

Original Article

Diagnosis and differentiation of prostate cancer hypoechoic hyperplasia nodule and low echo benign hyperplastic nodule using transrectal ultrasound

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Abstract: In the present study, we have investigated the differentiation of prostate cancer (PCa) hypoechoic hyperplasia nodule and low echo benign hyperplastic nodule using transrectal ultrasound. The patients subject to transrectal ultrasonography in our hospital from 2010 to 2015, and all patients need to be diagnosed by prostate biopsy under transrectal ultrasound guidance. There were the blood supply of grading have obvious difference PCa group and benign hyperplastic nodule group. The Vs and RI levels of PCa group were also higher than those of benign hyperplastic nodule group. Meanwhile, we found that the protein expression of VEGF, hMSH2, hMSH6, MMP2 and MMP9 in PCa group were lower than those of benign hyperplastic nodule group. Nevertheless, k-ras and B-Raf protein expression of PCa were higher than those of benign hyperplastic nodule group. Number of patient with irregular shape with burrs, calcification and rear attenuation were higher than those of benign hyperplastic nodule group. The Vs and RI levels of PCa group were also higher than those of benign hyperplastic nodule group. In conclusion, the results showed hypoechoic hyperplasia nodule and low echo benign hyperplastic nodule are important factors in diagnosis of PCa using transrectal ultrasound.

Keywords: Prostate cancer, hypoechoic hyperplasia nodule, low echo benign hyperplastic nodule, transrectal ultrasound

Introduction

Prostate cancer (PCa) is one of the malignant tumors with high incidence among elder people [1]. PCa incidence is significantly different from one to another place around the world, of which the mortality rate is high in Europe and the United States, behind only lung cancer [2]. Although China's PCa incidence is significantly lower than that in Europe or America, it is rising with gradual aging of society and people's changing eating habits in recent years, due to the differences in race and lifestyle [3].

The etiology and the pathogenesis of PCa are still not very clear, and the cause may be related to the following factors: age, race, family history, hormone and dietary factors [4]. The statistical analysis about the PCa incidence of Shanghai residents from 1973 to 1999 shows there have been 2884 cases of PCa patients

registered in Shanghai Cancer Registry for 27 years, the incidence shows a clear upward trend, and the standardized incidence rate rose to 5.5/100,000 (1997 to 1999) from 1.8/100,000 (1973 to 1975), increased by 205.6% [5]. The average annual changing rate is 6.1%. In the age structure of PCa cases, the proportion of older age groups is increased significantly. Furthermore, environmental exposures and lifestyle changes of residents also play a significant role in the incidence of Pca [5]. Since the beginning of 1999, China has entered the aging society, and as the aging situation becomes increasingly serious, China's aging population has entered into the rapid development stage [6]. By the end of 2007, the population aged 60 and over had reached 11.6% of the total national population, with the number of 153 million. It is predicted that by 2020 there will be 248 million elderly people in

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China, 17.2% of the total population, in which 30.67 million will be over 80 years old [6].

With the increased awareness of people for prostate disease and the gradual development of elderly prostate screening, the role of PCa imaging, especially ultrasound and MRI in clinical work becomes increasingly important [7]. Early detection and early treatment of PCa is the key to increase the efficacy and improve the prognosis [8]. Since the early symptom of clinical PCa has no specificity, difficult to be differentiated from benign prostate hyperplasia (BPH), with difficulty in early diagnosis, there is urgent need for further research clinically, and effective PCa diagnosis measures need to be taken, especially for early diagnosis.

Materials and methods

Collect the patient

Objects: the patients subject to transrectal ultrasonography in our hospital from 2005 to 2009, and all the prostate cancer and hyperplasia patients need to be diagnosed by prostate biopsy under transrectal ultrasound guidance. (1) PCa group: 74 cases of adenocarcinoma, patients aged between 34 and 92, with mean age 58.00 ± 13.51 . (2) Benign hyperplasia group: 51 cases, patients aged 40-87 years, with mean age 62.34 ± 14.37 . All these cases above had never taken any endocrine therapy and chemotherapy before surgery.

18 cases were selected with cancer foci located within the gland in prostate cancer group, showing hypoechoic. 31 patients were selected from benign hyperplasia group, who had hypoechoic nodules inside the gland. Hypoechoic nodules group: 16 patients, aged between 46 and 79 (mean 65 years). Hypoechoic benign nodules: 25 patients, aged between 40 and 80 (mean 68 years). There were 19 prostate cancer patients in this study. In 11 cases, the cancer foci were located outside the gland, while in 8 cases, the cancer foci were located in the gland. In addition, the suspected cases of prostate diseases in our hospital were selected from 2005 to 2009, in which 16 cases were finally diagnosed as normal.

