Comparison of systematic prostate biopsy and contrast-enhanced targeted biopsy using cadence contrast pulse sequencing technology

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Abstract

Introduction: Transrectal ultrasound-guided needle biopsy of the prostate may miss a substantial fraction of clinically relevant cancers. Microbubble contrast agents enhance the imaging of microvasculature in the prostate. A new algorithm, Cadence Contrast Pulse Sequencing (CPS), has the advantage of superior sensitivity and stronger contrast agent signals, and it works in real time, using second-generation contrast agents. To compare the prostate cancer (PCa) detection rate of CPS-targeted biopsies (CPS-TB) with conventional ultrasound-guided systematic biopsies (SB).

Materials and Methods: This prospective study was performed December 2010–June 2011 and included 110 consecutive patients with PSA levels of 2.5–10 ng/ml. Patients scheduled for initial prostate biopsy: 78; patients referred for re-biopsy: 32. Using an endocavity transducer, we obtained up to five directed biopsy cores from areas with abnormal vascular enhancement after injection of ultrasonographic contrast agent, SonoVue. Subsequently, another investigator performed a 12-core SB in standard spatial distribution. We used McNemar’s test to detect statistically significant differences between CPS-TB and SB detection rates.

Results: For first biopsies, PCa detection rate in the abnormal CPS group was 67.5% (27/40) for CPS-TB and 52.5% for SB (21/40; \(P=0.031\)). CPS evaluation had 90% sensitivity for detecting PCa and 72.91% specificity, with a 67.5% positive predictive value (PPV) and a 92.1% negative predictive value (NPV). On repeat biopsy, the results were comparable for sensitivity (91.6%) and NPV (95.2%), but there was lower specificity (47.6%) and PPV (34.3%). The detection rate was slightly higher for CPS-TB (54.54%, 6/11) compared to SB (36.36%, 4/11); however, McNemar’s test revealed no statistically significant differences in PCa detection in areas with CPS abnormal enhancement (\(P=0.50\)).

Conclusions: CPS-TB is superior to SB for PCa detection. The targeted approach detected more cancers with a lower number of biopsy cores.

Key words: microbubbles, prostate biopsy, prostate cancer, ultrasound
Introduction

Prostate cancer is the most commonly diagnosed malignancy in men [1] and the second most common cause of cancer-related death [2]. Gray-scale transrectal ultrasound (TRUS) does not detect prostate cancer with adequate reliability [3]. Peripheral zone prostate cancer demonstrates hypoechogenicity on prostate ultrasound (US) in only 50–70% of cases, and transition zone malignancies are even more frequently isoechoic, or even hyperechoic. The equivocal nature of prostate cancer has led to the development of extended biopsy schemes that use random systematic biopsy (SB) in addition to directed cores from a hypoechoic lesion with the aim of improving prostate cancer detection [4].

Tumor growth induces neovascularization [5], and the increase in microvessel density patterns can lead to improved detection of cancer [6]. Prostate cancer blood vessels grow faster than normal vessels and never fully mature; thus, they are small and irregular. By contrast, benign tumors have larger, more regular blood vessels [7,8]. The flow within intratumoral neovessels (10–40 µm diameter) is undetectable with conventional transrectal Doppler US, because of the limited spatial resolution of US equipment and slow flow in these vessels [9]. These vessels may be visualized with new techniques, such as contrast-enhanced US imaging.

Over the last few years, new imaging techniques have been developed that enable microbubble imaging even in the microvasculature, with lower destruction rates [6]. A new algorithm permits detection of the nonlinear fundamental echo (i.e., the strongest signals from bubbles) together with higher-order harmonic signals, with the advantage of superior sensitivity and stronger contrast agent signals for improved lesion detection and characterization [10]. This algorithm has been marketed under the name Cadence Contrast Pulse Sequencing (CPS), and it works in real time with continuous observation, using second-generation contrast agents. By imaging with a low mechanical index, the amount of microbubble destruction is minimized, prolonging the effective period for diagnostic imaging and allowing the microbubbles to progress further into the microvasculature [11]. The purpose of this study was to assess the utility of CPS enhanced-targeted biopsy (CPS-TB) compared to SB for prostate cancer detection in men with PSA levels of 2.5–10 ng/ml.

