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Clinical aspects of the treatment of breast fibroadenomas with high-intensity focused ultrasound (HIFU)

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The main method of treatment of fibroadenomas of the mammary glands to date is surgical. Surgery is often accompanied by complications: hematoma, inflammation, divergence joints, pain in the surgery, etc. Introduction of new technologies of minimally invasive alternative to open surgery are laparoscopic surgery; as a large number of studies conducted in the field of laser, cryo -, thermal ablation. But really noninvasive methods of practical medicine are radiation and chemotherapy, both methods have a lot of side effects. At the present time there was the possibility of introducing a new non-invasive method of treatment of breast fibroadenomas: HIFU-therapy. High-intensive focused ultrasound (HIFU) has declared itself as a new clinical method for non-invasive local treatment of tumors. The author is given etiology, classification, treatment of breast fibroadenomas, a brief overview of the concept of HIFU-therapy, the mechanism of action HIFU-therapy, HIFU device used for the treatment of mammary tumors, evaluation methods the performance of ablation, the criteria for cure.

Key words: fibroadenoma, High-intensive focused ultrasound, HIFU-ablation.

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СҮТ БЕЗІ ФИБРОАДЕНОМАСЫН ЖОҒАРЫ ҚАРҚЫНДЫ ФОКУСТЕЛГЕН УЛЬТРАДЫБЫСПЕН (HIFU) ЕМДЕУДІҢ КЛИНИКАЛЫҚ АСПЕКТІЛЕРІ

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Бұрын сүт безі фиброаденомасын емдеудің негізгі әдісі хирургиялық болып саналды. Хирургиялық тәсіл гематома, қабыну, тігіс сетінеуі, отадан кейінгі аймақтың ауырсынуы және т.б. секілді жағымсыз белгілері болды. Аз инвазивті жаңа технологияларды енгізудің нәтижесінде ашық хирургиялық тәсілге альтернатива ретінде лапароскопиялық хирургия қолданылады. Сонымен қатар, лазерлік, крио - термо-, абляция тәсілдері көп зерттеліп келеді. Алайда көптеген кемшіліктеріне қарамастан таңдаулы, инвазивті емес әдіс ретінде сәулелік пен химиотерапия әдісдері саналады. Қазіргі уақытта сүт безі фиброаденомасын емдеуде жаңа, инвазивті емес HIFU тәсілін енгізу мүмкіндігі пайда болды. Ісіктерді емдеуде HIFU тәсілі өзін инвазивті емес жаңа клиникалық әдіс ретінде таныта білді. Мақалада авторлар сүт безі фиброаденомасының этиологиясын, жіктелуін, емдеу әдісін, HIFU емінің қысқаша түсінігін, әсер ету механизмін, HIFU аппаратын, абляция тиімділігін бағалау әдісін баяндады.

Маңызды сөздер: фиброаденома, жоғары қарқынды фокустелген ультрадыбыс, HIFU-абляция.

КЛИНИЧЕСКИЕ АСПЕКТЫ ЛЕЧЕНИЯ ФИБРОАДЕНОМ МОЛОЧНЫХ ЖЕЛЕЗ ВЫСОКОИНТЕНСИВНЫМ ФОКУСИРОВАННЫМ УЛЬТРАЗВУКОМ (HIFU)

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Основным методом лечения фиброаденом молочных желез до настоящего времени являлся хирургический. Хирургическое вмешательство нередко сопровождается осложнениями: гематома, воспаление, расхождение швов, боли в области оперативного вмешательства и т.д. Вследствие внедрения новых технологий малоинвазивных методов альтернативой открытой хирургии являются лапароскопическая хирургия; так же большое количество исследований проводится в области лазерной, крио -, термо- абляций. Однако действительно неинвазивными методами практической медицины остаются лучевая и химиотерапии, при этом оба метода имеют массу побочных эффектов. В настоящее время появилась возможность внедрения нового неинвазивного метода лечения фиброаденом молочных желез: HIFU-терапия. Высокоинтенсивный фокусированный ультразвук (HIFU) заявил о себе как новый клинический метод неинвазивного локального метода лечения опухолей. В статье авторами дана этиология, классификация, методы лечения фиброаденом молочных желез, краткий обзор понятия HIFU-терапии, механизм действия HIFU-терапии, аппарат HIFU применяемый для лечения опухолей молочных желез, методы оценки эффективности абляции, критерии излечения.