Transrectal ultrasonography

During the examination, the patients appropriately filled the bladder, with left lateral position

and knees bent close to the chest. The probe was smeared by a little coupling agent, a condom was worn with the outer coated by paraffin oil, and then the probe was inserted into the anus till the prostate image could be seen. Firstly, horizontal and vertical two-dimensional ultrasound scanning was conducted; foci shape, echo, with or without rear attenuation, sound Halo and microcalcification were observed carefully; then color Doppler flowing imaging (CDFI) was applied to test the maximum flow velocity (Vs) and resistance index (RI) inside the foci or at the systole of marginal artery. The sample volume ≤ 2 mm; the included angle of beam and blood flow < 60 degrees; each datum was measured by 3 times and the mean value was taken. Color Doppler flowing imaging (CDFI) was used for blood supply classification (blood flow display is divided into four levels, 0 means rare blood flow and star-shaped; 1 means slightly more flow signal, showing rod shape and twig-like; 2 means rich blood flow signals, rod-shaped and branched; 3 means very abundant flow signals, showing branch-shape and clusters plexiform). All the information and data are saved and stored.

Ultrasound feature comparison between prostate cancer group and benign nodular hyperplasia group

The two groups were compared in terms of echo (hypoechoic), shape (irregular burrs), rear attenuation, sound halo, microcalcification rate, blood supply classification, peak value of velocity in systolic period (Vs), and resistance index (RI).

Ultrasound feature comparison between hypoechoic nodules group and hypoechoic nodules benign group

The two groups were compared in terms of shape (irregular burrs), rear attenuation, microcalcification rate, peak value of velocity in systolic period (Vs), and resistance index (RI). The patient took left lateral supine position. Firstly a conventional transrectal ultrasonography (fundamental) was used to observe prostate in order to determine the observation section. Then CnTI was started, and sound power output was adjusted to make sweeping investigation in the low mechanical index status. Ultrasound contrast agent SonoVue from Bracco Company was used. Bolus injection technique

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Table 1. The primers are as follows

	Forward	Reverse
GAPDH	5'-GACCTGACCTGCCGTCTA-3'	5'-AGGAGTGGGTGTCGCTGT-3'
VEGF	5'-GAGCAGAAGTCCCATGAAGTGAT-3'	5'-CAATCGGACGGCAGTAGCTT-3'
k-ras	ATTCCTACTAGGACCATAGGT	AAACAGGTGGTTATAGACGG
Braf	5'-CTTCCCCAGACCGCGATTC-3'	5'-CGACCACCTCTATGGTGACCT-3'
hMSH2	5'-GAGTCAAGCAGATGTTGCCTC-3'	5'-TGTGTCTCATGTTGGCCTT-3';
hMSH6	5'-ACAAGGGGCTGGGTTAG-3'	5'-CGTTGCATTGCTCTCAGTATTC-3'
MMP2	5'-GAGTTGGCAGTGAATACCT-3',	5'-CCAAGAAGTCTGCATCTTCT-3'
MMP9	5'-CTTCGAGGGCCACTCCTACT-3'	5'-CAGTGACGTCGGCTCGAGT-3'

Table 2. Compared with Two-dimensional ultrasonographic characteristics of PCa and benign hyperplastic nodule

Group	n	Hypoecho	Appearance (irregular, burr)	Acoustic halo	Calcification	Rear attenuation
		Number (%)	Positive cases (%)	Positive cases (%)	Positive cases (%)	Positive cases (%)
PCa	74	42 (56.76)	63 (85.14)	26 (35.14)	29 (39.19)	31 (41.89)
BHN	39	14 (35.90)	6 (15.38)	15 (38.46)	4 (10.26)	6 (15.38)
<i>P</i> value		0.048	0.000	0.837	0.001	0.006

PCa, Prostate cancer; BHN, benign hyperplastic nodule.

was applied for all the injection speeds. Built-in timer of ultrasound was started, to continuously observe the real-time changes of key regional perfusion and echo intensity. Dynamic and static images are stored in the internal hard disk. At last starting time of angiographic enhancement and end time of developing of each group were recorded through playback, to observe the enhancement features of each lesion.

Angiographic characteristics comparison of all the groups

Normal prostate outer gland group, normal prostate inner gland group, prostate outer gland cancer lesion group and inner gland cancer lesion group were compared in starting time of angiographic enhancement and end time of developing to see if there is difference.

