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Influencing factors analysis for high intensity focused ultrasound ablation in treatment of uterine fibroids.

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Abstract

This study aims to analyse the influencing factors for High Intensity Focused Ultrasound (HIFU) ablation in treatment of uterine fibroids. Fifty-one uterine fibroids patients with 76 uterine fibroids were enrolled in this study. All patients received the HIFU ablation of uterine fibroids. The treatment efficacy was evaluated. The residual rate of ablation was calculated. The influencing factors related to the treatment outcome of HIFU ablation were analysed. Results showed that, in 76 uterine fibroids, 25 (32.9%) cases obtained effective treatment outcome, with residual rate ≥ 50%, and 51 (67.1%) cases obtained remarkably effective treatment outcome, with residual rate<50%. The treatment outcome had significant difference among subserous, submucous and intramural fibroid type (χ^2=6.614, P=0.037), among fibroid position of posterior wall, fundus uteri and anterior wall (χ^2=11.410, P=0.003), between fibroid size of <5 cm and ≥ 5 cm (χ^2=4.259, P=0.039), and among low, equal and high contrast enhancement (χ^2=6.153, P=0.046). The logistic regression analysis showed that, the fibroid position was the independent risk factor of treatment outcome, with odds ratio of 2.545 (1.175-5.513). In conclusion, the fibroid type, fibroid position, fibroid size, and contrast enhancement are significantly related to the outcome of HIFU ablation in treatment of uterine fibroids. The fibroid position is the independent risk factor for treatment outcome.

Keywords: High intensity focused ultrasound, Ablation, Influencing factors, Uterine fibroids.

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Introduction

Uterine fibroids are the most common benign tumors in the reproductive organs of women of childbearing age [1]. Uterine fibroids are often accompanied by menorrhagia, prolonged menstruation, dysmenorrhea, frequent urination, abdominal distension, constipation, infertility and other symptoms, which need the clinical treatment [2]. Surgical resection is the most clinically commonly used method for the treatment of uterine fibroids. However, it is difficult to satisfy the fertility requirement of women of childbearing age [3]. Therefore, more and more people begin to seek new noninvasive treatment methods for this disease. High Intensity Focused Ultrasound (HIFU) ablation is an emerging non-invasive treatment modality for tumors. It has advantage of safety, effectiveness, less adverse reaction, and preservation of organ integrity, and has become a new method for the treatment of uterine fibroids [4-7]. The principle of HIFU ablation of solid tumor is that, the extracorporeal low energy ultrasound is focused in the target tissues in body. The sound energy is converted into heat energy, which instantly generates high temperatures in the focal region (60-100°C), resulting in protein denaturation and coagulative tissue necrosis [8]. At present, there are a large number of clinical studies on HIFU ablation of uterine fibroids [9-11]. The ablation of most uterine fibroids can obtain good outcome, but in uterine fibroids, the ablation rate is very low. There are many factors in pathological and ultrasound aspects which lead to different treatment outcomes. The present study systematically analysed the influencing factors for HIFU ablation in the treatment of uterine fibroids. The objective was to provide certain reference for the clinical application of HIFU ablation.

Patients and Methods

Patients

Fifty-one uterine fibroids patients with 76 uterine fibroids who were treated with HIFU ablation in The Fourth Hospital of Xi'an from May 2012 to January 2016 were enrolled in this study. The age of patients was 28-60 y old, with the average age of 42.3 ± 5.4 y. The patients presented menorrhagia, prolonged menstruation, dysmenorrhea, frequent urination, abdominal distension and other symptoms. The uterine fibroids were diagnosed according to the clinical symptoms, gynecological examination and ultrasound or Computed Tomography (CT) examination. The inclusion criteria were as follows: i) the patients were diagnosed with uterine fibroids; ii) the patients had given birth, with no requirement of reproduction; ii) the diameter of fibroids was 2-8 cm; iv) the patients had no artificial abortion within 3 months. The exclusion criteria were as follows: i) the clinical symptoms

were not confirmed by gynecological examination, ultrasound or CT examination; ii) the ultrasound indicated suspected adenomyosis; iii) the patients had lower abdomen skin ulceration or infection; iv) the patients were in the menstrual, pregnancy or lactating period; v) the patients were complicated by endometriosis, ovarian neoplasms, endometrial cancer or polycystic ovary syndrome. This study was approved by the ethics committee of The Fourth Hospital of Xi'an. Written informed consent was obtained from all participants.