Materials and methods

This prospective study (December 2010–September 2011) included 105 consecutive patients, mean age 63.5 ± 6.7 years (range 50–76 years), with negative digital rectal examination (DRE) and transrectal grey-scale ultrasonography, with PSA values of 2.5–20 ng/ml (6.4 ± 2.3 ng/ml). The trial had appropriate institutional ethics committee approval before study onset and the informed consent was obtained from all participants.

All examinations were performed using an EC9-4 transducer (9–4 MHz) mounted on an Accuson S2000 (Siemens), with software that provides CPS imaging. Prostate biopsies were obtained using an automated Tru-cut biopsy gun and 18 gauge cutting needles. Study exclusion criteria were prostatitis within 3 months of biopsy, active urinary tract infection, or any clinically unstable cardiac condition within 7 days prior to administration of the US contrast agent. Ciprofloxacin capsules (500 mg) were administered orally, for a 1 day course of antibiotic premedication. A cleansing enema was administered before the procedure. A topical anesthetic sterile gel (Instillagel) was applied at the time of DRE.

The US contrast agent used in this study was SonoVue (Bracco SpA, Milan, Italy), supplied as a lyophilized product in a septum-sealed vial, reconstituted by injecting 5 mL of saline through the septum, followed by hand agitation. We injected the agent (2.4 ml intravenous bolus injection flushed with 10 mL of 0.9% sodium chloride, with a maximum dose of 4.8 mL, via a cannula placed in the antecubital vein) and started our contrast-enhanced ultrasonography using CPS mode, with a probe frequency of 4.0 MHz and a mechanical index (MI) of 0.04.

Prostate scanning was performed in the transverse plane as the probe was slowly swept from the prostate base to the apex to assess those areas with fast and increased contrast enhancement (10–20 s after contrast injection). To observe and examine suspicious lesions repeatedly, we used the flash replenishment technique, which uses high-power flash pulses to destroy contrast microbubbles. When the system returns to low MI real-time imaging, the inflow of the microbubbles can be observed dynamically [12]. Up to five directed biopsy cores were obtained from areas of abnormal vascular enhancement were performed and interpreted by a radiologist with 15 years’ experience in prostate ultrasound. Contrast-enhanced ultrasonography was always performed before SB to avoid biop-
sy-induced hyperemia on the contrast-enhanced imaging study.

Subsequently, another investigator, who was blinded to the contrast-enhanced findings, performed a 12-core SB in standard spatial distribution. The following fragments were taken from each prostatic lobe: one from the posterolateral area at the base, two from mid-gland (far lateral peripheral zone and peripheral zone), two from the apex (one laterally directed and the other medially directed), and one from the transitional zone.

Prostate biopsy cores were sent to the pathology laboratory in separate vials and were processed in separate cassettes. Biopsy cores were reviewed by two uropathologists and reported as cancer with an assigned Gleason score for each biopsy core, prostatic intraepithelial neoplasia, inflammation, or benign prostatic tissue. Ultrasound findings (CPS and B-mode TRUS) were correlated with step-section histology. To analyze data we used MedCalc V.11.6.1.0 (t-test; McNemar test to compare cancer detection for targeted and systematic biopsy) and Mann-Whitney test (http://faculty.vassar.edu/lowry/utest.html) to compare Gleason scores obtained by SB versus TB, with P < 0.05 considered to indicate statistical significance.