QPCR of VEGF, k-ras, B-Raf, hMSH2, hMSH6, MMP2 and MMP9

Total RNA was extracted from tissues samples from selected patients or volunteers using Trizol reagent (Invitrogen) according to the manufacturer's instructions. The VEGF, k-ras, B-Raf, hMSH2, hMSH6, MMP2 and MMP9 miRNA expressions were determined by quantitative

RT-PCR using the SY-BR@Green (TaKaRa) on ABI StepOne PCR instrument. The primers are as follows at **Table 1**.

Western blot analysis

Tissue samples were collected and homogenated with ice-cold lysis buffer containing protease inhibitors. Supernatant was harvested to measure the protein content BSA protein assay kit (Thermo scientific, USA). 30 µg of protein was subjected onto 10-12% SDS-PAGE and transferred into PVDF membrane (Bio-Rad). The membrane was incubated with blocking buffer for 1 h at room temperature, washed three times

with TBST (0.05% tween-20) and probed overnight at with primary antibody against EGFR, k-ras, Braf, hMSH2, hMSH6, MMP2, MMP9, VEGF and β-actin (1:3000, Santa Cruz Biotechnology, CA, USA). The membrane was incubated with horseradish peroxidase (HRP) conjugated secondary antibody (1:2000, Santa Cruz Biotechnology, CA, USA) for 1 h after washing three times in TBST. The ECL kit (Beyotime Institute of Biotechnology, Jiangsu, China) and X-ray films were used for visualization.

Statistical analysis

All data are expressed as mean ± standard deviation (S.D.). Significant differences between groups were ascertained by one-way analysis of variance (ANOVA), followed by SPSS 19.0 software. Statistical analyses were performed using the Student's t-test and a *P* < 0.05 was considered significant

Results

Compared with two-dimensional ultrasonographic characteristics of PCa and benign hyperplastic nodule

Hypoechoic lesion rate of PCa group was 56.76% and higher than that benign hyperplas-

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Table 3. Compared with Blood supply and hemodynamic index classification of PCa and benign hyperplastic nodule

Group	N	Blood supply classification				Vs (cm/s)	RI
		Level 0 cases (%)	Level 1 cases (%)	Level 2 cases (%)	Level 3 cases (%)		
PCa	74	16 (21.62)	38 (51.35)	14 (18.92)	4 (5.41)	44.0±15.30	0.76±0.10*
BHN	39	25 (64.10)	4 (10.26)	7 (17.95)	3 (7.69)	17.32±4.65	0.51±0.03
P value		0.003				0.007	0.031

PCa, Prostate cancer; BHN, benign hyperplastic nodule. *P < 0.05 (cancer group compared with hyperplasia group).

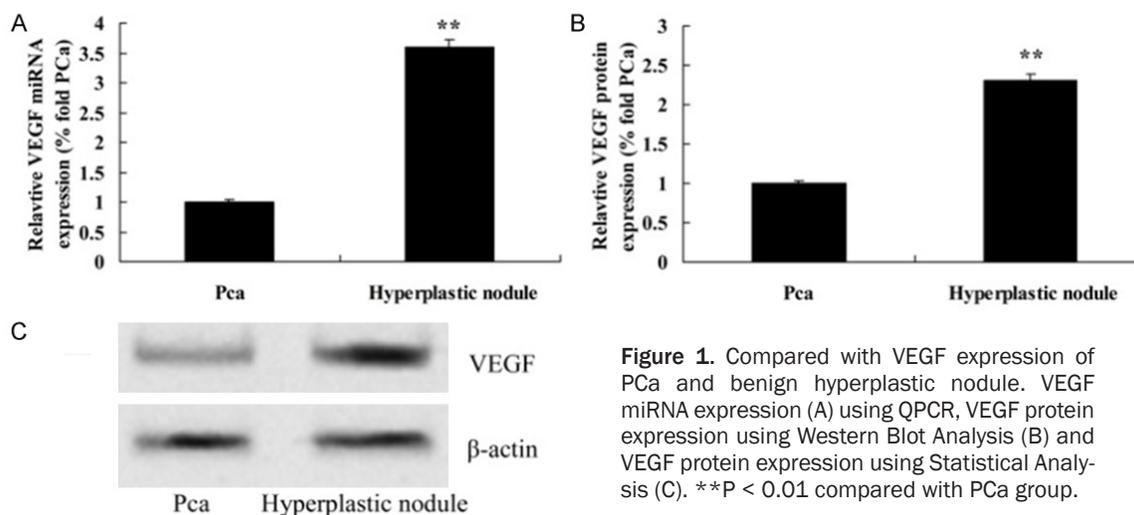


Figure 1. Compared with VEGF expression of PCa and benign hyperplastic nodule. VEGF miRNA expression (A) using QPCR, VEGF protein expression using Western Blot Analysis (B) and VEGF protein expression using Statistical Analysis (C). **P < 0.01 compared with PCa group.

