REVIEW ARTICLE

THE USE OF ULTRASOUND GUIDED HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) IN THE TREATMENT OF UTERINE FIBROIDS: AN OVERVIEW

DOI: 10.36740/WLek202202139

Yoana Ivanova[1], Dobromir Dimitrov[2], Kameliya Dimitrova[3], Aparajeya Shanker[3], Angel Yordanov[1]
[1]DEPARTMENT OF GYNECOLOGIC ONCOLOGY, MEDICAL UNIVERSITY PLEVEN,PLEVEN, BULGARIA
[2]SURGICAL ONCOLOGY DEPARTMENT, MEDICAL UNIVERSITY PLEVEN, PLEVEN, BULGARIA
[3]FACULTY OF MEDICINE, MEDICAL UNIVERSITY PLEVEN, PLEVEN, BULGARIA

ABSTRACT

Uterine fibroids are the most common benign gynecological neoplasms, with a higher prevalence in women aged between 30 and 50 years old. Fibroids may be asymptomatic, but in some cases, they can affect seriously the quality of life of the patients. In some cases, we can recommend expectant management for asymptomatic patients. Management depends on the size and location of fibroids, the age of the patient, symptoms, desire for future childbearing and the experience of the gynecologist. Medical therapy includes hormonal contraceptives, tranexamic acid, and nonsteroidal anti-inflammatory drugs (reduce heavy menstrual bleeding). Gonadotropin-releasing hormone agonists or selective progesterone receptor modulators are used mostly preoperatively. Surgical treatment includes hysterectomy, myomectomy – invasive and minimally invasive. Non-surgical management include uterine artery embolization, and focused ultrasound surgery.This review aims to present the role of High-Intensity Focused Ultrasound in the treatment of uterine fibroids.

KEY WORDS: uterine fibroids, Focused Ultrasound Surgery, High-Intensity Focused Ultrasound, Ultrasound guided High-Intensity Focused Ultrasound

Wiad Lek. 2022;75(2):545-549

INTRODUCTION

Uterine fibroids (UF) are the most common benign tumour pathology in women. The incidence of UF is associated with age, with a higher incidence in women between 30 and 50 years [1]. UF affects between 70-80% of all women, as they could be symptomatic or in the most cases – asymptomatic. When symptomatic, patients with UF present with a range of symptoms such as abnormal uterine bleeding, anemia, feeling of pelvic pressure and / or pelvic pain, infertility dyspareunia, constipation, pollakiuria, frequent nocturnal urination, symptoms of overactive urinary bladder [2]. In some patients, the UF may present with ureteral compression with resulting hydronephrosis and pyelonephritis [3].

The pathophysiology of UF has not been discovered. Existing theories indicate the combined effect of estrogen, progesterone and insulin-like growth factors may interact together to create conditions in the uterus for fibroid formation [4]. There is a hypothesis that the growth of UF depends on the difference between content of oestrogen receptors in endometrium and myometrium. If the concentracion is lower in the myometrium than the endometrium, this oestrogen may contribute to tumour enlargement by increasing the production of extracellular matrix. There is a data that progesterone also affects UF, especially in young women, because increases the mitotic activity of myomas. Tumour enlargement may be provoked by down-regulating apoptosis in the fibroids [5].

Modern treatment approaches include the usage of medical management, surgical management – which could be invasive and minimally invasive and non-surgical methods. Surgical methods include hysterectomy (vaginal, abdominal, laparoscopic or robotic), myomectomy (hysteroscopic, laparoscopic, robotic or by laparotomy), while non-surgical management is presented by procedures like uterine artery embolization and focused ultrasound surgery [5].