HIFU ablation

In all patients, the routine ultrasound, contrast-enhanced ultrasound and Magnetic Resonance Imaging (MRI) examination were performed within one week before treatment, JC200 HIFU tumor therapy system (Chongqing Haifu Medical Technology Co., Ltd., Chongqing, China) was used for HIFU ablation of uterine fibroids. The parameters of this equipment were as follows: diameter of energy transducer, 20 cm; focal length, 15 cm; frequency, 1 MHz; treatment power, 240-400 W. The real-time monitoring instrument supporting this system was My-Lab70 type B-mode ultrasound machine (Baisheng (Shenzhen) medical equipment Co., Ltd., Shenzhen, China). The monitoring probe was placed in the center of the energy transducer, and could rotate horizontally. The frequency of monitoring probe was 1.0-8.0 MHz. The ultrasound scanning positioning was performed under the guidance of computer, and the treatment channel was established. After positioning, the focal point was moved, and the conformal ablation treatment of target area was completed through the combination of dots, lines and planes in focal region.

Evaluation of treatment efficacy

MRI examination was performed before and 1 month after treatment. The typical MRI manifestation of ablation region was the no contrast agent perfusion in enhanced T1W1 sequence, which indicated the coagulative necrosis in this region. The volume of uterine fibroid (V) was measured and calculated as follows: $V=0.5233 \times a \times b \times c$, in which a, b and c were the longitudinal, transverse and thick diameter of fibroid. The volume of ablation region (V1) was measured and calculated as follows: $V_1=0.5233 \times a_1 \times b_1 \times c_1$, in which a_1, b_1 and c_1 were the longitudinal, transverse and thick diameter of fibroid region without contrast medium perfusion. The residual rate of ablation was calculated as follows: residual rate $(\%)=(V-V_1)/V \times 100$. According to the modified standard of Response Evaluation Criteria in Solid Tumors (RECIST) and the MRI imaging characteristics of uterine fibroids before and after treatment, the curative effect evaluation standard of HIFU ablation of uterine fibroids was as follows: 100%>residual rate ≥ 50%, effective: residual rate<50%, remarkably effective; residual rate=100%, ineffective.

Statistical analysis

All statistical analysis was carried out using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). The enumeration data were presented as number and rate, and the comparison among different groups was performed using χ^2 test. The multivariate analysis with logistic regression was performed on the influencing factors related to the treatment outcome of HIFU ablation. $P<0.05$ was considered as statistically significant.

Results

General characteristic of uterine fibroids

In 76 uterine fibroids, there were 29 (38.2%) cases in patients with age ≥ 40 y and 47 (61.8%) cases in patients with age<40 y. Forty-two (55.3%) uterine fibroids were in patients with treatment history, and 34 (44.7%) uterine fibroids were in patients without treatment history.

Overall treatment outcome

In 76 uterine fibroids, 25 (32.9%) cases obtained effective treatment outcome, with residual rate ≥ 50%, and 51 (67.1%) cases obtained remarkably effective treatment outcome, with residual rate<50%. All the patients had no moderate or severe side effects, and 15 patients (29.4%) had mild side effects. Two patients suffered from superficial second-degree skin burn around the ultrasound channel, and relieved by active treatment. The other side reactions included vaginal secretion abnormity, abdominal pain, and hip and lower limb soreness, and did not need special treatment.

Relationships of general patient characteristics with treatment outcome

As shown in Table 1, there was no significant difference of treatment outcome between uterine fibroids in patients with age ≥ 40 y and with age<40 y ($\chi^2=0.054$, $P=0.871$), or between uterine fibroids in patients with and without treatment history ($\chi^2=0.160$, $P=0.689$).

Table 1. *Relationships of patient general characteristics with treatment outcome.*

Characteristic		Residual rate (n (%))		χ2	P
		≥ 50% (n=25)	<50% (n=51)		
Age (y)				0.054	0.871
	≥ 40	10 (40.0)	19 (37.3)		
	<40	15 (60.0)	32 (62.7)		
Treatment history				0.16	0. 689
	No	12 (48.0)	22 (43.1)		
	Yes	13 (52.0)	29 (56.9)		

Relationships of fibroids characteristics with treatment outcome

The treatment outcome had significant difference among subserous, submucous and intramural fibroid type ($\chi^2=6.614$, $P=0.037$), among fibroid position of posterior wall, fundus

uteri and anterior wall (χ^2=11.410, P=0.003), between fibroid size of <5 cm and ≥ 5 cm (χ^2=4.259, P=0.039). There was no significant difference of treatment outcome between abdominal wall thickness of <2.5 cm and ≥ 2.5 cm (χ^2=0.057, P=0.812) (Table 2).