tic nodule group was 35.90% (P = 0.048, **Table 2**). Meanwhile, we found that irregular shape with burrs rate of was 85.14% and observably higher than that of benign hyperplastic nodule group was 15.38% (P = 0.000, **Table 2**). The calcification and rear attenuation of PCa group were 39.19% and 41.89%, respectively, in which were also higher than those of benign hyperplastic nodule group were 10.26% and 15.38%, respectively (P = 0.000 and 0.006, **Table 2**). But, acoustic halo rate of PCa group was similar to that of benign hyperplastic nodule group (**Table 2**).

Compared with blood supply and hemodynamic index classification of PCa and benign hyperplastic nodule

In our study, there were the blood supply of grading have obvious difference PCa group and benign hyperplastic nodule group (P = 0.003, **Table 3**). The Vs and RI levels of PCa group were 44.00±15.30 and 0.76±0.10, respectively, in which were also higher than those of benign hyperplastic nodule group was 17.32±4.65 and 0.51±0.03, respectively (P = 0.007 and 0.031, **Table 3**).

Compared with VEGF expression of PCa and benign hyperplastic nodule

In our study, we found that the VEGF miRNA expression of PCa was lower than that of benign hyperplastic nodule group (**Figure 1A**). Within the same tumor, the VEGF protein expression of PCa was also lower than that of benign hyperplastic nodule group (**Figure 1B, 1C**).

Compared with k-ras expression of PCa and benign hyperplastic nodule

To further study the role of k-ras expression in tissue samples, k-ras miRNA and protein expressions were detected. There were remarkable increases in k-ras miRNA and protein expressions of PCa patient tissue samples compared with benign hyperplastic nodule group (**Figure 2A-C**).

Compared with Braf expression of PCa and benign hyperplastic nodule

To evaluate the compared with Braf expression of PCa and benign hyperplastic nodule, the miRNA and protein expression of Braf was mea-

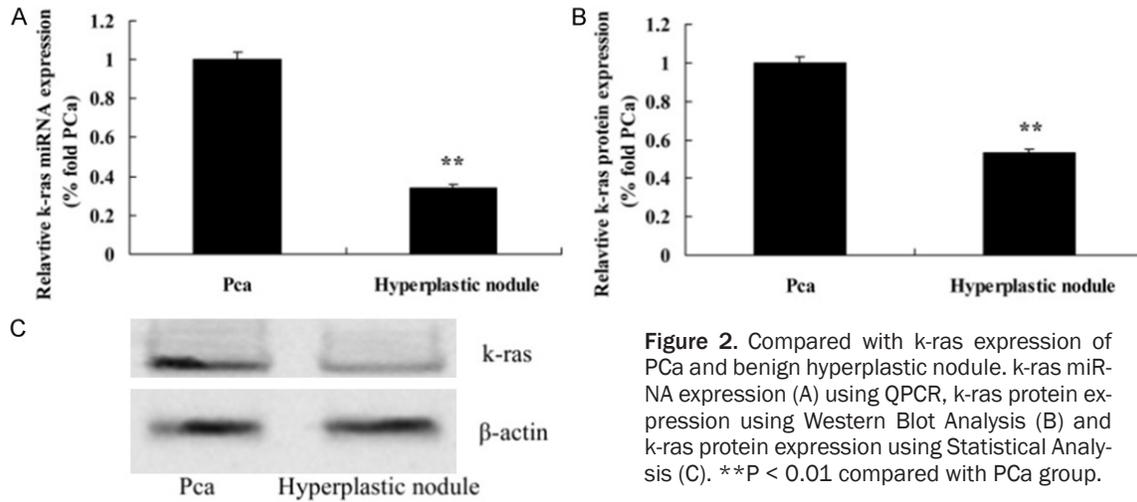


Figure 2. Compared with k-ras expression of PCa and benign hyperplastic nodule. k-ras miRNA expression (A) using QPCR, k-ras protein expression using Western Blot Analysis (B) and k-ras protein expression using Statistical Analysis (C). **P < 0.01 compared with PCa group.

