Prostate Cancer Vascularity: Superb Microvascular Imaging Ultrasonography with Histopathology Correlation

Authors' Contribution:
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Data Collection B
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Data Interpretation D
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Background: The aim of this study was to evaluate the association between prostate cancer (PCa) vascularity detected by superb microvascular imaging (SMI) and Gleason score in biopsy specimens.

Material/Methods: A total of 119 patients with suspected PCa before biopsy underwent gray-scale ultrasound (US), color Doppler ultrasound (CDUS), and SMI imaging between June 2018 and March 2019. Vascularity quantity was assessed by SMI and compared with that of CDUS. The vessel parameter was also compared with the Gleason score. The sensitivity of PCa was compared between transrectal ultrasound guided systematic biopsy (SB) and SMI-guided targeted biopsy (SMI-guided TB).

Results: Pathology confirmed 74 of 119 patients had PCa. The microvascular quantity of PCa patients was significantly higher than that of non-malignant patients. SMI detected blood vessels in 97.3% (72/74) in the malignant group, while CDUS identified blood flow signals in 90.5% (67/74) of the PCa group. SMI visualized enriched microvascular in PCa of Gleason 8 (54.5%) and Gleason 9 (92.3%). There was a positive correlation between microvascular quantity detected by SMI and Gleason score, with a correlation coefficient of 0.373 (P<0.001). SMI-guided TB cores were significantly more likely than SB cores to detect PCa (OR=12.83, P<0.001).

Conclusions: SMI could be promising as a useful imaging technique in the detection and characterization of PCa. There was a positive correlation between microvascular quantity detected by SMI and Gleason score.

MeSH Keywords: Microvessels • Prostatic Neoplasms • Ultrasonography • Ultrasonography, Doppler, Color

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Background

Prostate cancer (PCa) ranks as the second most frequent neoplasm in men, accounting for more than 0.3 million cancer-related death in men globally [1]. Transrectal ultrasound (TRUS) was first described in the 1960s, and became widely applied since late 1980s for detecting PCa [2]. TRUS-guided prostate biopsy has therefore become one of the most commonly applied method to diagnose PCa. However, the sensitivity and specificity remain quite low due to the non-uniform characteristics of PCa on the conventional gray-scale ultrasound (US) images [3,4]. Previous studies applied color Doppler ultrasonography (CDUS) to improve the PCa detection rate [5,6], due to the association between angiogenesis and tumor growth [7]. CDUS measures the frequency shift in ultrasound waves as a function of blood velocity and direction, applying wall filtering to remove undesired slow blood flow signals that may be caused by slow, soft tissue motion [8]. In that way, nonvascular artifacts could be eliminated. Meanwhile, signals from very low-velocity vessels can also be removed if the wall filter setting is too high. In other words, CDUS is not capable of detecting microvessels, especially those with lower blood flow velocity. That may lead to lower sensitivity rates in detecting smaller or less aggressive cancers.

Recently, superb microvascular imaging (SMI) has emerged as an innovative ultrasound technique. SMI applies a multi-dimensional filter to demonstrate very low flow signals with less motion artifacts [9]. Consequently, the application of SMI may provide more detailed microvascular information associated with PCa. Bigler et al. firstly described the significantly positive correlation between microvascular and PCa [10], followed by many other researches indicating the possibility of using the degree of blood flow signals as a predictor of potential malignancy [11–13].

The Gleason grading system is a cornerstone in the diagnosis and management of prostatic neoplasms since 1966 [14] with an update version in 2005 [15]. Increased CDUS blood flow signals tend to indicate more aggressive tumors with higher Gleason grading scores [16,17]. Despite the promising findings, we doubted over the efficiency of CDUS in evaluating corresponding Gleason scores and the sensitivity of PCa recognition, due to the limitation that low-velocity blood flow and small vessels are prone to color dropout. Therefore, to counter this, the present study aimed to apply a novel technology (SMI) in differentiating benign and malignant prostate lesions, by comparing the detection rate of true-positive cases of SMI-guided targeted biopsy (SMI-guided TB) and TRUS-guided 10-core systematic biopsy (SB). Furthermore, the second goal of the study was to apply SMI in observing vascularity of PCa in a comparison of CDUS with a more accurate correlation with Gleason score.