Relationships of HIFU ablation parameters with treatment outcome

As shown in Table 3, the treatment outcome had significant difference among low, equal and high contrast enhancement (χ^2=6.153, P=0.046). There was no significant difference of treatment outcome among low, equal and high ultrasonic echo intensity (χ^2=0.700, P=0.705), among homogeneous, slightly homogeneous and inhomogeneous echo uniformity (χ^2=0.582, P=0.747), or between therapeutic power of <300 w and ≥ 300 w (χ^2=0.318, P=0.573).

Results of logistic regression analysis

The significant variables in single factor analysis, including fibroid type, fibroid position, fibroid size and contrast enhancement were assigned with the data (Table 4), and the logistic regression analysis was performed on them. Results showed that, the fibroid position was the independent risk factor of treatment outcome. The OR value of fibroid position was 2.545 (1.175-5.513) (Table 5). The logistic regression equation was as follows: P=Exp (-1.889 +0.934 × fibroid position).

Table 2. *Relationships of fibroids characteristics with treatment outcome.*

Characteristic		Residual rate (n (%))		χ^2	P
		≥ 50% (n=25)	<50% (n=51)		
Fibroid type				6.614	0.037
	Subserous	9 (36.0)	12 (23.5)		
	Submucous	13 (52.0)	18 (35.3)		
	Intramural	3 (12.0)	21 (41.2)		
Fibroid position				11.41	0.003
	Posterior wall	12 (48.0)	11 (21.6)		
	Fundus uteri	11 (44.0)	17 (33.3)		
	Anterior wall	2 (8.0)	23 (45.1)		
Fibroid size				4.259	0.039
	<5 cm	14 (56.0)	16 (31.4)		
	≥ 5 cm	11 (44.0)	35 (68.6)		
Abdominal wall thickness				0.057	0.812
	<2.5 cm	12 (48.0)	23 (45.1)		
	≥ 2.5 cm	13 (52.0)	28 (54.9)		

Table 3. *Relationships of HIFU ablation parameters with treatment outcome with treatment outcome.*

Parameters		Residual rate (n (%))		χ2	P
		≥ 50% (n=25)	<50% (n=51)		
Contrast enhancement				6.153	0.046
	Low	10 (40.0)	12 (23.5)		
	Equal	12 (48.0)	19 (37.3)		
	High	3 (12.0)	20 (39.2)		
Ultrasonic echo intensity				0.7	0.705
	Low	5 (20.0)	7 (13.7)		

	Equal	8 (32.0)	15 (29.4)		
	High	12 (48.0)	29 (56.9)		
Echo uniformity				0.582	0.747
	Homogeneous	4 (16.0)	6 (11.8)		
	Slightly homogeneous	9 (36.0)	16 (31.4)		
	Inhomogeneous	12 (48.0)	29 (56.9)		
Therapeutic power				0.318	0.573
	<300 w	12 (48.0)	21 (41.2)		
	≥ 300 w	13 (52.0)	30 (58.8)		

Table 4. *Data assignment of variable for logistic regression analysis.*

Variable	Data assignment
Fibroid type	0: Subserous; 1: submucous; 2: intramural
Fibroid position	0: Posterior wall; 1: fundus uteri; 2: anterior wall
Fibroid size	0: <5 cm; 1: ≥ 5 cm
Contrast enhancement	0: low; 1: equal; 2: high

Table 5. *Results of logistic regression analysis.*

Variable	B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP (B)	
							Lower	Upper
Fibroid type	0.635	0.383	2.757	1	0.097	1.888	0.892	3.995
Fibroid position	0.934	0.394	5.616	1	0.018	2.545	1.175	5.513
Fibroid size	0.886	0.569	2.423	1	0.12	2.426	0.795	7.405
Contrast enhancement	0.69	0.384	3.235		0.072	1.994	0.94	4.228
Constant	-1.889	0.721	6.866	1	0.009	0.151		