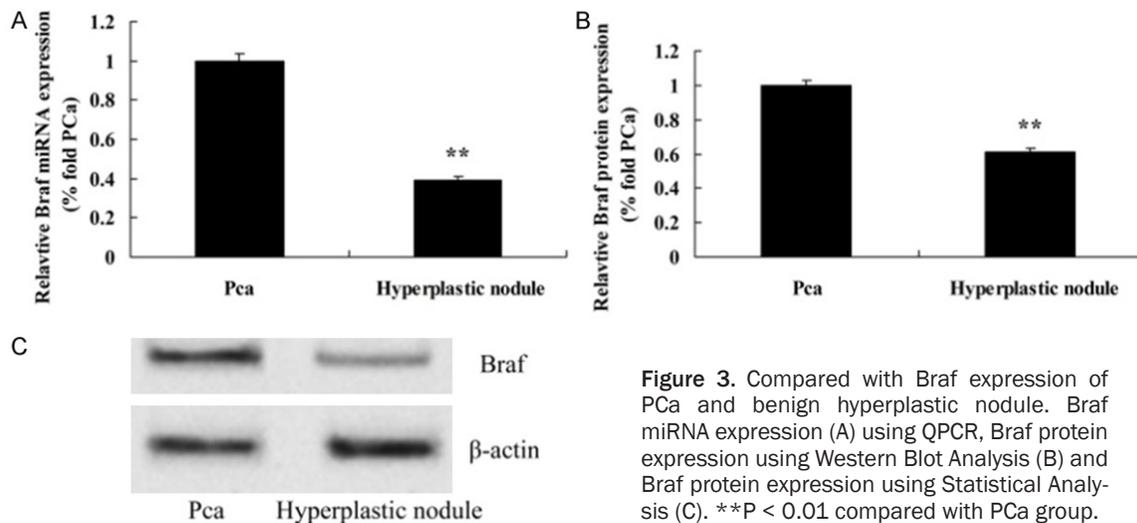


Figure 3. Compared with Braf expression of PCa and benign hyperplastic nodule. Braf miRNA expression (A) using QPCR, Braf protein expression using Western Blot Analysis (B) and Braf protein expression using Statistical Analysis (C). **P < 0.01 compared with PCa group.

sured in all tissue samples from this study. We found that Braf protein expression of PCa group was very higher than those of benign hyperplastic nodule group (**Figure 3A-C**).

Compared with hMSH2 and hMSH6 expression of PCa and benign hyperplastic nodule

We used QPCR and Western Blot Analysis to detected the compared with hMSH2 and hMSH6 expression of PCa and benign hyperplastic nodule. As shown in **Figure 4A-C**, hMSH2 and hMSH6 miRNA or protein expression of PCa group were lower than those of benign hyperplastic nodule group.

Compared with MMP2 and MMP9 expression of PCa and benign hyperplastic nodule

To evaluate the compared with MMP2 and MMP9 expression of PCa and benign hyper-

plastic nodule, MMP2 and MMP9 miRNA and protein expression was analyzed. **Figure 5A-C** showed that MMP2 and MMP9 miRNA and protein expression were observable lower than those of benign hyperplastic nodule group.

Compared with two-dimensional ultrasonographic characteristics of low echo carcinoma nodule group and low echo benign hyperplastic nodule group

In PCa group, 16 patients (88.89%), 7 patients (38.89%) and 8 patients (44.44%) were observed irregular shape with burrs, calcification and rear attenuation, respectively (**Table 4**). In benign proliferation group, 4 patients (12.90%), 3 patients (9.68%) and 5 patients (16.13%) were observed irregular shape with burrs, calcification and rear attenuation, respectively (**Table 4**). These indexes of PCa group were