Material and Methods

Patient selection

Between June 2018 to March 2019, 130 consecutive men, aged 44–82 years, with suspected PCa were referred to our hospital. The patients were referred due to the following reasons: palpable abnormalities were found at digital rectal examination; or the prostate-specific antigen (PSA) level exceeded the normal range (0–4.0 ng/mL). Exclusion criteria were defined as follows: incomplete US images (n=5); not consent to biopsy (n=4); or unwilling to join the study (n=2). All enrolled patients were notified of the examinations and procedure, and patient informed consents were obtained. Approval for the present study was obtained from the Ethic Committee of our hospital.

Ultrasonography protocol

All examinations were obtained with the following protocol. All patients were asked to be in the left lateral decubitus position, then one radiologist (YC.Z) with 8 years of experience in TRUS started the entire examination in the following order: gray-scale US, CDUS, and SMI. All gray-scale US, CDUS, and SMI were performed on a TOSHIBA Aplio 500 (Toshiba Medical System Corporation, Tokyo, Japan), equipped with a 7 MHz probe. All the images were obtained from both transverse and sagittal planes.

Gray-scale imaging was performed at 5-mm intervals from the level of the seminal vesicles to the apex of the prostate in the axial orientation. Sagittal scanning was performed at 5° intervals (i.e., oblique sagittal imaging) from the right to left lateral aspects of the gland. CDUS and SMI were conducted using the same method. The velocity scales of both CDUS and SMI were adjusted to 1.0–2.0 cm/s.

Vascular quantity was classified, as absent (G0), minimal (G1), or marked (G2), depending on the amount of blood flow in the region of interest (ROI). G0 referred to the absence of blood flow; minimal or G1 vascularity referred to a low quantity of small vessels and/or a main vessel; and marked or G2 vascularity was defined as the visualization of more than 4 vessels. One radiologist (J.S) with 15 years' experience in prostate sonography graded prostate vascularity of CDUS and SMI based on the semi-quantitative criteria. He was blind to the pathological findings.

Biopsy technique and pathologic analysis

A 10-core systematic biopsy was performed with a transrectal gray-scale US approach, using 18-gauge Tru-Cut-type needles. The biopsy specimens were obtained and placed with

Table 1. Baseline characteristics.

	Non-malignant	PCa	p
No. of patients	45	74	N/A
Age (years)	68.18±9.49	72.46±3.19	<0.001*
PSA (ng/ml)	12.50±7.10	18.84±11.69	<0.001*
PSAD (ng/ml/ml)	0.26±0.11	0.51±0.34	<0.001*
Prostate volume (ml)	36.37±15.13	45.05±19.46	0.169
PCa Location			N/A
TZ	N/A	18 (24.3%)	
PZ	N/A	56 (75.7%)	

PSA – prostate-specific antigen; PSAD – prostate-specific antigen density; TZ – transitional zone; PZ – peripheral zone. * Indicates statistically significant difference.

Table 2. Vascularity quantity detected by CDUS and SMI in benign and malignant prostate lesions.

		G0		G1		G2		z	p
CDUS	PCa	7	(9.5%)	46	(62.2%)	21	(28.4%)	8.153	<0.001*
	Non-malignant	40	(88.9%)	5	(11.1%)	0	(0.0%)		
SMI	PCa	2	(2.7%)	30	(40.5%)	42	(56.8%)	8.582	<0.001*
	Non-malignant	36	(80.0%)	9	(20.0%)	0	(0.0%)		

CDUS – color Doppler ultrasonography; SMI – superb microvascular imaging. * Indicates statistically significant difference between PCa and non-malignant lesions.