Ключевые слова: фиброаденома, высокоинтенсивный фокусированный ультразвук, HIFU-абляция.

Introduction

Mammary glands are complex clear differentiation of physiological and pathological changes, as well as various types of benign diffuse pathology. This is because the structure of the mammary gland is not only different from women, but also in one and the same depending on the age, the reproductive system, and even menstrual period. According to modern concepts, the mammary glands are under hormonal influence multifactorial. Breast cancer is the target organ for sex steroid hormones. Furthermore, it was found that they have an effect of pituitary hormones, adrenal cortex, thyroid, pancreas and others [1].

Benign breast changes are among the most common diseases of women of various age groups and include various clinical, morphological characteristics and the etiologic processes. Benign breast disease in the female population spread to 30-70% of cases [7], due to the increasing incidence of this disease and the fact that some forms of proliferative epithelial hyperplasia accompanied regarded as a background of increased risk of breast cancer [8]. Despite the successes of the diagnosis and treatment of tumors of the breast, differential diagnosis, competent supervision, combined and complex treatment of malignant tumors occupy an important place. In the structure of morbidity and mortality from malignant neoplasms of the female population of Russia took the breast cancer in 1996. 1st place, and the absolute number of cases has increased to 39 thousand (1991 in. - 31.9 thousand), dead - to 19.6 thousand, similar situation in Kazakhstan last 5 years 2011-2015. Several authors [2-6] attach great importance to identify preclinical stages of breast cancer, cancer in situ.

Fibroadenoma - one of the particular breast disease and composes 95% of all benign tumors. Malignancy with fibroadenoma can reach 3% [9].

Etiology

Development of fibroadenomas consider multifactorial. Risk factors include various hormonal disorders in the female body such as menstrual disorders, inflammatory diseases of the genital organs, abortion, abandonment of breastfeeding and thyroid disease, stress, and so on.

Classification

Allocate 3 histological types of breast fibroadenoma:

- perikanalikularis(51%);
- intrakanalikularis (47%);
- mixed (2%);

Methods of treatment for breast fibroadenoma

So far, the detection of fibroadenoma larger than 1.0 cm is an indication for surgical treatment. The following methods of surgical treatment:

- sectoral resection (removal of the tumor together with surrounding tissues);
- enucleation (husking) - remove only the tumor.

Open surgery has a fairly high rate of complications, causes immunosuppression, which increases the risk of postoperative complications. Patients experience pain after the surgery, the recovery period can be long enough. Technological progress «shifts the bar» in favor of less invasive methods. Laparoscopic surgery, minimally invasive techniques radiofrequency, microwave, laser, cryoablation increasingly replace open surgery with the natural reduction in bed days, the cost of treatment, mortality associated with the intervention. The term «tumor ablation» is a direct thermal or chemical effect on tumor tissue for the purpose of its destruction. The most frequent tumor ablation performed with ultrasound, at least - MRI or CT guidance. All ablation of tumors can be divided into two categories: chemical and thermal ablation of the ablation. Chemical ablation is performed with ethanol, acetic acid, and other agents. Thermal ablation is divided into two groups of cold (cryoablation) or heat. Principles of thermal effects on tissue using electrical energy were first presented Jaques-Arsène d'Arsonval in 1892. In 1948, the main factors described Pennes interaction energy and heat the tissue by creating a biothermal equation [10], where in determining the extent of thermal damage to the tissue into account the absorption properties of tissue its thermal conductivity, density, the metabolic rate of heating tissue, the degree of vascular perfusion and its corresponding energy loss. Since then, methods have been developed multiple tissue ablation. Among the most common are radiofrequency ablation, cryoablation, laser interstitial ablation, microwave ablation [11], with the energy of the occasion for the tumor using special conductors - «applicators». When radiofrequency ablation are special electrodes with microwave ablation - «antenna», laser ablation - light guide fibers with cryoablation - a special hollow needle with a partial vacuum insulation, through which the tumor is fed liquid argon at a temperature of minus 196°C. When ultrasonic ablation need to introduce special conductors have: the treatment is performed without breaking the skin or mucosa. To date, high-intensity focused ultrasound ablation (HIFU) is really the only non-invasive method of destruction of local tumor focus, which the authors rightly called «surgery of the future» [12].