The choice of treatment depends mostly on patient preference with special regard to childbearing, choice of preserving uterus, chance of success of achieving treatment milestones, improving symptoms and overall health status of the patient [6]. The medical management of uterine fibroids include anti-fibrinolytic agents, non-steroidal anti-inflammatory drugs (NSAIDs), combined hormonal contraceptives, progesterone-only treatments, selective progesterone receptor modulators (SPRMs), anti-progestins, aromatase inhibitors, and gonadotropin releasing hormone (GnRH) agonists or antagonists [6]. Although other pharmacologic classes are being studied, current data does not show evidence of symptom or clinical improvement [6]. The fibroids characteristics, such as number, size and location, sympthoms, patients age and fertility desire, determine the type of treatment , especially

when considering minimally-invasive versus open surgery and myomectomy versus hysterectomy [7, 8]. Non invasive methods like Focused ultrasoud surgery (FUS), are divided in two main groups MRI (Magnetic Resonance Imaging) guided and Ultrasound guided High Intensity Focused Ultrasound (USgHIFU) [9].

THE AIM

This review aims to present the role of High-Intensity Focused Ultrasound in the treatment of uterine fibroids, the importance of searching for new non-invasive ways for treatment, to reveal the mechanisms and the safety protocols, and also to compare it with the surgical treatment of uterine fibroids.

REVIEW AND DISCUSSION

HISTORICAL PERSPECTIVES AND FUTURE LANDSCAPES OF FOCUSED ULTRASOUND

The use of focussed ultrasound begins with the discovery of ultrasound as a therapeutic modality in 1930, when the thermal effects of ultrasound on tissue were discovered [10]. In particular, ultrasound was used in physiotherapy, where the newly discovered thermal effects of ultrasound were used to treat tendonitis, synovitis and bursitis [10]. The use of focused ultrasound was pioneered by the experimentation of the Fry brothers, who, in the 1950s, experimented with the use of focussed ultrasound waves for the treatment of Parkinson's disease [11].

The subsequent years of experimentation led to the development of newer devices and newer areas of possible application of High-Intensity Focused Ultrasound (HIFU). Currently, HIFU is used in gynaecology for the treatment of UF and also in the treatment of benign, non-neoplastic diseases of the vulva [12, 13]. The use of HIFU in prostate hyperplasia is its most widespread use [14].

The future of HIFU is indeed bright as more areas of its application are being discovered. Current research into the expansion of the use of HIFU in the management of oncological disease shows that it is a safe and effective non-invasive method of targeting tumours [15]. Studies have shown positive results when investigating tumour shrinkage, patient safety, post-procedure complications. HIFU, both MRI and Ultrasound guided, have a variety of future applications, especially in patients that meet the suitable criteria [15].

WORKING PRINCIPLE

High Intensity Focused Ultrasound utilizes ultrasound waves to raise the temperature of tissue above 65 degrees Celsius. The High Intensity ultrasound wave is directed towards a very specific anatomical site at particular depth. This allows the sparing of surrounding tissues and is a precise method for targeting tissues [16]. HIFU is similar to diagnostic ultrasound in principle, the only difference is that HIFU, as its name implies, functions by generating ultrasound waves at intensities that are several magnitudes higher than imaging/diagnostic ultrasound [17]. The therapeutic range of HIFU is between 100 W/cm^2 and 10,000 W/cm^2 [18]. The main objective is to utilize the thermal and mechanical effects of high intensity ultrasound waves to achieve tissue ablation through coagulative necrosis. Cell destruction through coagulative necrosis is achieved when the temperature of tissue is raised to 60 degrees celsius for 1 second. As a safety measure, the exposure does not last longer than 1 second [17].

The ultrasound wave is focussed to achieve the desired effects on tissue. HIFU transducers are designed to focus the beam through spherical, concave or sometimes flat surfaces of transducers. In some cases, acoustic lens are used for adjusting the ultrasound beam so that it is focused at a specific focal point (Fig 1). Aside from the thermal effects of HIFU, the mechanical effects of ultrasound are utilized to achieve acoustic cavitation, which aid in tissue destruction [18].

