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Comparison of Contrast Enhanced Color Doppler Targeted Biopsy to Conventional Systematic Biopsy: Impact on Gleason Score

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Purpose: Prostate cancer grading with Gleason score is an important prognostic factor. This prospective randomized study compares ultrasound systematic biopsy vs contrast enhanced color Doppler targeted biopsy for the impact on Gleason score findings.

Materials and Methods: We examined 690 men (mean age 56 years, range 41 to 77) with a serum total prostate specific antigen of 1.25 ng/ml or greater, a free-to-total prostate specific antigen ratio less than 18% and/or a suspicious digital rectal examination. Contrast enhanced color Doppler targeted biopsies with a limited number of cores (5 or less) were performed in hypervascular areas of the peripheral zone during administration of the ultrasound contrast agent Sonovue™ (Bracco, Milano, Italy). Ten systematic biopsies were obtained in a standard spatial distribution. Cancer detection rates and Gleason score were compared.

Results: Prostate cancer was identified in 221 of 690 subjects (32%) with a mean prostate specific antigen of 4.6 ng/ml (range 1.4 to 35.0). Prostate cancer was detected in 180 of 690 subjects (26%) with contrast enhanced color Doppler targeted biopsy and in 166 of 690 patients (24%) with systematic ultrasound biopsy. The Gleason score of all 180 cancers detected on contrast enhanced color Doppler targeted biopsy was 6 or higher (mean 6.8). The Gleason score of all 166 cancers detected on systematic biopsy ranged from 4 to 6 and mean Gleason score was 5.4. Contrast enhanced color Doppler targeted biopsy detected significantly higher Gleason scores compared to systematic biopsy (Wilcoxon rank sum test $p < 0.003$).

Conclusions: Contrast enhanced color Doppler targeted biopsy detected cancers with higher Gleason scores and more cancer than systematic biopsy. Therefore, contrast enhanced color Doppler seems to be helpful in the grading of prostate cancer, which is important for defining prognosis and deciding treatment.

Key Words: biopsy; ultrasonography, Doppler, color; prostatic neoplasms

In 2006 an estimated 230,000 new prostate cancer cases occurred in the United States. In the last few decades the prostate has been the leading site for a new diagnosis of cancer in American and European men.¹ The current standard of care to detect prostate cancer is the assessment of PSA and DRE. In patients with suspicious DRE or increased PSA ultrasound guided systematic biopsy of the prostate for cancer detection is performed.²

The most commonly used system for grading prostate cancer is the Gleason score.³ The Gleason grading system is based on a low power microscopic description of the architectural criteria of PCA. The system describes a score between 2 and 10, with 2 being the least aggressive and 10 being the most aggressive. This score is the sum of the 2 most common patterns (grades 1 to 5) of tumor growth found. To be counted, a pattern (grade) needs to occupy more than 5% of the biopsy specimen.

Prostate cancer grading by the Gleason score is an important prognostic factor.⁴ The impact of grade on the risk of tumor progression and ultimately death from PCA is high in Gleason 7–10 tumors, intermediate in Gleason 6 tumors but low in Gleason 2–5 cancers. Gleason 6–10 tumors carry a continuously increasing risk of death for up to 15 years of followup after conservative management.⁵

The process of screening for prostate cancer is complicated by the definition of significant disease that requires therapy. Conservative management may be reasonable for lower grade, localized prostate cancer.

Tumor volume (stage), tumor grade (Gleason score) and microvessel density are all predictors of significant disease.^{6,7}

An ideal approach to the diagnosis of prostate cancer should limit the number of patients subjected to needle biopsy and should detect significant disease with a limited number of targeted biopsy cores. Therefore, a biopsy technique which can improve the detection of clinically significant cancers would be desirable.

Cancerous tissue generally grows more rapidly than normal tissue and demonstrates increased blood flow compared to normal tissue.⁸ A microbubble US contrast agent may be used to improve the detection of tumor vascularity. In a previous study we found that CECD targeted biopsy improves the detection of cancer.⁹ In the present study we evaluated the impact of CECD targeted biopsy combined with systematic biopsy to compare the impact on the Gleason score of the 2 techniques.