The mechanism of action of high-intensity focused ultrasound

Describes the three basic mechanisms of damaging action of HIFU [13-14].

The first and main - a mechanism of thermal ablation. High power ultrasound has the unique property to penetrate through healthy tissue without damaging them, but when focused by emitter lens in a small area causing instant during a second, raising the temperature to 90°C, sufficient for the development of coagulation necrosis. So there is a lesion and necrosis. Surface and the surrounding tissue focus in this case remain intact. The ability of ultrasound to cause necrosis in the tumor, located at a considerable distance from the source of ultrasound, ultrasonic ablation allows to consider the method of non-invasive surgery. The second mechanism, unfortunately, less predictable and controllable, acoustic cavitation is the mechanism that leads to tissue necrosis as a result of mechanical and thermal stress. Ultrasound causes vibration in the tissues, and the molecular structures are subjected to the next compression and expansion. During the negative phase of the ultrasonic wave in phase vacuum gas solution passes into the gaseous state and is transformed into micro bubbles, which oscillate in time with the ultrasonic waves. When you reach the size of the wave resonant frequency bubbles burst through mechanical shock. During bubble collapse the acoustic pressure is several thousand Pa same temperature reaches 2000-5000°C, which causes the death of the tissue [15]. The presence of cavitation depends on the length of the pulse, its frequency and intensity [16]. The probability of such phenomenon does not exist under the action of the ultrasound diagnostic, but when exposed to high-intensity focused ultrasound, this factor should be taken into account. Damage to the vascular tumor that occurs in the process of ultrasonic ablation, is the third mechanism of tissue damage [17-21]. HIFU- exposure causes direct damage to the blood vessels that feed tumors, thereby disconnecting the supply of oxygen,

broken trophic tumor tissue. In fact, it is impossible to isolate at least one of these mechanisms, the effect of ultrasound ablation, they all occur at the same time in the markup screen. Coagulative necrosis caused by exposure to high-intensity focused ultrasound, the total biological effect caused by heat, cavitation and destruction of tumor vessels. Observed changes in the tissues after exposure of focused ultrasound with high intensity due to the appearance of a homogeneous zone of necrosis [22]. The border between the zone of necrosis and healthy tissue body clear enough, the transition zone is only a few cells. The volume of necrotic tissue after treatment coincides with the volume of the primary tumor. However Oncology canons for operation as was possible ablastics necessary to "block" the tumor by at least 1 cm. Therefore, the zone comprises a tumor ablation zone and on the periphery of the tumor from the normal, non-tumor tissue. Subsequently, within 7 days after treatment the inflammatory response develops that includes the migration of polymorphonuclear leukocytes in the deep zone of the lesion, formation of granulation tissue containing immature fibroblasts and new capillaries are formed along the periphery of the necrotic zone [23]. Within two weeks after the ultrasound ablation peripheral part of the treated area is replaced by proliferating fibrous tissue. The repair process has not yet been studied in detail, but the morphological studies show a gradual shrinkage of tissue in the treated volume and substitution of necrotic tissue by fibrous tissue.