**Results**

The overall prostate cancer detection rate on first biopsy was 38.46% (30/78), and CPS detected areas of abnormal enhancement in 40 patients (51.2%). The prostate cancer detection rate in the abnormal CPS group was 67.5% (27/40), whereas SB detected cancer in only 21 of these 40 men (52.5%; P = 0.031, McNemar’s test). Thirteen patients (32.5%) showed areas with suspicious contrast enhancement that were negative for malignancy on the histopathological report; in eight of these cases (61.5%), the benign tissue was associated with areas of chronic inflammation. The prostate cancer detection rate in the normal CPS group was 7.89% (3/38), and overall cancer detection by SB was 30.76% (24/78). With SB, the sensitivity for cancer detection (80%, 24/30) was lower compared to the detection rate of CPS-TB (90%, 27/30). Cancer was detected by TB alone in six patients and by SB alone in three patients. In two of three patients in whom prostatic adenocarcinoma was detected only by SB, the positive cores were located in the transitional zone; in the remaining case, the core was located in the central zone.

The overall prostate cancer detection rate on repeat biopsy was 21.87% (7/32), and CPS detected areas of abnormal enhancement in 11 patients (34.37%). The prostate cancer detection rate in the abnormal CPS group was 54.54% (6/11), whereas SB detected cancer in only four of these 11 men (36.36%; P = 0.50, McNemar’s test). Five patients (45.45%) showed areas with suspicious contrast enhancement that were negative for malignancy on the histopathological report; in three cases, the benign tissue was associated with areas of chronic inflammation. The prostate cancer detection rate in the normal CPS group was 4.76% (1/21), and overall cancer detection for SB was 15.62% (5/32). Using transrectal gray-scale biopsy, the sensitivity for cancer detection (71.42%, 5/7) was
lower compared to the detection rate of CPS-TB (85.71%, 6/7). Cancer was detected by TB alone in two patients and by SB alone in one patient (the positive core was located in the transitional zone).

CPS evaluation had a sensitivity for detecting prostate cancer of 90% and a specificity of 72.91%, with a 67.5% positive predictive value (PPV) and a 92.1% negative predictive value (NPV) on first biopsy. On repeat biopsy, the sensitivity was 91.66%, specificity 47.61%, PPV 34.37%, and NPV 95.23%.

On first biopsy, CPS-targeted cores were positive in 53/138 (38.40%) cores and in 55/936 (5.87%) SB-cores (odds ratio 9.98, 95% CI 6.44 to 15.47, \( P < 0.0001 \)). On re-biopsy, CPS-targeted cores were positive in 15/42 (35.71%) TB-cores and in 14/384 (3.64%) SB-cores (odds ratio 14.68, 95% CI 6.42 to 33.55, \( P < 0.0001 \)). When we took into account only the patients with CPS enhancement, TB-cores were three-fold likely to be positive for cancer compared with SB-cores on first biopsy (49/480, 10.20%) (odds ratio 3.76, 95% CI 2.44 to 5.79, \( P<0.0001 \)) and detected four times as many patients with prostate cancer per biopsy core than SB-cores on re-biopsy (12/132, 9.09%) (odds ratio 3.92, 95% CI 1.70 to 9.05, \( P = 0.0013 \)). The Gleason score on first biopsy was 6.7 ± 1.14 for CPS-TB and 6.66 ± 1.3 for SB (\( P = 0.4654 \), Mann–Whitney test). On repeat biopsy, the Gleason score was 6.6 ± 1.03 for TB and 6.2 ± 0.83 for SB (\( P = 0.4654 \), Mann–Whitney test).

**Discussion**

SB may miss up to 38% of clinically relevant cancers [13], and urologists are faced with the dilemma of managing patients with a negative initial prostate biopsy in whom clinical or pathological risk for prostate cancer still exists [14]. Moreover, the PPV of transrectal US-guided biopsies is low and many unnecessary biopsies are performed, with an enhanced risk of procedure-related morbidity. Various imaging modalities, such as magnetic resonance imaging, have been assessed with regard to their value in the detection of CaP. However, there is a need for less time-consuming and more cost effective procedures in urology [15]. Microbubble contrast agents provide a practical solution to the problem of imaging microvasculature in the prostate [9]. Real-time visualization of blood flow and TB of tumoral foci is beneficial and could be helpful in decreasing the number of cores per biopsy or eliminating the necessity of repeat biopsy.