There are two major imaging modalities used in HIFU, MRI and ultrasound. Both modalities are utilized for targeting tissue, intraoperative beam localization and therapeutic monitoring post procedure [18]. MRI allows for high contrast imaging with precise spatial assessment but is limited because it does not allow real-time monitoring like ultrasound. The advantage of the MRI over ultrasound in HIFU is that it is the only modality to allow real time thermometric assessment, however, research into new technology is underway to expand the capabilities of ultrasound in this regard [18].

Contrast agents play an important role in HIFU, and the use of contrast agents in ultrasound is termed Contrast Enhanced Ultrasound (CEUS). Their application is important for the diagnosis of tumours, as a guiding tool in HIFU therapy and for assessing ablation during and after the procedure. Contrast agents form microbubbles in blood vessels which create acoustic changes in tissues, allowing for an increase in effectiveness of tumour ablation. A number of contrast agents are used, such as SonoVue (sulfur hexafluoride) and Sonazoid (Perfluorobutane), among others. A number of studies have demonstrated their safety and effectiveness [19-21]. We demonstrates a case of a patient with uterine fibroids treated USgHIFU (Fig 2A-C).

The HIFU JC system is an ultrasound guided device that allows real-time imaging during tumour ablation procedures. It consists of two transducer heads - one is diagnostic and operates at 3.5 MHz, and the other is the therapeutic, which operates at 1.6 MHz. This system lets precise targeting of tissue while monitoring patient movement and possible displacement of target point [23]. Coagulative necrosis presents as areas of hyperechoic spots (Fig. 2C). The patient is positioned on the HIFU table under which a special container filled with degassed water is placed. Degassed water is an efficient conductor of ultrasound waves and also fulfills the purpose of cooling the skin and subcutaneous tissue, preventing skin burns [22, 23].

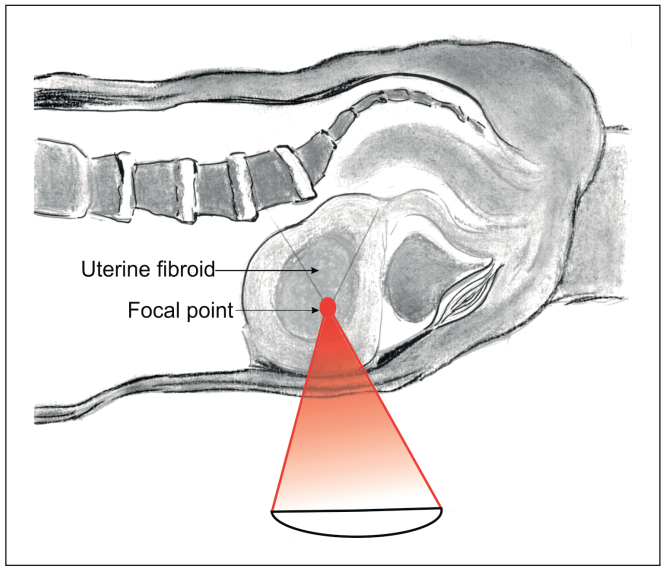

Fig. 1. Principle of HIFU ablation.

PATIENT SELECTION CRITERIA

Patient selection criteria is essential to the success of HIFU in the treatment of UF. The patient selection criteria was based on a prospective study establishing a clinical protocol for the use of HIFU in the treatment of UF, conducted by our institution (Table. I) [24]. Contrast enhanced MRI of the pelvis was used as the primary imaging modality [24].

Excluding criteria for HIFU ablation are these which may indicate a manignancy - low hemoglobin levels (less than 70 g/L), LDH exceeding 500 U/l, rapidly growing fibroid and heteroinsive zones with liquid-equivalent MRI zones.

Preoperative preparation of a patient before HIFU ablation of a myoma:

1. Taking a medical history
2. Examination by an internist
3. Gynecological examination
4. MRI examination
5. Three-day special diet before FUS
6. Preparation of the gastrointestinal tract - taking a cleanser the day before the procedure
7. Ablation is performed 3-5 days after menstruation

PROCEDURE

MAIN PROCEDURE

Preoperatively, the patient is catheterized for controlling the amount of urine in the bladder and for providing intracorporeal cooling. If required, serum at a certain temperature is introduced in the catheter and this allows for intraoperative temperature control. The patient is then sedated enough to achieve muscle relaxation but also to ensure effective communication with the operative team. The patient can communicate any discomfort or pain and the operative team can respond accordingly [24].