MATERIALS AND METHODS

We examined 690 consecutive asymptomatic screening male volunteers with a serum total PSA of 1.25 ng/ml or greater and a free-to-total PSA ratio less than 18% (Tyrolean PSA screening study). DRE was not part of the screening process in this study, although it was done directly before biopsy. Patient age was 41 to 77 years old (mean age 56). Study exclusion criteria were clinical prostatitis within 1 month of biopsy, active urinary tract infection or contraindications to the US contrast agent Sonovue. For CECD US the Sequoia 512 unit (Siemens Medical, Mountain View, California), fitted with an endorectal end fire probe (EC10C5) operating at a Doppler frequency of 9.0 MHz was used. For gray scale US an endorectal probe unit fitted with a biplane probe (8808) operating at a gray scale frequency of 7.5 MHz (BK-Med, Copenhagen, Denmark) was used.

The night before biopsy all participants began a 5-day course of a fluoroquinolone antibiotic or an appropriate alternative antibiotic if there was a fluoroquinolone allergy. A cleansing enema was administered on the morning of biopsy. Patients were instructed not to ingest aspirin or nonsteroidal anti-inflammatory agents for at least 10 days before biopsy. CECD biopsy and SB were performed using a needle guidance device with the patient in the lithotomy position.

Up to 5 targeted biopsy cores were obtained during intravenous injection of Sonovue using a maximum dose of 2 ml. The contrast agent was prepared in standard fashion. Color Doppler system presets were optimized based on experience to detect contrast enhanced flow. Contrast enhanced imaging was always performed before systematic biopsies to avoid biopsy induced hyperemia on the contrast enhanced imaging study. CECD biopsy was performed into a maximum of 2 hypervascular areas in the PZ only. No targeted biopsies were performed in the TZ. This biopsy approach was done using a 9 MHz end fire probe which enables a single plane approach.

Subsequently another investigator blinded to contrast enhanced findings performed 10 SBs in standard spatial distribution. This biopsy was guided by gray scale US using an endorectal probe unit fitted with a biplane probe operating at a gray scale frequency of 7.5 MHz. Biopsies were obtained without regard to prostate US appearance. In the systematic approach 10 biopsies of the prostate were taken, 5 from each prostate side (1 core from the base, PZ from each side; 1 core from the mid gland, PZ from each side, 1 core from the apex, laterally directed, PZ from each side; 1 core from the apex, medially directed, PZ from each side; and 1 core from the TZ from each side).

Biopsies were obtained transrectally using an 18 gauge biopsy needle. Each biopsy core was reviewed by a pathologist and reported as cancer with an assigned Gleason score, or as prostatic intraepithelial neoplasia, inflammation or benign prostatic tissue.

For statistical analyses the Mann-Whitney U test was used. All statistical calculations were performed using

SPSS® 10.0 software with $p < 0.05$ considered statistically significant. Written patient informed consent was obtained before examination. The cancer detection rate and the assigned Gleason score for the 2 techniques were compared.

RESULTS

Mean patient age was 56 years (range 41 to 77), mean tPSA was 4.6 ng/ml (range 1.4 to 35.0), mean free-to-total PSA ratio was 12.83% (range 4% to 17.9%) and mean prostate volume was 35.5 ml (range 11 to 175). All 690 patients underwent prostate biopsy at our department, and of the 690 patients 138 (20%) had undergone prior prostate biopsy elsewhere.

Overall prostate cancer was identified in 221 of 690 subjects (32%). Prostate cancer was detected in 180 of 690 subjects (26%) with CECD targeted biopsy and in 166 of 690 patients (24%) with SB. Based on those cancers detected on biopsy using either technique sensitivity for cancer detection was 81% (180 of 221 cases) with targeted biopsy and 75% (166 of 221 cases) with systematic biopsy. Prostate cancer was detected with contrast enhanced imaging in 55 patients (7.9%) with negative systematic biopsy and was detected in 42 subjects (6%) only on systematic biopsy.

The Gleason score of all 180 cancers detected on CECD targeted biopsy was 6 or higher. The mean Gleason score detected on CECD biopsy was 6.8 whereas the Gleason score of all 166 cancers detected on SB ranged from 4 to 6. The mean Gleason score detected on systematic biopsy was 5.4. CECD biopsy detected significantly higher Gleason scores compared to systematic biopsy (Wilcoxon rank sum test $p < 0.003$, [figs. 1 and 2](#)).

Cancer detection by targeted biopsy was significantly greater in patients with only 1 hypervascular area vs those with multiple hypervascular areas in the PZ ($p = 0.014$). Presumably in men with only 1 hypervascular area an inflammatory cause of hypervascularity is less likely.