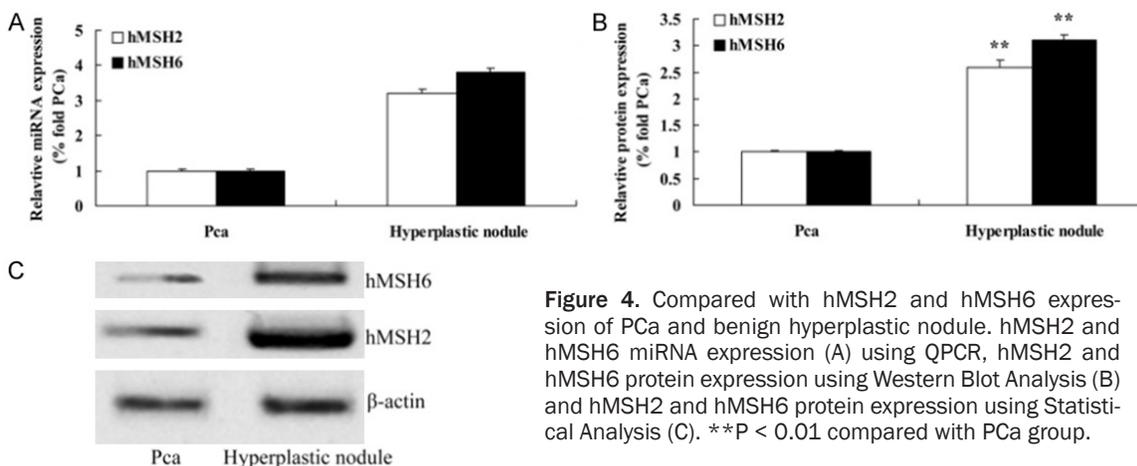


Figure 4. Compared with hMSH2 and hMSH6 expression of Pca and benign hyperplastic nodule. hMSH2 and hMSH6 miRNA expression (A) using QPCR, hMSH2 and hMSH6 protein expression using Western Blot Analysis (B) and hMSH2 and hMSH6 protein expression using Statistical Analysis (C). **P < 0.01 compared with Pca group.

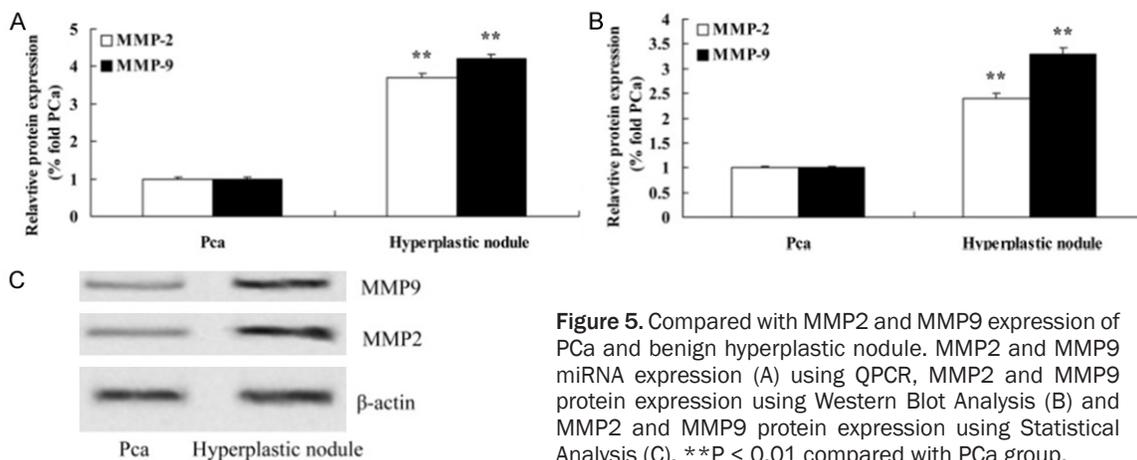


Figure 5. Compared with MMP2 and MMP9 expression of Pca and benign hyperplastic nodule. MMP2 and MMP9 miRNA expression (A) using QPCR, MMP2 and MMP9 protein expression using Western Blot Analysis (B) and MMP2 and MMP9 protein expression using Statistical Analysis (C). **P < 0.01 compared with Pca group.

Table 4. Compared with two-dimensional ultrasonographic characteristics of low echo carcinoma nodule group and Low echo benign hyperplastic nodule group

Group	N	Appearance (irregular, burr)	Calcification	Rear at-tenuation	Vs (cm/s)	RI
		Positive cases (%)	Positive cases (%)	Positive cases (%)		
PCa	18	16 (88.89)*	7 (38.89)*	8 (44.44)*	55.50±3.67*	1.14±0.13*
BP	31	4 (12.90)	3 (9.68)	5 (16.13)	19.42±1.61	0.45±0.04

PCa, Prostate cancer; BP, benign proliferation group; *P < 0.05 (cancer group compared with hyperplasia group).

markedly higher than those of benign proliferation group (Table 4).

Compared with blood supply and hemodynamic index classification of low echo carcinoma nodule group and Low echo benign hyperplastic nodule group

As expected, the Vs and RI levels of PCa group were 55.50±3.67 and 1.14±0.13, respectively,

in which were also higher than those of benign hyperplastic nodule group was 19.42±1.61 and 0.45±0.04, respectively (P = 0.007 and 0.031, Table 4).

Discussion

The prostate is a small organ with little blood flow and dense tissue,

in which blood supply is from the prostate artery [1]. Prostatic artery is divided into urethral branch and extracapsular branch after entering into the prostate; the former supplies to the bladder neck and the part gland surrounding the urethra, which is equivalent to inner gland, whereas the later supplies to the outer portion of the prostate gland, equivalent to outer gland. In the gland, blood vessel is small within slow flow [3, 9, 10]. Therefore, it is

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difficult to observe the distribution of blood flow in normal prostate and the foci and the characteristics of various parts by relying on common transrectal ultrasound.