Apparatus ultrasound ablation used to treat breast tumors

HIFU-ultrasonic system monitoring and control of the MRI-use for the treatment of mammary tumors [24]. In medical practice, as there are only a few models of industrial ultrasonic ablation. All ultrasound ablation devices are divided into two types: the extracorporeal treatments used for the treatment of tumors of several organs and apparatuses monofunctional destination. Machines for extracorporeal treatment of air medical focusing lenses of large diameter; with high emission intensity can reach; ultrasonic radiation has a high penetrating power, so these devices are capable of producing ablation at great depths within the body. Monofunctional purpose machines have small focusing lenses (medical sensors small size) with a short or ultrashort focal-range; radiation intensity is low. This device for transrectal prostate cancer treatment, the apparatus used in otorhinolaryngology for the treatment of vasomotor and allergic rhinitis, as well as specialized gynecological device for the treatment of diseases of the vulva and cervicitis.The most widespread multi-functional model for in vitro treatment, developed in China (Model JC Focused In the second device in vitro application of MRI is used as a method for guidance. This device is equipped with medical sensor 10 cm. In diameter, with an 8-cm radius of curvature radiation frequency of 1.5 MHz (GE Medical Systems, Milwaukee, WI) [25]. This unit is used to treat breast cancer. Another model with MRI-guided, having a commercial name of the ExAblate 2000 (InSightec-TxSonics, Ltd., Haifa, Israel), is used only for the treatment of patients with uterine cancer and breast tumors [26].

The system of guidance and monitoring the performance of treatment

An important factor is the ability to accurately control procedure. Currently, this is done in two ways: ultrasound monitoring in real time [27-28] or MRI [29-30]. When used to control the orientation of the MRI is performed by a temperature mapping: the affected area first designated ultrasonic shots of lower intensity than that required for the formation of zones of necrosis; local temperature rise in the tissue allows precise positioning of the ultrasound focus, and only then is the treatment high-intensity focused shots. Unfortunately, the system of the magnetic resonance guided via thermal mapping can be effectively used when the condition of immobility of the irradiated object. In cases where there is a strong body of respiratory excursion - the target MRI guidance is used. When ultrasound-guided diagnostic sensor located inside or near the therapeutic transducer for clear visualization of the ablation zone. Interposition of diagnostic and therapeutic module is fixed and stored. Therapeutic focus position is marked on the visual image. The therapeutic effect of HIFU clearly monitored for changes in gray scale in the treatment process. To obtain the most complete tumor tissue ablation requires that tumor ablation zone overlaps the hearth, at least 1 cm. MRI provides better visual picture, the possibility of temperature control, but significantly more expensive, more protracted procedure. Optimal areas of use: treatment of uterine fibroids and breast tumors. Ultrasound certainly has advantages in cost and availability, less time-consuming, the possibility of registration of changes in the hearth mode real time. The disadvantage is the inability to control the temperature in the hearth. Diagnostic ultrasound does not penetrate bone, and a hollow, gas containing bodies, but it can also be considered as an advantage, since the relative positions of the tumor and defining the data structures can carry out the correction of the ultrasonic beam direction for a more secure and complete ablation of the tumor, reducing the risk of damage to the hollow bodies.

Methods for assessing the performance of the ablation

In order to use the methods of follow-anatomical imaging (CT, MRI, ultrasound, digital subtraction angiography), as well as methods of physiological imaging: PET, PET-CT, scintigraphy. These methods provide accurate information about the state of the tumor tissue and perfusion cell function and changes in tumor size in the dynamic observation. During the ablation procedure in the treated volume ultrasound cavitation can be visualized as a sharp increase echogenicity inhomogeneous tissue distal to acoustic artifacts inherent gas bearing structures (cavitation effect is usually observed within a few minutes). Typically, increased echogenicity the treated tissue is preserved for a long time, but in a small percentage of cases developing tissue edema results in reduced echogenicity of the treated tissue. With dynamic ultrasound monitoring in the postoperative period in the tumor observed changes characteristic of the formation of foci of destruction of tissue with the formation of necrotic cavities; later at various periods, depending on organ appurtenance tumor volume decreases the ablation zone and the treated zone fibrosis. In the hearth disappears vascular pattern, but it must be remembered that the tumor ca. In be avascular by ultrasound before treatment. Much more clearly and quickly the effect of ablation can be detected by MRI or CT with contrast enhancement. Immediately after the procedure, ultrasound ablation observed cessation of the treated tumor tissue perfusion, altered signal characteristics on MRI and the density of tumor tissue in CT. These methods are very good opportunities for immediate and delayed evaluation of the effectiveness of the treatment and the volume of HIFU-induced influence of coagulation necrosis.