The patient is placed in the prone position on the operating table and the abdomen is immersed in a vat of degassed water, the temperature of which can be regulated by the operating team. A water balloon is placed between the transducer and the abdomen. The water balloon serves two functions, the first is to clear the intestinal loops around the tumour and to fixate the tumour in the acoustic pathway, the second function is to act as an acoustic lens to better focus the ultrasound beam.

Intraoperative imaging is then initiated to visualize the pelvis. After locating the tumour, the coordinates of the tumour are entered into the Model JC system for ablation planning. Sectional planes of the myoma are prepared digitally for ablation. Thermal ablation begins at low energy, usually at 50W and the patient response is noted. The energy of the HIFU beam is increased gradually till a maximum energy of 400 W. Diagnostic imaging allows for real-time visualization of the response of the tumour to ablative therapy. The presence of an hyperechogenic area indicates that coagulative necrosis has been achieved (Fig. 2C) [24].

Protocols for patient safety

Safety protocols are central to HIFU, and broadly revolve around temperature control. Factors that affect the safety

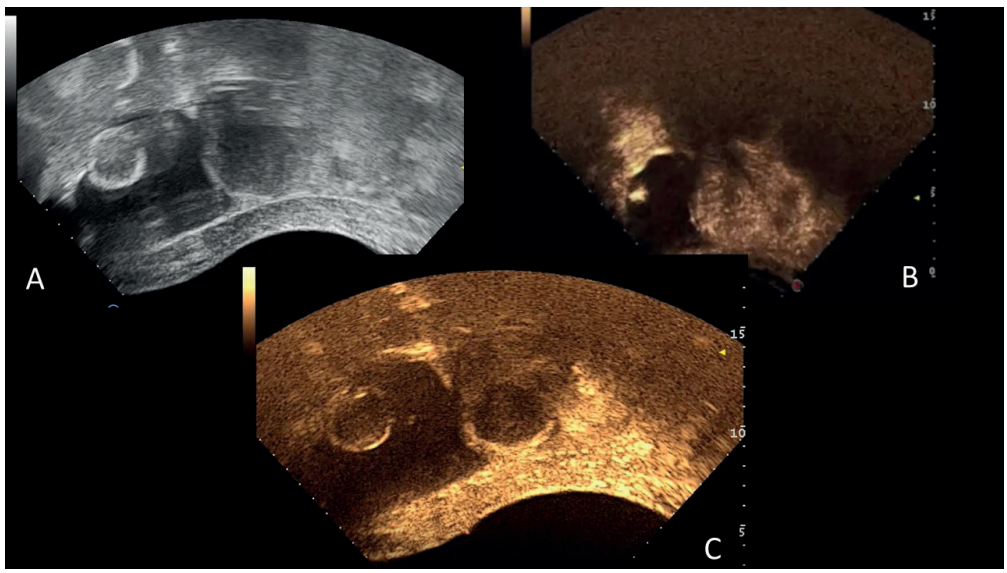

Fig. 2. An own case of a patient with uterine fibroids treated by ultrasound guided HIFU: A) a normal ultrasound image of the uterus fibroid and on the left, the urine-filled bladder and urethral catheter balloon are observed; B) 1.5 ml of Sonovue ultrasound contrast agent is injected and typical image of CEUS is observed - a well-supplied myoma is filled with "glowing" microbubbles that are present in the general circulation; C) an ablated fibroid with coagulative necrosis, as the microbubbles from the second dose of 1.5 ml Sonovue fill and enter only the uterine wall and other organs - the fibroid remains a "black" hole, which proves that the procedure was successful in achieving tumour ablation

Table I. Indicatoints and contraindications for HIFU.