With transrectal ultrasound contrast by micro-bubbles to develop tiny blood vessels within the prostate and improve the Doppler signal to noise ratio, the level, scope and form of blood flow distribution in the lesion and surrounding tissue can be shown more clearly. Therefore, we adopt this technique to observe the developing characteristics of the tiny blood vessels in normal prostate and foci and the difference between them.

Inner gland of the prostate is prone to hyperplasia, and outer gland is prone to cancer foci, which get blood-supply from two different arteries respectively, so we would like to use contrast agents in order to show the perfusion characteristics inside and outside the gland more clearly, and to see whether there is any difference between the two. The results show that after the injection of contrast agent, the outer gland group of normal prostate starts developing at 25.13 ± 2.54 s, and contrast agent completely disappears at 120.25 ± 11.51 s; the outer gland group of normal prostate starts developing at 27.36 ± 3.05 s, and contrast agent completely disappears at 130.44 ± 12.56 s; there is no significant difference in the start time and the end time of development ($P > 0.05$). The inner gland and the outer gland start developing almost simultaneously, and the contrast agent disappears almost at the same time as well.

The cancer lesion contrast enhancement of prostate outer gland starts at 16.32 ± 1.98 s, and the end time of developing is 116.3 ± 10.981 s; the cancer lesion contrast enhancement of prostate inner gland starts at 14.72 ± 1.81 s, the end time of developing is 125.32 ± 15.67 s. There is no significant difference in the enhancement start time and the end time of development ($P > 0.05$). Because the characteristics of tiny blood vessels inside and outside the gland under normal circumstances are substantially similar; when lesions occur, as long as the pathological characters are the same, there is no big difference in the revascularization between these two lesions.

Previously hypoechoic nodule within the prostate is regarded as a typical symptom of PCa.

The research of Xie et al. shows that the ultrasound images of most cancerous nodules show hypoechoic nodules in the peripheral zone, echo cancerous nodules account for 21.4% of all the cases, and no cancerous nodules with strong echo and hybrid echo can be seen [11]. It also suggests that ultrasonic examination should attach great importance to hypoechoic lesions in the prostate. We have found that the proportion of PCa hypoechoic nodules is 56.76%, while 35.90% are benign nodules, and the two have significant differences, $P = 0.048$, which indicates hypoechoic lesion should be emphasized at ultrasound diagnosis of PCa. However, according to statistics of the p -value, it seems there is significant difference, but the significance degree is not very high. Hypoechoic feature identification alone may result in a great error. The results show more than a third of benign nodules are also hypoechoic. For the identifications of hypoechoic foci located in inner gland and benign hypoechoic nodules require further study in conjunction with other sonographic features. Meanwhile, we found that the protein expression of VEGF, hMSH2, hMSH6, MMP2 and MMP9 in PCa group were lower than those of benign hyperplastic nodule group.

Attenuation refers to the energy decrease with increasing propagation distance during the acoustic wave propagation in the medium [12]. It is resulted mainly from the absorption, scattering and beam diffusion of acoustic wave by media. In malignancies, rear attenuation has high occurrence rate. There are many reports about the diagnosis importance of thyroid cancer and breast cancer, while there are few studies in the diagnostic value of PCa [13]. Our results show that the people in PCa group with the rear attenuation account for 41.89%, significantly higher than that of benign prostatic hyperplasia, 12.82% ($P = 0.006$), with significantly high difference. Rear attenuation symptom is very significant for the ultrasound diagnosis of PCa. Therefore, when rear attenuation occurs in lesion, it should be highly suspected to be malignancy.

Microcalcification is defined by multiple hyperechoic spots < 2 mm, clustered or scattered, with or without acoustic shadowing. Microcalcification is very important for the diagnosis of thyroid cancer and breast cancer, of which the diagnosis value is rarely studied in PCa

[14]. Microcalcification can be seen in many PCa lesions, significantly different from proliferated thick flaky calcification [15]. Our results show that it is valuable in the diagnosis of PCa. PCa patients with microcalcification account for 39.19%, significantly higher than that of benign prostatic hyperplasia, 10.26%, $P = 0.001$, with high difference significance. Therefore, once piled or scattered needle-like calcification is found within the lesion, it should be highly suspected to be malignancy.