a 10% formaldehyde solution in separate tubes and labelled accordingly. The patients first received a standard 10-core SB as follows: traditional sextant, and 4 cores in the lateral PZ. Then a second radiologist (Y.Z) took 2 to 3 cores (median: 2) SMI-guided TB from the targets designated by the SMI expert (J.S). An experienced pathologist assessed the pathologic findings, using standard slices prepared and stained with hematoxylin and eosin. The pathologist, who was blinded to the US results, also graded each PCa a corresponding Gleason score. We only included the pathologic finding of PCa in the analysis. The reference standard was the combination results of SB and SMI-guided TB. All of the 119 patients included in the present study received SB and SMI-guided TB since all of them were with visible lesions. We stored each patient's information, such as baseline characteristics, US images (including CDUS and SMI), and the pathological findings in our internal database.

Statistical analysis

Difference of demographic and clinical data between PCa group and non-malignant patients were analyzed using Student's t-test or the Mann-Whitney test. Vascularity grading detected by CDUS and SMI were compared between PCa and non-malignancy using the Wilcoxon rank-sum test. The correlation between vascular quantity and Gleason score was assessed using Spearman correlation coefficients. The by-patient comparison of PCa detection rate for SB and SMI-guided TB was assessed using McNemar's test. The by-core analysis between different Gleason groups was assessed by the Wilcoxon rank-sum test or chi-square test. An overall odds ratio (OR) was assessed for detection of PCa by SMI-guided TB versus SB. P<0.05 was considered as statistically significant. All data were analyzed by SPSS software (22.0, Chicago, IL, USA).

Results

Baseline characteristics

In total, PCa was detected in 74/119 (62.2%) patients in this study. Of the remaining 36 patients with benign prostatic hyperplasia, 9 had chronic prostatitis. The mean PSA of 62.2% patients with PCa was 18.84±11.69 ng/ml, significantly higher than that of benign patients (12.50±7.10) (p<0.001) (Table 1).
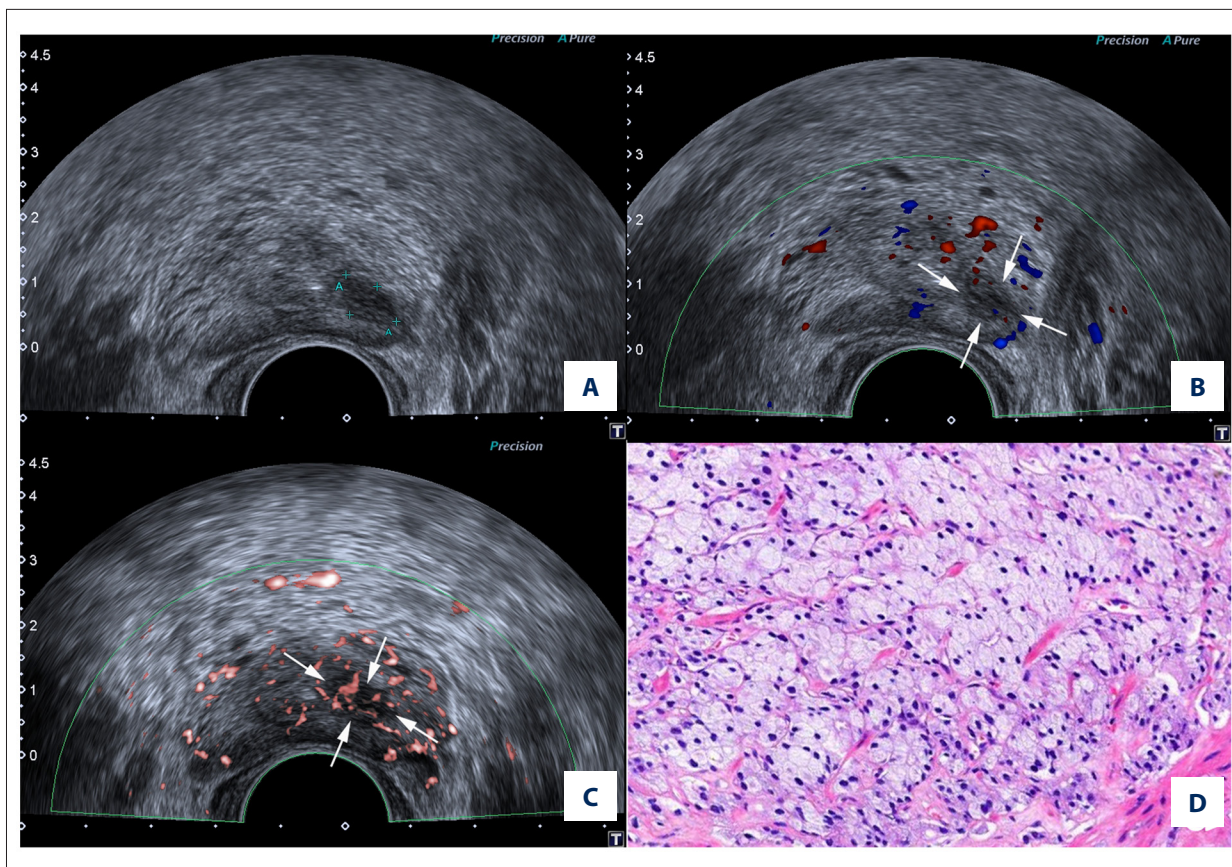
Figure 1. (**A–D**) US images from a 65-year-old man with a PSA level of 19.61 ng/ml. (**A**) Gray-scale image showing an oval hypoechoic lesion in the left gland. (**B**) Color Doppler image showing dot-like vessels in the lesion. (**C**) SMI image showing abundant blood flow signals. SMI-guided targeted biopsy toward the suspicious lesion demonstrated PCa with a Gleason score of 4+4.

