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Value of contrast-enhanced sonographic micro flow imaging for prostate cancer detection with t-PSA level of 4–10 ng/mL

Yi-Fen Guo, Feng-Hua Li*, Shao-Wei Xie, Jian-Guo Xia, Hua Fang, Hong-Li Li

Department of Ultrasound, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, 1630 Dongfang Rd., Shanghai 200127, China

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ABSTRACT

Objectives: To compare the efficiency of contrast-enhanced ultrasonographic micro flow imaging (MFI) with conventional transrectal ultrasound (TRUS) in detecting prostate cancer with serum total prostate-specific antigen (t-PSA) of 4.0–10.0 ng/mL. To evaluate the value of contrast-enhanced ultrasonographic MFI in detecting prostate cancer with t-PSA in diagnostic gray zone.

Methods: 47 patients with t-PSA 4.0–10.0 ng/mL underwent gray scale, power Doppler TRUS and MFI examinations before ultrasound guided biopsies. Biopsies were performed at twelve sites in the base, the mid-gland and the apex of the prostate in each patient, when there was no abnormal ultrasound finding. When an abnormality was present at MFI, the biopsy specimen from the corresponding site was directed toward the abnormal finding. With histological results of prostate biopsy as reference standards, we assessed the cancer detection of these three methods.

Results: 564 specimens were collected in this study, in which 101 were prostate cancer confirmed histologically. 152 of 564 specimens were demonstrated abnormal on MFI images, in which 71 were malignant and 81 were benign confirmed histologically. The sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) for MFI in detecting prostate caner were 70.3%, 82.5%, 80.3%, 46.7% and 92.7%, respectively. The sensitivity and NPV for MFI were significantly better than gray scale (38.6%, 86.9%) and power Doppler (32.7%, 86.0%) ($P < 0.001$) TRUS.

Conclusions: Contrast-enhanced ultrasonographic MFI could significantly improve the detection rate of prostate cancer with t-PSA in diagnostic gray zone (4–10 ng/mL) than conventional ultrasound.

1. Introduction

The annual incidence of prostate cancer has increased dramatically over the past decade such that prostate cancer is now the most commonly diagnosed visceral malignancy in men. Many recent reports have indicated that the incidence of prostate cancer in China is increasing rapidly. For example, in Shanghai, it is estimated that the incidence of prostate cancer increased from 1.8–2.4 per 100,000 in 1990 to 4.5–7.7 per 100,000 in 2000 and to about 10.0 per 100,000 in 2004 [1]. It has already gained increased attention from Chinese urologist owing to its rapid increasing incidence.

The diagnosis of prostate cancer has been traditionally based on 3 tools: digital rectal examination (DRE), prostate specific antigen (PSA) measurement, and transrectal ultrasound (TRUS) guided prostate biopsy [2].

Though PSA highly sensitive, it is organ specific and not cancer-specific, which results in difficulties in discriminating malignant and benign prostatic status in men with only slight elevations of PSA [3]. A level of total PSA of 4.0 ng/mL has traditionally been used as the threshold for consideration of a prostate biopsy, recognizing that 30–35% of men in the PSA range of 4–10 ng/mL (diagnostic gray zone) will be found to have cancer [4].

TRUS is universally used as the initial investigation in case of suspicion for prostate cancer and to guide needle biopsies of the prostate. Prostate cancer does not present as solitary round mass, but is known to be a multifocal disease and that is what makes diagnosing prostate cancer difficult. The classic gray scale ultrasound description for prostate cancer is a hypoechoic lesion, but prostate cancer may also appear echogenic or isoechoic. At least one-quarter of the prostate cancer lesions are isoechoic, and consequently not all tumors are identified on TRUS. Even a combination of TRUS with needle-guided prostate biopsies has a low sensitivity and specificity [5]. Because of the limitations of conventional ultrasound in detecting prostate cancer are well-known, new imaging modalities have therefore been proposed as an alternative to

* Corresponding author at: Department of Ultrasound, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, 1630 Dongfang Rd., Pudong New Area, Shanghai 200127, China. Tel.: +86 21 68383211; fax: +86 21 58394262.

E-mail addresses: guoyifen@gmail.com (Y.-F. Guo), li_fenghua3211@163.com (F.-H. Li), shaoweixie@yahoo.cn (S.-W. Xie), doctorxiajg@yahoo.com.cn (J.-G. Xia), huafang12@126.com (H. Fang), lihliwl@163.com (H.-L. Li).

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identify and characterize tumors. Tumor growth is associated with angiogenesis, increased vascularity, and abnormal blood flow patterns because of an increased need of oxygen and nutrients due to expansive growth of malignant tissues [6]. Microvessels of prostate tumors have been shown to range in diameter from 10 to 50 μm [7], which is well below the 1-mm-resolution limit of Doppler imaging [8]. Development of ultrasound contrast agents has increased the detectable ultrasound signal from the blood pool, thus improving cancer detection [9].

Micro flow imaging (MFI) is a new contrast-enhanced ultrasonographic modality using low-mechanical index (MI) CEUS and an accumulative imaging technique to show blood vessels after a flash with high transmission power ultrasound exposure. It has been developed to improve the visualization of microbubbles in the microcirculation [10].

In this study, we compared the efficiency of MFI with gray scale and power Doppler TRUS in detecting prostate cancer with t-PSA in diagnostic gray zone (4–10 ng/mL).