In the first group of our series, CPS-TB detected more cancers compared with SB but the difference was not statistically significant, except for the detection rate in patients with abnormal enhancement where CPS-TB revealed a significant amount of cancers. On repeat biopsy, the results were comparable with those from first biopsy for sensitivity and NPV, but specificity and PPV were lower. The overall detection rate was slightly higher for CPS-TB compared to SB. However, McNemar’s test showed no statistically significant difference in the overall cancer detection rate for detection of prostate cancer in areas with CPS abnormal enhancement.

Areas of chronic inflammation were important sources of false-positive results on first and repeat biopsies. Inflammatory disease was identified on first biopsy in 61.5% of cases with CPS enhancement but negative for biopsy, and in 60% of cases on repeat biopsy. Moreover, benign prostatic hyperplasia (BPH) often displays hypervascularity. Miterberger et al. showed that short-term treatment with 5α-reductase inhibitors prior to contrast-enhanced prostate US reduces prostatic blood flow in normal prostate, BPH, and prostatitis, whereas cancerous areas remain hypervascular; thus, this method may improve prostate cancer detection [16]. Contrast enhancement as a function of time and objective assessment of time-intensity curves may help to differentiate between malignant and benign enhancement [17]. CPS-TB was not sufficiently accurate for the detection of cancers in the transitional zone; this is probably related to the heterogeneous and intense contrast enhancement associated with areas of BPH.

The majority of cancers detected only by SB were located in the transitional prostate zone: two patients on first biopsy and one on repeat biopsy. After excluding patients with transitional zone cancers, the difference in overall prostate cancer detection between CPS-TB and SB became statistically significant on first biopsy (\( P = 0.031 \), McNemar’s test), but on repeat biopsy the detection rate did not become statistically significant (\( P = 0.5 \), McNemar’s test). Future studies should focus on improving enhancement for these areas and developing better ways of differentiating between malignant and benign tissue.

The number of TB cores on first and re-biopsy were more likely to be positive for cancer compared to SB cores. This suggests that CPS imaging can identify prostate areas with a high probability of containing prostate cancer. CPS-TB detected higher mean Gleason scores on repeat biopsy compared to SB, but
the results were not statistically significant. On first biopsy, the mean Gleason score was comparable for TB and SB. Aigner et al. performed CPS-TB and subsequently SB in 44 patients with suspicious CPS findings. They found that the Gleason scores determined by the two techniques were not significantly different [18]. Others studies, such as that of Mitterberger et al., found that Gleason scores based on the findings of contrast-enhanced color Doppler TB were significantly higher than those based on SB findings [19]. Future randomized, controlled, multicenter studies are needed to further validate the value of contrast enhancement in the diagnosis of clinically significant prostate cancer.

There are some limitations to our study because we only assessed patients with a PSA level of 2.5–10 ng/ml; no correlations were made with final radical prostatectomy specimens, CPS-TB were performed only by one trained investigator and we have no data on interobserver variability; we used bolus administration only while studies have found that infusion technique has the advantage of longer contrast agent duration [12][20].

Conclusion

Contrast-enhanced US using CPS may be a useful technique for more accurate identification of malignant lesions. A normal CPS contrast signal could help to exclude patients who do not have prostate cancer due to its high sensitivity and NPV. This approach may help us to detect a greater number of prostate cancers with a lower number of biopsy cores, which would limit the morbidity associated with prostate biopsy. We achieved an increase in cancer detection by combining targeted and systematic techniques.

References