Vascularity findings of benign and malignant prostate

There was a significant difference in the vascularity index between the PCa group and non-malignant group (P<0.001). CDUS identified blood flow signals in 90.5% (67/74) of the PCa group. SMI detected blood vessels in 97.3% (72/74) in the malignant group (Table 2). In comparison, the majority of prostates in the non-malignant group showed no vascularity using CDUS (88.9%, 40/45) and SMI (80.0%, 36/45). In terms of the number of vessels visualized, CDUS showed that 62.2% (46/74) of the PCa was graded as G1 (Figure 1) and 28.4% (21/74) of them were graded as G2. SMI showed that 97.3% (72/74) of PCa had vascular signals, including 56.8% (42/74) of them with rich blood flow vessels (Figure 2). These findings support that SMI is a superior imaging method for identifying both high-velocity and low-velocity vessels.

Vascularity quantity of PCa lesions with Gleason scores of 6–9

Our study demonstrated a positive correlation between the vascularity quantity and Gleason score in PCa, with a correlation

Table 3. Correlation between vascularity quantity detected by CDUS and SMI and biopsy Gleason score.

Gleason score	R	P
CDUS	0.286	0.013*
SMI	0.373	0.001*

CDUS – color Doppler ultrasonography; SMI – superb microvascular imaging. * Indicates statistically significant difference.