2. Materials and methods

2.1. Patients and study design

Between May 2008 and January 2010, 47 patients with serum t-PSA level of 4.46–9.79 ng/mL (mean ± SD: 6.84 ± 1.30 ng/mL, median: 6.94 ng/mL) were enrolled in this study. The patients were 58–85 years (mean ± SD: 68.5 ± 6.9 years, median: 68 years). Study exclusion criteria was clinical diagnosis of prostatitis within 1 month of biopsy, active urinary tract infection, and contraindications to the US contrast agent SonoVue® (Bracco, Milan, Italy), including New York Heart Association stage IV heart failure. This study was approved by the Ethics Committee of Renji Hospital and written patient informed consent was obtained from each patient before the examination.

The night before the biopsy, all participants began a 4-day treatment with a fluoroquinolone antibiotic or appropriate alternative antibiotic if they had a fluoroquinolone allergy. A cleansing enema was administered on the morning of biopsy. Patients were instructed not to take aspirin or nonsteroidal anti-inflammatory agents for at least 7 days before biopsy.

Ultrasound examinations were performed with a Technos DU8 scanner (Esaote SpA, Genoa, Italy) and a 3- to 9-MHz EC123 end fire endocavitary probe by an investigator with 3 years of experience in TRUS and CEUS. Gray scale TRUS examination was performed first, followed by power Doppler, and finally, MFI. Gray scale examination followed a standard protocol of transverse imaging from base to apex. Power Doppler ultrasound examination followed a standard sequence of transverse imaging from base to apex. The settings of power Doppler ultrasound were as follows: frequency, 6.3 MHz; PRF, 1.0 kHz; filter, M; gain, 113 dB. After gray scale and power Doppler TRUS examinations, we selected three transverse planes from the base, the mid-gland, and the apex and performed MFI. If an abnormality presented in gray scale or power Doppler on a transverse plane, we performed the MFI on this particular transverse plane. If there was no suspicious finding in the entire prostate, we used the three above described transverse planes. MFI was performed using SonoVue. The settings of the machine for MFI were as follows: depth, 36–64 mm; gain, 120 dB; and frame rate, 7–10 frames/s. The contrast agent was prepared in a standard fashion and administered three times with a dosage of 2.4 mL each time through a 20-gauge intravenous cannula within 1–2 s, followed by a flush with 5 mL of 0.9% normal saline solution to ensure no residual contrast agent remained in the cannula. Each plane was observed continuously for 50 s. When all the contrast agents were eliminated from the prostate, we began the next injection. The interval between each injection ranged from 4 to 8 min. The entire examination lasted about 17–25 min. Digital cine clips of typical conventional ultrasonographic images and of the whole MFI examination were recorded on the internal hard disk of the scanner for subsequent analysis. The images of MFI were analyzed offline by the other two investigators with more than 4 years of experience in CEUS and familiar with MFI of the prostate. When they did not agree on the evaluation results, the images were evaluated by another experienced investigator with 6 years of extensive experience in CEUS and familiar with MFI of prostate. All these reviewers were from our department and they were off site.

2.2. Gray scale, power Doppler TRUS and MFI interpretation

An abnormality was considered when gray scale US showed an echotexture abnormality or a contour deformity. Abnormalities in echotexture included a definite hypoechoic focus in the outer gland or an area of heterogeneous echotexture. Contour deformity was defined as a focal bulge of the prostate contour. Power Doppler images were evaluated bilaterally and considered abnormal when a focal area of either increased or asymmetry vascularity was seen. Lesions (nodule, area of heterogeneous echotexture, contour deformity in gray scale, and increased or asymmetry vascularity in power Doppler) and landmarks like urethra, cysts, or calcifications were carefully recorded to assure good overlap of MFI and biopsy. The MFI abnormalities were categorized into four patterns: (1) indistinct separation between the inner and outer glands; (2) asymmetrical or focal increased enhancement in the outer gland; (3) enhancement with focal defect; and (4) enhancement in the outer gland equal to that of the inner gland [11]. All the locations with MFI abnormalities were in a computer database.

2.3. TRUS-guided prostate biopsy

TRUS-guided biopsy of the prostate was performed after the image analysis. All specimens were obtained with an 18-gauge biopsy needle. After recognizing the landmarks, biopsy was performed on these transverse planes, which had been selected to perform MFI. When there was no abnormal finding, biopsy was performed at 12 sites in each patient: the lateral and medial portion of bilateral base, the lateral and medial portion of bilateral mid-gland, the lateral and medial portion of bilateral apex. When an abnormality was present at MFI, the biopsy specimen from the corresponding site was directed toward the abnormal finding.

2.4. Histological evaluation

For histological evaluation, the biopsy specimens were put into separate bottles and labeled according to gland location (base, mid-gland, or apex, left or right, medial, or lateral). All the specimens were evaluated by the same pathologist, who was blinded to the results of ultrasound.

2.5. Statistical analysis

For statistical analysis, McNemar test was applied to compare the sensitivity, specificity and accuracy for gray scale, power Doppler and MFI. A χ^2 test or Fisher exact test was used to compare the positive predictive value (PPV) and negative predictive value (NPV) for gray scale, power Doppler and MFI. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 13.0 software (SPSS Inc., Chicago, IL).