Performance criteria of cure

To confirm the complete ablation of the tumor, as well as a suspected recurrent tumor growth is a bar held biopsy. Most dynamic control is performed by imaging. Basically, the tumor volume is compared before and after treatment. However, a comparison of this parameter may be less informative than the assessment of tumor tissue perfusion. Necrotic tissue often replaced by fibrous tissue and fibrous tissue resorption process may be delayed for a long time (this happens, for example, ultrasound ablation mammary tumors) [31,32]. When using imaging techniques primarily estimated prevalence of tumor tissue and it's restructuring; to a lesser extent the physician must rely on the change in tumor volume.

Conclusion

Ultrasonic ablation method as surgery, relates to local therapies. Unlike other surgical and minimally invasive techniques (radiofrequency, -cryo, -laser ablation) HIFU- ablation occurs without compromising the integrity of the skin and soft tissue damage near the tumor, is the only non-invasive method. Unlike other types of minimally invasive ablation, at which dissipation of energy occurs naturally in proportion to the distance from the conductor, inserted in the center of the tumor, HIFU has no restrictions on the size of the tumor. The method is safe, has certainly fewer complications than surgery. In the course of treatment there is a real and objective possibility of control procedures. HIFU therapy breast fibroadenoma is a promising method non-invasive applying for its wide use in the treatment of benign tumors.

References

1. Dolgih V.T. Opuholevyj rost (Tumor growth), M.: *Medicinskaja kniga*, 2001, 81 p.
2. Dovgavljuk A.Z. Rak molochnoj zhelezy: jetiologija, klinika, diagnostika, lechenie, voprosy mediko-social'noj jekspertizy i reabilitacii (Breast cancer: etiology, clinical features, diagnosis, treatment, questions of medical and social expertise and rehabilitation), *Posobie dlja vrachej*, SPb: Mega-print, 2001, 203 p.
3. Plohov V.N. Otdalennye rezul'taty organosberegajushhih operacij pri rake molochnoj zhelezy (Long-term results of organ operations in breast cancer), *Onkologija na rubezhe XXI veka. Vozmozhnosti i perspektivy, Sbornik tezisov, M.*, 1999, pp. 294-295.
4. Trapeznikov N.N., Aksel' E.M. Statistika zlokachestvennyh novoobrazovanij v Rossii i stranah SNG (Statistics malignancies in Russia and the CIS), Trapeznikov N.N., Aksel' E.M., Moskva: RONC im. NN. Blohina, 2001.
5. Bijker N., Peterse J.L., Duchateau L. et al. Risk factors for recurrence and matastasis after breast-conserving therapy for ductal carcinoma in situ, Ahalysis of EORTC trial 10853, *EJC*, 2000, No. 36 (Suppl. 5), 120 p.
6. Semiglazov V.V. Karcinoma in situ molochnoj zhelezy -morfologicheskie i klinicheskie problemy (Carcinoma in situ breast cancer and clinical problems -morfologicheskie), *Prakticheskaja onkologija,* 2002, No 3 (1), pp.60-68.
7. Semiglazov V.F., Kanaev S.V., Bugrov L.I. Promezhutochnye rezul'taty randomizirovannogo issledovanija «Ocenka roli adjuvantnoj luchevoj terapii v organosohranjajushhem lechenii raka molochnoj zhelezy» (Interim results of a randomized study «Assessing the role of adjuvant radiotherapy in organ-preserving treatment of breast cancer»), *Voprosy onkologii,* 1998, No. 4, pp. 436-439.
8. Chajka V.K. Molochnaja zheleza ot 0 do 18 (The mammary gland is from 0 to 18), V.K. Chajka, M.Ju. Sergeenko, S.A. Lasachko, Doneck: Al'mateo, 2006, 120 p.
9. Kampovoj-Polevoj E.B., Chistjakov S.S. Klinicheskaja mammologija (Clinical mammalogy), Moskva 2006,141 p.
10. Pennes HH. Analysis of tissue and arterial blood temperatures in the resting human forearm, J *Appl Physiol*, 1948, No.1, pp. 93-122.
11. Vogl TJ, Helmberger TK, Mack MG, Reiser MF (eds). Percutaneous Tumor Ablation in Medical Radiology, Springer-Verlag, Berlin, Heidelberg, New York, 2008, 258 p.
12. Kennedy JE, ter Haar GR, Cranston D. High Intensity Focused Ultrasound: surgery of the future? *Brit J Radiol*, 2003, No. 76, pp. 590-599.
13. Hill CR, Rivens I, Vaughan M, et al. Lesion development in focused ultrasound surgery: a general model, *Ultrasound Med Biol,* 1994, No. 20, pp. 259-269.
14. Vaughan M, ter Haar G, Hill CR, et al. Minimally invasive cancer surgery using focused ultrasound: a pre-clinical, normal tissue study, *Br J Radiol*, 1994, No. 67, pp. 267-274.
15. Mason TJ. A sound investment. *Chem Ind*, 1998, pp. 878-882.
16. Hynynen K. The threshold for thermally significant cavitation in dogs' thigh muscle in vivo, *Ultrasound Med Biol*, 1991, No. 17, pp. 157-169.
17. Wu F, Chen WZ, Bai J, et al. Tumor vessel destruction resulting from high-intensity focused ultrasound in patients with solid malignancies, *Ultrasound Med Biol*, 2002, No.28, pp. 535-542.
18. Delon-Martin C, Vogt C, Chignier E, et al. Venous thrombosis generation by means of high- intensity focused ultrasound, Ultrasound Med Biol, 1995, No. 21, pp.113-119.
19. Rivens BH, Rowland IJ, Denbow M, et al. Vascular occlusion using focused ultrasound surgery for use in fetal medicine, Eur J Ultrasound, 1999, No. 9, pp. 89-97.
20. Hynynen K, Chung A, Colucci V, et al. Potential adverse effects of high-intensity focused ultrasound exposure on blood vessels in vivo, Ultrasound Med Biol, 1996, No. 22, pp.193-201.
21. Vaezy S, Martin R, Kaczkowska P, et al. Use of high-intensity focused ultrasound to control bleeding, *J Vase Surg*, 1999, No.29, pp. 533-542.
22. Wu F, Chen WZ, Bai J, et al. Pathological changes in human malignant carcinoma treated with high-intensity focused ultrasound, *Ultrasound Med Biol*, 2001, No.27, pp. 1099-2006.
23. Chen L, Rivens I, ter Haar GR et al. Histological changes in rat liver tumours treated with high intensity focused ultrasound,