Blood supply to malignant tissue is different from that to benign tissue. When PCa angiogenesis is increased, it is generally considered that microvessel density (MVD) is increased [16]. Many scholars have found the MVD of PCa is twice of that of approximated benign tissue in histology [17]. Doppler ultrasound shows tumor blood flow characteristics, which makes transrectal ultrasound become the evaluation approach of PCaMVD with minimal invasion [18]. In recent studies, prostate blood signal has been categorized into 0-3 levels, normal prostate blood 0-1 level, and PCa at 1-2 level [19]. Our results show that there are significant differences between PCa group and benign hyperplasia group in blood supply level ($P = 0.003$); PCa group is higher than benign group in revascularization level, and the difference significance is high. The lesion with rich blood supply in the prostate should be suspected to be malignancy.

The blood flow change in lesions is related to the angiogenesis within the tumor, which is characterized by coarse capillaries and sinus-like gap, no smooth muscle in vascular wall with only a small number of connective tissues, the tumor cells close to the small blood vessels wall, low elasticity, high resistance, and the arteriovenous fistula of arteriovenous shunt among blood vessels [20]. The microvascular change in tumor tissue area is directly reflected by abnormal parameters of small arteries detected by CDFI. Numerous studies show the arteriovenous fistula and the blood flow with high speed and high resistance appear gradually in PCa, and the blood flows with different resistance can be detected in the same area. When peak flow (VSP) is > 15 cm/s and resistance index (RI) is > 0.75 , the sensitivity of PCa diagnosis is up to 87.5%, with specificity 92.4% and positive predictive value 84%. The blood

supply of PCa patient is more abundant than that of benign prostatic hyperplasia patient, in which partial blood shows clustered plexiform, the repeatability of blood flow is excellent, attention should be paid to the lesions in which $RI \geq 0.75$ within the prostate. Vs of adenocarcinoma group is found to be significantly higher than that of hyperplasia group. The blood flow perfusion, speed and resistance in adenocarcinoma nodules are increased compared with hyperplasia nodules. There is rare research about the nodules of outer gland cancer alone. Our results show that Vs of PCa and benign hyperplasia are 44.00 ± 15.30 and 17.32 ± 4.65 ($P = 0.007$), RI is 0.76 ± 0.10 and 0.51 ± 0.03 ($P = 0.031$), respectively. Vs and RI in PCa group are significantly higher than those of benign group. It proves Vs and RI are important for the diagnosis of PCa.

As cancer cells grow fast, showing infiltrative growth, the sonographic image of them has particular characteristics. The cases with irregular shape with burrs in hypoechoic nodules group account for 88.89%, significantly higher than that of benign group, 12.90%, ($P < 0.05$); the ones with micro-calcification account for 38.89%, significantly higher than that of benign group, 19.68% ($P < 0.05$); the ones with rear attenuation account for 44.44%, significantly higher than 16.13% of benign group ($P < 0.05$). It is indicated that irregular shape with burrs, microcalcifications and rear attenuation are of great value for the identification of benign or malignant hypoechoic gland nodules.

Histopathologic change of the disease with histological changes will pass the abnormal hemodynamic stage firstly. As the oxygen consumption of BPH tissue is increased, hypoxia occurs in local tissues, which stimulates the growth of blood vessels and increase blood flow perfusion [21]. On this basis, PCa occurs at the same time. At the absence of blood vessels, the tumor obtain nutrients and excrete metabolic products mainly dependent on the diffusion of surrounding tissues; in neovascularization period, a large number of new blood vessels grow within the tumor, with significantly increased blood perfusion, which is related to the arteriovenous shunt in the tumor in addition to vascular growth factor produced by tumor [22]. And the tumor grows rapidly, the stratum vascular has not been developed soundly, with poor flex-

ibility in wall, more blood flows in the sinus between cells, and the blood flow resistance is increased significantly. The data show that Vs and RI of the prostate hyperplasia with inner gland PCa are significantly higher than those of hyperplasia nodules.

There are no significant differences in perfusion characteristics of the blood supply between inner and outer gland of the normal prostate and the corresponding parts of prostate cancer. Shape (irregular, burrs), microcalcification, high blood supply classification, rear attenuation, high Vs, high RI and hypoecho are all important for the diagnosis of prostate cancer. The faint sound is not helpful for ultrasound diagnosis of prostate cancer. The identification of benign and malignant lesions in hypoechoic gland should be further studied in conjunction with other sonographic features. Further studies in the perfusion characteristics of prostate cancer blood inside and outside the prostate gland and the corresponding parts contribute to the awareness of prostate cancer diagnosis. Irregular shape with burrs, microcalcification, rear attenuation, Vs and RI are helpful for the identification of malignant or benign hypoechoic nodules of inner gland.

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Disclosure of conflict of interest

None.

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