Indications	Contraindications
Clinical diagnosed fibroid	Pregnancy
Dysmenorrhea, secondary anemia, sterility, abnormal menstrual cycle	Endometriosis
The diameter of the node should be greater than 2 cm when it is on the anterior uterine wall and larger than 4 cm when it is located in the area of the posterior uterine wall	Cervical fibroids
Consent to HIFU	Submocosal/Subserosal fibroid with pedicle
Consent for uterus preservation and refusal of hysterectomy	Diameter of posterior wall fibroid less than 3.5 cm
Low and moderate grade vascularization of fibroid nodules (T2 hypo to medium intense)	Large postoperative abdominal scar or foreign body implants in the acoustic path
Less than 4 fibroid nodules	Radiation dose over 45 Gy in the pelvis
BMI lower than 30	Hypovascular fibroid nodule
Distance between skin and the farthest depth of fibroid on the posterior wall is less than 9 cm.	Subcutaneous fat thickness greater than 10 cm
	Malignancy such as uterine sarcoma, endometrial cancer etc

limitations are the vascularization of the tumour, patient characteristics such as age, comorbidities and general status. The energy of the HIFU beam does not exceed 400 W and usually ranges between 200 to 400 W. An interval of 3 seconds is maintained between each successive ultrasound shot and it is not recommended to use a maximum power of 400 W. For every 300 seconds of ablation time, the procedure is paused for 5 to 7 minutes. This allows for minimizing the risk of thermal and cavitation injuries to tissues. Maintaining a distance between the mucous membrane and ultrasound rays, and between the sacrum and the ultrasound rays is central to patient safety. The procedure is stopped if tumour ablation is achieved or if the patient expresses discomfort or pain.

SonoVue dosage in HIFU is 25 mg dissolved in 5 ml of saline, with 1.5 ml being administered before, during and after HIFU ablation. After each dose, 10 ml of saline is administered intravenously [25, 26]. When using Sonazoid, it is necessary to make one application for 30 minutes before the onset of ablation and it provides the presence of contrast for about 60 minutes in the bloodstream. Reconstitution is performed according to the manufacturer's instructions [25]. After the procedure, the patient must remain in the prone position for 10 minutes to allow the cooling of abdominal skin.

POST PROCEDURE STATUS

OUTCOMES

The clinical outcomes of patients who underwent HIFU are comparable to other therapeutic interventions. HIFU is a safe measure and can be argued to be a suitable alternative to other therapeutic methods [24, 27]. Although meta-analyses comparing Uterine Artery Embolization (UAE) and HIFU have been conducted, they are limited by the low number of studies included and also do not address the outcomes as they relates to pregnancies, both successful or otherwise [28]. Patients who have undergone HIFU report lower post operative pain, fever, and return to their daily lives sooner than those who undergo invasive surgical procedures like hysterectomies [24]. The comparison between UsgHIFU and laparoscopic myomectomy shows a comparability in improvement of QoL inwomen and fewer significant clinical complications and adverse events and with faster recovery [29].

HIFU as a treatment for uterine fibroids is dependent on strict adherence to the Patient Selection criteria and deviations, such as variations in tumour size, increase reintervention rates [30]. Recovery time in patients who have underwent HIFU is lower and the number of pregnancies is also higher than those who underwent UAE or other surgical interventions [31]. The most significant advantage of HIFU was the lower incidence of postoperative pain and discomfort, these adverse outcomes did not present with permanent sequelae or death [28]. Significant improvements in the Quality of Life after 36 months indicated that patients who underwent HIFU reported comparable or higher Quality of Life [31].