Analysis by subject demonstrates no significant improvement in the detection of prostate cancer with CECD targeted biopsy compared to SB (McNemar's test $p = 0.53$). Based on analysis of individual biopsy cores, the detection rate of CECD targeted biopsy (11% or 379 of 3,417 cores) was better than the SB detection rate (5.7% or 400 of 6,900 cores, $p < 0.001$, see table)

DISCUSSION

Transrectal ultrasound guided SB of the prostate is the standard technique for diagnosing prostate cancer.³ In the present study CECD imaging detected more prostate cancers than SB (26% vs 24%). In the literature the detection rate of systematic biopsy is often approximately 40%. However, this is obtained in patients with a PSA greater than 4.0 ng/ml.¹⁰ Because we are dealing with a PSA screening population with low PSA cutoff values, the detection rate is lower. Furthermore, CECD detected cancers with a significantly higher Gleason score. All prostate cancers detected on SB showed a Gleason score between 4 and 6. The mean Gleason score for cancers detected on SB was 5.4. The Gleason score of all cancers detected on CECD biopsy varied between 6 and 9 (mean 6.8, $p < 0.003$). The 17 cancers that were missed with CECD imaging were TZ cancers with a Gleason score of 4 to 5.

Published studies based on the Connecticut tumor registry show no loss of life expectancy in conservatively treated men with a Gleason score of 2 to 4 and only a modest risk of death at scores of 5 and 6.¹¹ Therefore, based on our results contrast enhanced imaging was more likely to detect clinically significant cancer in our series. The detection of clinically significant cancers with the targeted approach may have been related to improved detection of smaller vessels (microvessels) when using contrast medium. The study by Ismail et al in 1997 was the first to suggest that a signal seen on color Doppler ultrasound could be a marker of higher

Gleason score and associated with a higher likelihood of cancer recurrence.¹² Louvar et al reported that cancer in hypervascular areas visualized on conventional color Doppler were 3-fold more likely to have a Gleason score of 7 or greater than cancers from normal or low flow areas.⁸

Distribution of Gleason scores detected by targeted biopsy and/or systematic biopsy in 221 patients with prostate cancer

	Gray Scale US	Contrast Enhanced US	Both US Techniques	Totals
Gleason score:				
4	7			7
5	10			10
6	25	26	95	146
7		16	26	42
8		10	3	13
9		3		3
Totals	42	55	124	221

Other previous works reported the value of CECD in a prospective study in 230⁹ and 380 male screening volunteers,¹³ and found that targeted biopsies based on CECD detected as many cancers as systematic biopsies with fewer than half the number of biopsy cores. Our results confirm these findings, but in comparison we emphasize the results of Gleason score findings and, thus, the more clinically significant cancer.

Halpern et al included in a previous study 100 subjects with suspected prostate cancer.¹⁴ They correlated harmonic gray scale enhancement with sextant biopsy. The micro-bubble agent used was Definity™ (DuPont Pharmaceuticals). Based on cancers detected on needle biopsy, they demonstrated a significant improvement in sensitivity for cancer detection from 38% at baseline to 65% after infusion of Definity. Furthermore, those lesions detected on contrast enhancement were generally larger and with a higher Gleason sum. Again our results confirm these findings, meaning that more clinically significant cancers were detected. In another approach Halpern et al evaluated targeted prostate biopsies directed toward areas of intense contrast enhancement and found a statistically significant increase in the positive biopsy rate for these targeted biopsy sites.¹⁵

A recently completed clinical trial used microbubble enhanced imaging with Imagent® to direct targeted biopsy of the prostate. They evaluated 301 subjects with harmonic gray scale, color Doppler and power Doppler US.¹⁶ Cancer was detected in 363 biopsy cores from 104 of 301 subjects (35%), including 15.5% (175 of 1,133) of cores targeted to areas of contrast enhancement and 10.4% (188 of 1,806) of sextant cores (p <0.01). Among subjects with cancer, targeted cores were twice as likely to return a positive biopsy (OR 2.0, p <0.001). Although targeted biopsy detected 11% (11 of 104) of cancers not found with the sextant approach, targeted biopsy failed to detect 20% (21 of 104) of cancers. The majority of cancers missed by the targeted approach were at the apex of the prostate. The low proportion of cores targeted to the apex suggests that contrast enhancement is less efficacious at the apex. Based on these findings they recommended a contrast enhanced targeted biopsy strategy with additional cores at the apex of the prostate to maximize cancer detection and minimize the number of biopsy cores.

