced pain before treatment. Partial or complete pain relief was achieved in 75% of patients in the group receiving HIFU together with chemotherapy and in 51.6% of patients in the group receiving only chemotherapy [38].

Encouraging results were observed in patients with advanced stages of malignant neoplasms of the kidneys. In one study, 13 patients underwent HIFU therapy. After treatment, 90% of patients reported a reduction in pain. In 2 patients, the stage of cancer was lowered, which allowed for radical nephrectomy [33].

The results of these studies are promising, not only because pain relief was successful in most of the treated patients, but also because HIFU therapy demonstrated stable local control of the tumor or led to a decrease in the stage. The noninvasiveness of HIFU therapy makes this treatment available to patients with concomitant diseases who cannot undergo surgery.

Conclusion:

Summarizing the above, it should be noted that HIFU therapy will play an important role in the treatment of cancer patients. Having significant advantages, such as non-invasiveness, high efficiency and accuracy of treatment, rapid and long-term relief of pain syndrome, the minimum number of complications allows the use of HIFU for the treatment of malignant neoplasms of various localizations and stages. In addition, HIFU therapy can be combined with all other types of anti-cancer treatment. HIFU therapy significantly improves the quality of life and leads to an increase in the survival rate of cancer patients.

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