The introduction of FUS as an opportunity for leading choice in patients with fibroid disease requires research and greater experience among European patients, as well as the comparison of the method with other surgical approaches. This was conducted in Oxford - IDEAL non-randomized prospective study. It involves 2411 patients with symptomatic fibroids, and they have the right to choose the treatment approach. All patients are premenopausal, the uterus is enlarged at least as much as 10 gestational weeks, with no more than 3 myomas, and the maximum allowable size of a single fibroid is 10 cm. 1353 women chose HIFU, 586 requested myomectomy and 472 underwent hysterectomy. The study proves that both quality of life and symptoms have improved significantly faster in the HIFU group. Significant side effects occurred in 0.2% of the HIFU group and in 12.6% of patients who underwent surgery. The mean time to hospitalization was 4/8/10 days for the three groups, respectively. At 6-month follow-up, the pregnancies

occurred were 7/1/0, respectively, and at 12-month follow-up 21/3/0. After 12 months, there was a need for re-intervention at 14/0/0, respectively, which is 1% for the HIFU group and 0 for those who underwent surgical treatment. The conclusion proves similar effectiveness in improving the quality of life and the response to symptoms, as in the HIFU group there is a significant short hospital stay, as well as early return to work and a small percentage of side effects [32].

COMPLICATIONS

The most common adverse effects in HIFU are postoperative pain, discomfort and mild skin burns. However, none of these adverse effects have presented with long term sequelae or death [28]. The need for reintervention is another possible complication, however, reintervention rates are consistently low in HIFU patients [27], and this can be avoided as long as patient selection criteria is adhered to [31]. Over a period of 4 years (between 2011-2015), 10,310 patients were followed up in China to investigate complications. Retrospectively, 4136 side effects were identified in 2367 patients (23%). They most often complained of pain in the lower abdomen 21.9% (2253/10310), followed by the presence of minimal vaginal discharge 11% (1136 patients), 6.9% reported sacro-coccygeal pain. The complaints subsided without treatment for about a week. Thirteen patients (0.1%) reported tingling or pain in diseased limbs that lasted between 2 weeks and 2 months. Among the more serious complications were skin burns in 21 women (0.2%) and colon damage in 2 of the patients (0.02%). The burns were of 2nd and 3rd degree and were found mainly in women with scars on the lower abdomen. It was found that patients who had perforation of the intestine did not follow the protocol for cleansing the stomach - the intestinal tract before the intervention, as well as the use of high energy in ablation [27].

CONCLUSION

The use of UsgHIFU as a therapeutic intervention for uterine fibroids is an area of promising results. Its primary advantage is that it can be performed non-invasively and without the need for general anesthesia. Clinical outcomes for HIFU in general are promising in the treatment of uterine fibroids, and should be recommended for patients who fit the selection criteria. The Patient Selection Criteria is essential to positive outcomes of UsgHIFU and care should be taken to ensure that patients meet this criteria for optimal outcomes. Further research comparing the various modalities of therapeutic interventions should be conducted to suggest standardized protocols of care.