coefficient of 0.373 (SMI, P=0.001) and 0.286 (CDUS, P=0.013), respectively (Table 3). Most Gleason 7–9 PCa lesions (Gleason 7: 67.6% G1; Gleason 8: 63.6% G1; and Gleason 9: 61.5% G1) had few small vessels identified by CDUS examination (Table 4). In contrast, SMI detected more vascularity in those PCa lesions. For example, 92.3% (12/13) of Gleason 9 PCa lesions shown marked blood flow signals via SMI detection while 38.5% (5/13) of them were visualized of more than 4 vessels by CDUS method. SMI detection found that all PCa lesions with a Gleason score of 7–9 had blood vessels. In contrast CDUS
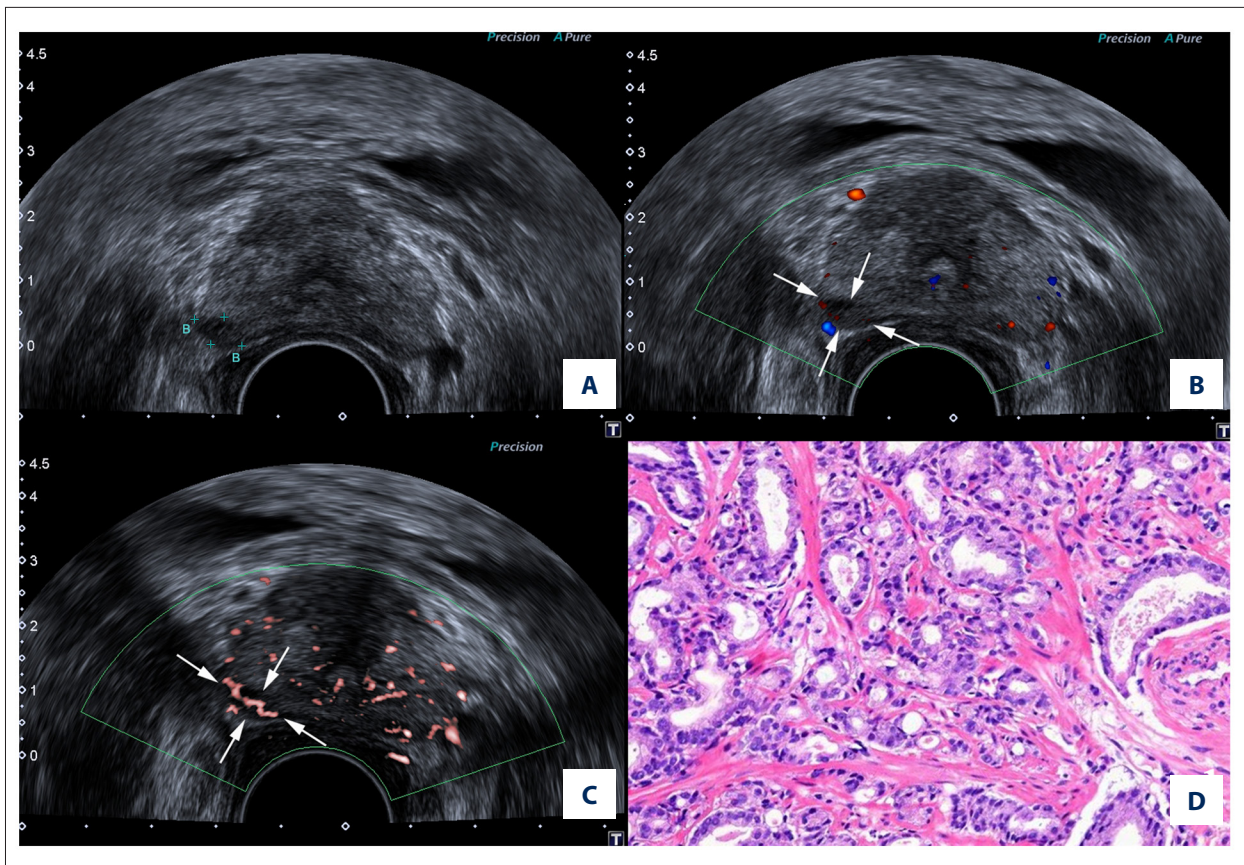
Figure 2. (**A–D**) US images from a 69-year-old man with a PSA level of 17.83 ng/ml. (**A**) Gray-scale image showing an oval hypoechoic lesion in the right gland. (**B**) Color Doppler image showing little dot-like vessels in the lesion. (**C**) SMI image showing enriched blood flow signals. Both SMI-guided targeted biopsy and systematic biopsy demonstrated PCa with a Gleason score of 4+3.

Table 4. vascularity visualized by CDUS and SMI of PCa lesions with Gleason scores of 6–9.