Discussion

Uterine fibroids are one of the most common gynecological diseases. With the increase of age, the incidence of uterine fibroids is higher and higher, especially among postmenopausal women [12]. However, most of the patients with uterine fibroids have no obvious clinical symptom or manifestation. Only 1/4 women of childbearing age suffer from uterine fibroids which are complicated by symptoms such as increased menstruation [13]. The surgery is often performed for the treatment of uterine fibroids, but the surgical trauma is large, and the postoperative recovery period is longer, with existence of complication risk [14]. The total hysterectomy is also used for treating uterine fibroids. Although the ovaries can be retained, it can lead to degenerative changes of ovarian function, which results in the metabolic abnormalities and systemic immune function decline, and causes vaginal dryness and discomfort and decreased libido [15]. Therefore, retention of the uterus has become a trend for therapy of uterine fibroids. Considering the harm of surgical trauma and complications, more and more extensive researches are focused on the non-operative treatment in recent years. The application of simple drug treatment can only exert short-term effect in the treatment period. Once the drug is withdrawn, the disease recurrence will happen [16]. The uterine artery embolization can well solve the myoma disease, but the embolization sequela and ovarian dysfunction after treatment appear in some patients, which seriously affect the life quality of patients [17].

HIFU ablation is a commonly used non-invasive treatment technique in recent years. It is mainly applied to the treatment of benign and malignant solid tumors, and has achieved remarkable outcome in the treatment of uterine fibroids. The HIFU treatment can cause the coagulation necrosis of uterine fibroids. This makes uterine fibroids to be in a static state, with the loss of responsiveness to sex hormones. The changes of clinical symptom and ultrasound imaging of HIFU treatment have the effects the same with gynecological surgery [18]. In addition to effectively destroying tumor tissues, HIFU ablation can avoid the damage of ultrasound to normal tissues surrounding tumor, achieving the purpose of minimally invasive treatment [19]. Previous studies point out that, HIFU ablation is a safe and effective method for treatment of uterine fibroids [4-7]. For uterine fibroids patients who have the intention for pregnancy, HIFU ablation can effectively retain the pregnancy ability, and give good recovery of uterine cavity morphological change caused by myoma [20]. The principles of HIFU treatment for uterine fibroids are based on the high-intensity ultrasound thermal effect. The ultrasonic reflection and scattering can produce different effects on the treatment

outcome. The internal environment, blood supply and location of myoma will affect the clinical efficacy of treatment [21]. Therefore, it is necessary to clarify the influencing factors for the treatment outcome of HIFU ablation for uterine fibroids, and to make intervention to these factors.

The present study systematically analysed the influencing factors of HIFU ablation in the treatment of uterine fibroids. Results showed that, the treatment outcome had significant difference among subserous, submucous and intramural fibroid type (χ^2=6.614, P=0.037), among fibroid position of posterior wall, fundus uteri and anterior wall (χ^2=11.410, P=0.003), between fibroid size of <5 cm and ≥ 5 cm (χ^2=4.259, P=0.039). In addition, the treatment outcome had significant difference among low, equal and high contrast enhancement (χ^2=6.153, P=0.046). This indicates that, fibroid type, fibroid position, fibroid size and contrast enhancement are the important factors which affect the outcome of HIFU ablation. Results of logistic regression analysis showed that, the fibroid position was the main risk factor of treatment outcome. The possible reasons may be that, the ultrasonic energy permeates the abdominal wall, and focuses on target fibroids. Before reaching the posterior myomas, the ultrasonic beam passes the abdominal wall and normal muscle wall at uterus side, and the energy attenuation is obvious. The position of fibroid at anterior wall is generally shallow, and the ultrasonic beam cannot pass the normal muscle wall, so the energy reaching the target tissue is relatively higher. The fibroid at the posterior wall is adjacent to the sacrum, and the sacrum is in back field of focused ultrasound. The patient is easy to suffer from sacrococcygeal pain and hip pain during treatment. This is not conducive to dosage delivery. In addition, the nerve plexus is dense at the sacrum. When treating the fibroid at the posterior wall, the heat conduction stimulates the nerves, and the probability of neurotoxicity is increased. This also leads to the incomplete ablation [22].

In conclusion, the fibroid type, fibroid position, fibroid size, and contrast enhancement are significantly related to the outcome of HIFU ablation in treatment of uterine fibroids. The fibroid position is the independent risk factor for treatment outcome. Controlling of these factors can improve the treatment efficacy and reduce the complications. For example, in treatment of submucous fibroids, fibroids at posterior wall or fibroids with size<5 cm, the local injection of anhydrous alcohol and iodine oil can change the ultrasound environment and promote the energy deposition, thus promote the ablation efficiency. This study still has some limitations. Firstly, the sample size is relatively small. Larger sample size will make the results more convincing. In studies, the sample size should be amplified for obtaining more satisfactory outcomes. Secondly, there may be many other factors affecting the outcome of HIFU ablation for uterine fibroids. This should be further investigated.

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