REFERENCES

1. De La Cruz MS, Buchanan EM. Uterine Fibroids: Diagnosis and Treatment. Am Fam Physician. 2017;95(2):100-107.
2. Vilos GA, Allaire C, Laberge PY, Leyland N; SPECIAL CONTRIBUTORS. The management of uterine leiomyomas. J Obstet Gynaecol Can. 2015;37(2):157-178. doi: 10.1016/S1701-2163(15)30338-8.
3. Hoellen F, Bohlmann M. New Concepts in the Therapeutic Management of Myoma. EMJ Repro Health. 2015;1(1):87-94
4. Levy BS. Modern management of uterine fibroids. Acta Obstet Gynecol Scand. 2008;87(8):812-23. doi: 10.1080/00016340802146912.
5. Tochie JN, Badjang GT, Ayissi G, Dohbit JS. Physiopathology and Management of Uterine Fibroids. 2020. doi: 10.5772/intechopen.94162. Available from: https://www.intechopen.com/books/fibroids/physiopathology-and-management-of-uterine-fibroids
6. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. Int J Gynaecol Obstet. 2020;149(1):3-9. doi: 10.1002/ijgo.13102.
7. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update 2016; 22: 665–686.
8. Bhave Chittawar P, Franik S, Pouwer AW, Farquhar C. Minimally invasive surgical techniques versus open myomectomy for uterine fibroids. Cochrane Database Syst Rev. 2014;(10):CD004638.
9. Zhang C, Jacobson H, Ngobese ZE, Setzen R. Efficacy and safety of ultrasound-guided high intensity focused ultrasound ablation of symptomatic uterine fibroids in Black women: a preliminary study. BJOG. 2017;124 Suppl 3:12-17. doi: 10.1111/1471-0528.14738.
10. Miller DL, Smith NB, Bailey MR, Czarnota GJ, Hynynen K, Makin IR; Bioeffects Committee of the American Institute of Ultrasound in Medicine. Overview of therapeutic ultrasound applications and safety considerations. J Ultrasound Med. 2012;31(4):623-34. doi: 10.7863/jum.2012.31.4.623.
11. Christian E, Yu C, Apuzzo ML. Focused ultrasound: relevant history and prospects for the addition of mechanical energy to the neurosurgical armamentarium. World Neurosurg. 2014;82(3-4):354-65. doi: 10.1016/j.wneu.2014.06.021.
12. Zhang L, Rao F, Setzen R. High intensity focused ultrasound for the treatment of adenomyosis: selection criteria, efficacy, safety and fertility. Acta Obstet Gynecol Scand. 2017 Jun;96(6):707-714. doi: 10.1111/aogs.13159.
13. Ye M, Deng X, Mao S, Xue M. High intensity focused ultrasound treatment for non-neoplastic epithelial disorders of the vulva: Factors affecting effectiveness and recurrence. Int J Hyperthermia. 2015;31(7):771-6. doi: 10.3109/02656736.2015.1053101.
14. Bachu VS, Kedda J, Suk I, Green JJ, Tyler B. High-Intensity Focused Ultrasound: A Review of Mechanisms and Clinical Applications. Ann Biomed Eng. 2021 Sep;49(9):1975-1991. doi: 10.1007/s10439-021-02833-9.
15. Siedek F, Yeo SY, Heijman E, et al. Magnetic Resonance-Guided High-Intensity Focused Ultrasound (MR-HIFU): Overview of Emerging Applications (Part 2). Rofo. 2019;191(6):531-539. doi: 10.1055/a-0817-5686.
16. Lyon PC, Rai V, Price N, Shah A, Wu F, Cranston D. Ultrasound-Guided High Intensity Focused Ultrasound Ablation for Symptomatic Uterine Fibroids: Preliminary Clinical Experience. Ultraschall Med. 2020;41(5):550-556. doi: 10.1055/a-0891-0729.
17. Zhou YF. High intensity focused ultrasound in clinical tumor ablation. World J Clin Oncol. 2011;2(1):8-27. doi: 10.5306/wjco.v2.i1.8.
18. Elhelf IAS, Albahar H, Shah U, Oto A, Cressman E, Almekkawy M. High intensity focused ultrasound: The fundamentals, clinical applications and research trends. Diagn Interv Imaging. 2018;99(6):349-359. doi: 10.1016/j.diii.2018.03.001.
19. Tung YS, Liu HL, Wu CC, Ju KC, Chen WS, Lin WL. Contrast-agent-enhanced ultrasound thermal ablation. Ultrasound Med Biol. 2006 Jul;32(7):1103-10. doi: 10.1016/j.ultrasmedbio.2006.04.005.