Ultrasound Med Biol, 1993, No. 19, pp. 67-74.
24. Stewart EA, Gedroyc WM, Tempany CM, et al. Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique, *Am J Obstet Gynecol*, 2003, No.189, pp. 48-54
25. Hynynen K, Pomeroy O, Smith DN et al. MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: A feasibility study, *Radiology* 2001, No. 219, pp. 176-185.
26. Gianfelice D, Khiat A, Boulanger Y, et al. Feasibility of magnetic resonance imaging-guided focused ultrasound surgery as an adjunct to tamoxifen therapy in high-risk surgical patients with breast carcinoma, J Vase Interv Radiol, 2003, No.14, pp. 1275-1282.
27. Wu F, Wang ZB, Wang ZL, et al. Changes in ultrasonic image of tissue damaged by high intensity ultrasound in vivo, J *Acoustic Soc Am*, 1998, No. 103, pp. 2869.
28. Souchon R, Bouchoux G, Maciejko E, et al. Monitoring the formation of thermal lesions with heat-induced echo-strain imaging: a feasibility study, *Ultrasound Med Biol*, 2005, No.31, 251-259.
29. Jolesz FA, Hynynen K. Magnetic resonance image-guided focused ultrasound surgery, Cancer J, 2002, No.8, pp.100-112.
30. Vimeux FC, De Zwaet JA, Palussiere, et al. Real-time control of focused ultrasound heating based on rapid MR thermometry, *Invest Radiol*, 1999, No.34, 190-193.
31. Wu F, Wang ZB, Cao YD, et al. Changes in biologic characteristics of breast cancer treated with high-intensity focused ultrasound, *Ultrasound Med Biol*, 2003, No.29, pp.1487-1492.
32. Wu F, Wang ZB, Zhu H, et al. Extracorporeal high intensity focused ultrasound treatment for patients with breast cancer, Breast *Cancer Research and Treatment*, 2005, No.92, pp.51-60.