		Gleason 6	Gleason 7	Gleason 8	Gleason 9	P
SMI	G0	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001*
	G1	3 (60.0%)	16 (47.1%)	10 (45.5%)	1 (7.7%)	
	G2	0 (0.0%)	18 (52.9%)	12 (54.5%)	12 (92.3%)	
CDUS	G0	4 (80.0%)	2 (5.9%)	1 (4.5%)	0 (0.0%)	<0.001*
	G1	1 (20.0%)	23 (67.6%)	14 (63.6%)	8 (61.5%)	
	G2	0 (0.0%)	9 (26.5%)	7 (31.8%)	5 (38.5%)	

CDUS – color Doppler ultrasonography; SMI – superb microvascular imaging. PCa – prostate cancer. * Indicates statistically significant difference.

examination found that 3 out of 69 PCa lesions with a Gleason score >6 had no vascularity.

"By-patient" analysis

Table 5 presents the biopsy results from 10-core SB and SMI-guided TB. SB detected 58.1% (43/74) of PCa lesions while SMI-guided TB detected 89.2% (66/74) of PCa lesions. In comparison, 31 PCa patients were missed by SB and 5 patients were undergraded by SB. For example, 6 patients were graded as Gleason 9 by SB results, whereas SMI-guided TB results suggested an additional 2 patients with Gleason 9 PCa lesions. The Gleason 6 PCa detection rate was higher for SB (10.8%, 8/74) than for SMI-guided TB (1.4%, 1/74) (P=0.016).

Table 5. By-patient analysis: SMI-guided targeted biopsy *vs.* systematic biopsy.

SB	SMI-guided TB				
	Benign	**Gleason 6**	**Gleason 7**	**Gleason 8**	**Gleason 9**
Benign	45	0	4	20	7
Gleason 6	7	1	0	0	0
Gleason 7	1	0	12	3	0
Gleason 8	0	0	0	11	2
Gleason 9	0	0	0	0	6

SMI – superb microvascular imaging; TB – targeted biopsy; SB – systematic biopsy.

"By-core" analysis

PCa was detected in 146 (10.2%) of 1437 cores, including 70 (28.3%) of 247 SMI-guided TB, 65 (9.1%) of 714 sextant cores, and 11 (2.3%) of 476 peripheral zone cores. SMI-guided TB cores (28.3%, 70/247) were significantly more likely than SB cores (6.4%, 76/1190) to detect PCa (OR=12.83, P<0.001).

Discussion

The results of this study demonstrate that SMI has a significant advantage over CDUS for detecting PCa through observing microvascularity. Numerous studies have suggested that vascularity might be a vital prognostic indictor of aggressive behavior in different types of tumors, such as carcinomas of the liver [18], breast [19], thyroid [20], and bladder [21]. Therefore, to better classify PCa, we used the concept of lesion vasculature to further distinguish benign prostate diseases from PCa.

In the present study, we evaluated the blood flow signals in both benign prostatic diseases and PCa by using CDUS and SMI. The advent of SMI has made it possible to obtain information concerning the microvascular of the prostate. Most PCa shows greater blood flow signals than in non-malignant patients (p<0.001). SMI detected blood flow signals in 97.3% of the PCa group, while CDUS only identified 90.5%. Our findings are in agreement with those of Tang et al. [22], who reported abnormal blood flow signals were detected in 90.7% (49/54) of PCa by CDUS. Similarly, Sen et al. demonstrated that 88.2% (30/34) of PCa were visualized, with only 33.3% (2/6) of benign lesions showing increased vessels [23]. However, none of the researchers assessed the correlation between vascularity quantity and malignant tumors using CDUS. That might due to the limited capability of CDUS, in that only the larger feeding vessels were able to be detected by this technique [24].