20. Cheng C, Xiao Z, Huang G, Zhang L, Bai J. Enhancing ablation effects of a microbubble contrast agent on high-intensity focused ultrasound: an experimental and clinical study. BJOG. 2017 Aug;124 Suppl 3:78-86. doi: 10.1111/1471-0528.14744.
21. Huang L, Zhou K, Zhang J, et al.. Efficacy and safety of high-intensity focused ultrasound ablation for hepatocellular carcinoma by changing the acoustic environment: microbubble contrast agent (SonoVue) and transcatheter arterial chemoembolization. Int J Hyperthermia. 2019;36(1):244-252. doi: 10.1080/02656736.2018.1558290.
22. Peek MCL, Wu F. High-intensity focused ultrasound in the treatment of breast tumours. Ecancermedicalscience. 2018;12:794. doi: 10.3332/ecancer.2018.794.
23. Haar GT, Coussios C. High intensity focused ultrasound: physical principles and devices. Int J Hyperthermia. 2007 Mar;23(2):89-104. doi: 10.1080/02656730601186138.
24. Dimitrov D, Zhou K, Karamanliev M, et al. Introducing clinical protocol for ultrasound-guided high-intensity focused ultrasound ablation of uterine fibroids in patients in Europe, provided from experienced Chinese center-prospective comparative. Biomed Res. 2018;29 (17):3378-3384
25. Dietrich CF, Averkiou M, Nielsen MB, et al. How to perform Contrast-Enhanced Ultrasound (CEUS). Ultrasound Int Open. 2018;4(1):E2-E15. doi: 10.1055/s-0043-123931.
26. Orsi F, Monfardini L, Bonomo G, Krokidis M, Della Vigna P, Disalvatore D. Ultrasound guided high intensity focused ultrasound (USgHIFU) ablation for uterine fibroids: Do we need the microbubbles? Int J Hyperthermia. 2015;31(3):233-9. doi: 10.3109/02656736.2015.1004134.
27. Lin L, Ma H, Wang J, Guan H, Yang M, Tong X, Zou Y. Quality of Life, Adverse Events, and Reintervention Outcomes after Laparoscopic Radiofrequency Ablation for Symptomatic Uterine Fibroids: A Meta-Analysis. J Minim Invasive Gynecol. 2019;26(3):409-416. doi: 10.1016/j.jmig.2018.09.772.
28. Liu L, Wang T, Lei B. Uterine Artery Embolization Compared with High-intensity Focused Ultrasound Ablation for the Treatment of Symptomatic Uterine Myomas: A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 2021;28(2):218-227. doi: 10.1016/j.jmig.2020.11.004.
29. Wang F, Tang L, Wang L, Wang X, Chen J, Liu X, Gong Y. Ultrasound-guided high-intensity focused ultrasound vs laparoscopic myomectomy for symptomatic uterine myomas. J Minim Invasive Gynecol. 2014;21(2):279-84. doi: 10.1016/j.jmig.2013.09.004.
30. Choe YS, Lee WM, Choi JS, Bae J, Eom JM, Choi E. Clinical characteristics of patients with leiomyoma who undergo surgery after high intensity focused ultrasound (HIFU). Obstet Gynecol Sci. 2019;62(4):258-263. doi: 10.5468/ogs.2019.62.4.258
31. Ji Y, Hu K, Zhang Y, Gu L, Zhu J, Zhu L, Zhu Y, Zhao H. High-intensity focused ultrasound (HIFU) treatment for uterine fibroids: a meta-analysis. Arch Gynecol Obstet. 2017;296(6):1181-1188. doi: 10.1007/s00404-017-4548-9.
32. Chen J, Li Y, Wang Z, McCulloch P, et al. Committee of the Clinical Trial of HIFU versus Surgical Treatment for Fibroids. Evaluation of high-intensity focused ultrasound ablation for uterine fibroids: an IDEAL prospective exploration study. BJOG. 2018;125(3):354-364. doi: 10.1111/1471-0528.14689.

ORCID and contributionship:
Yoana Ivanova - 0000-0002-2215-9202 [A,D]
Dobromir Dimitrov - 0000-0003-3313-1093 [E-F]
Kameliya Dimitrova - 0000-0003-1418-6179 [B-C]
Aparajeya Shanker - 0000-0001-6305-8152 [B-C]
Angel Yordanov - 0000-0002-7719-382X [E-F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Angel Yordanov
Department of Gynecologic Oncology,
Medical University Pleven, Pleven, Bulgaria
e-mail: angel.jordanov@gmail.com

Received: 20.06.2021
Accepted: 24.01.2021

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article