In turn, SMI emerged to overcome the shortage of CDUS in depicting slower blood flow velocity. Karaca et al. evaluated blood flow in the testicles of small children using both CDUS and SMI [25]. Their study found a significant difference between the vascularity quantity detected by CDUS and SMI. The average vessel quantity detected by SMI was nearly twice that detected by CDUS. In breast carcinoma, Park et al. further confirmed SMI's capability in depicting blood flow signals. Their study demonstrated that the number of vessels detected by SMI was significantly higher than with CDUS. Our findings also demonstrated that more vessels were visualized by SMI than by CDUS. Among 74 PCa, 52 PCa were visualized with increased (G2) blood flow by SMI, whereas only 21 of them were graded as G2 by CDUS, and 62.2% of PCa were shown to have fewer small vessels by CDUS, while 70.3% of them were shown to have marked vascularity by SMI. These findings support that SMI is a superior imaging method for identifying high-velocity and low-velocity vessels.

In addition, it is widely believed there is a close link between microvascularity density in PCa tissues and the Gleason score [26]. The Gleason score is considered as a vital factor that contributes to the significance of tumors [27]. Therefore, we further compared the vascularity of tumors with different Gleason scores to determine whether the vascular parameter can reflect the change in Gleason scores. Our findings indicated that increased blood flow signals were positively correlated with higher Gleason grade (CDUS, R=0.286, p=0.013; SMI, R=0.373, p=0.001). The majority PCa of Gleason 8 (54.5%) and Gleason 9 (92.3%) presented rich (G2) blood flow vessels in SMI examination. CDUS visualized a smaller quantity of vascular (G1) in more than half of PCa lesions rated as Gleason 8 (63.6%) and Gleason 9 (61.5%). The results were consistent with previous publications. Ismail et al. were the first to show that blood flow signals revealed by CDUS can be a marker of higher Gleason score, which has higher potential for cancer recurrence [28]. Louvar et al. conducted a retrospective study investigating the histologic evaluations of microvascularity in patients with benign and malignant prostate tissues by CDUS [29]. Their findings suggested that hypervascular areas of PCa detected by CDUS were 3 times more likely

to have cancers graded as Gleason 7 or higher than cancers from normal or lower blood flow areas. In our study, SMI-guided TB (89.2%) revealed a higher correct identification of total PCa than SB (58.1%) (P<0.001). Especially for advanced PCa lesions (Gleason ≥8), SMI-guided TB resulted in true-positive findings in 49 patients (66.2%), whereas SB produced correct identification of 25.7% (19/74) PCa lesions (Gleason ≥8). Advanced PCa shows the strong association between profound increase in vasculature and angiogenesis [30]. Due to the high sensitivity of SMI in depicting small, low-flow vessels (<0.1 mm), targeted biopsy towards a local abnormal region with rich micro blood flow signals on a SMI image can increase detection of true-positive cases of PCa.

Multiparametric magnetic resonance imaging (MRI) is widely used in determining PCa. However, MRI-guided biopsy is a costly and time-consuming method that is not appropriate for all patients, especially those with implants, pacemakers, or claustrophobia [26]. Therefore, SMI-targeted TB could be an alternative solution to increase the accuracy of SB for those who cannot undergo MRI scans, as well as those with lower invasion.

The study had several limitations. First, this was the first study evaluating PCa using SMI, which was performed at a single center with a small number of participants. Therefore, further prospective studies with larger study sample sizes are recommended. Second, all the US images were obtained by the same radiologist. Ultrasonography examination and interpretation are operator-dependent, so future studies should control for interobserver differences in evaluation of imaging findings.

Conclusions

This study evaluated and compared blood flow signals in patients with malignant and benign prostate lesions using color Doppler ultrasonography (CDUS) and superb microvascular imaging (SMI). The findings showed that SMI was superior to CDFI in visualizing the microvasculature in prostate cancer (PCa). In addition, there was a positive correlation between vascularity quantity and Gleason score. In summary, SMI-guided targeted biopsy is a simple method for PCa detection, with a higher true-positive rate and more accurate Gleason score, thus suggesting a more appropriate therapeutic plan than with use of conventional systematic biopsy.

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