In our patients targeted biopsies based on CECD findings were obtained from suspicious hypervascular areas

only, and in all cases we have found a hypervascular area. In our experience we do not have problems identifying hypervascular areas at the apex, although it might be more difficult. This might be due to the fact that we are dealing with a PSA screening population (low PSA, younger age, smaller glands). In summary, targeted biopsies were performed in hypervascular areas only, and we have not found a difference in detecting such areas at the apex, mid gland or base. Therefore, no additional biopsies were performed based on the previously stated assumption that there might be less hypervascularity at the apex area.

As previously mentioned we have found on CECD US in the majority of patients only 1 suspicious, hypervascular area in the PZ of the prostate. Multiple biopsies from this single lesion of the PZ have been performed. This seems to be the important point of our approach because multiple biopsies from 1 lesion might reduce upgrading or downgrading of Gleason score in biopsy specimens and obviously Gleason grading is improved. Furthermore, this will allow exact treatment planning. Whereas in SB there was a lower grade of Gleason score detected and, therefore, Gleason upgrading is most likely.

It has to be mentioned that in the pathological literature there is ongoing controversy about the Gleason scoring system.¹⁷ This scoring system has evolved and many pathologists now believe that a reading of Gleason grade 1 or 2 is inaccurate on needle biopsy if not on surgical specimens. Therefore, the high percentage of patients in the SB data having a Gleason score of 4 and 5 could be difficult to interpret, and in other institutions these may have been upgraded. However, these are the results which we obtained from the pathology reports. Efstathiou et al, who investigated PSA based serial screening, reported that PSA screeners were less likely to have Gleason score 7 to 10 cancer, which is in line with our results and might further explain the higher number of Gleason 6 cancers on systematic biopsy.¹⁸

The reason we used 2 ultrasound systems is based on the fact that the needle tract resulting from CECD targeted biopsy can be more easily detected when using the same US unit. With the use of a different system (different scanning planes [transverse and sagittal] with a lower B-mode frequency [7.5 MHz transmitted by most endorectal probes/ state-of-the-art systems]) the chance of detecting the hyperechoic needle tract from CECD biopsy cores is low and, therefore, reduces a bias in the systematic approach.

Another reason we used 2 ultrasound systems is that only the Sequoia system has a high color Doppler frequency (9.0 MHz) and allows for improved detection of small vessels such as tumor vessels. Hypoechoic areas are a typical pattern of prostate cancer on gray scale US. However, because we are dealing with a PSA screening population (PSA cutoff of 1.25 ng/ml) the chance of detecting hypoechoic areas is low and, therefore, the value of targeting such areas is limited.¹⁹

One limitation of our study is that the prostate biopsy findings were not correlated with final radical prostatectomy specimens as done by Sedelaar et al.²⁰ They used 3D-CEPDU in 70 patients with biopsy proven prostate cancer and correlated findings to the final radical prostatectomy specimens. In total 153 prostate tumors were found in the 70 prostate specimens, including 61 tumors less than 5 mm and 93 tumors 5 mm or larger. The diagnosis of clinically significant and insignificant prostate cancer was made in up to 88% of the patients. Diagnosis by imaging improved from 61% (43 of 70 of the prostate cancers) for standard detection tools to an average of 86% (60 of 70 prostate cancers) with 3D-CE-PDU. They concluded that 3D-CE-PDU improves the detection of PCA but its use in the clinic is questionable because indications are still unclear. Therefore, an additional study comparing CECD targeted biopsy with radical prostatectomy Gleason score findings would be desirable.

Another limitation of this study is that the rating of vascularity is subjective and objective measurement is necessary but missing. Furthermore, we did not focus on hypo-echoic areas of the prostate. However, as previously stated this is less relevant.¹⁹

CONCLUSIONS

Our results add support to the growing body of literature that CECD targeted biopsy can improve the detection of prostate cancer with a limited number of biopsy cores. Contrast enhanced biopsy techniques may allow identification of more aggressive cancers.

Abbreviations and Acronyms

3D-CE-PDU	=	3-dimensional contrast enhanced power Doppler ultrasound
CECD	=	contrast enhanced color Doppler
DRE	=	digital rectal examination
PCA	=	prostate cancer
PSA	=	prostate specific antigen
PZ	=	peripheral zone
SB	=	systematic biopsy
TZ	=	transition zone
US	=	ultrasound

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FIGURES

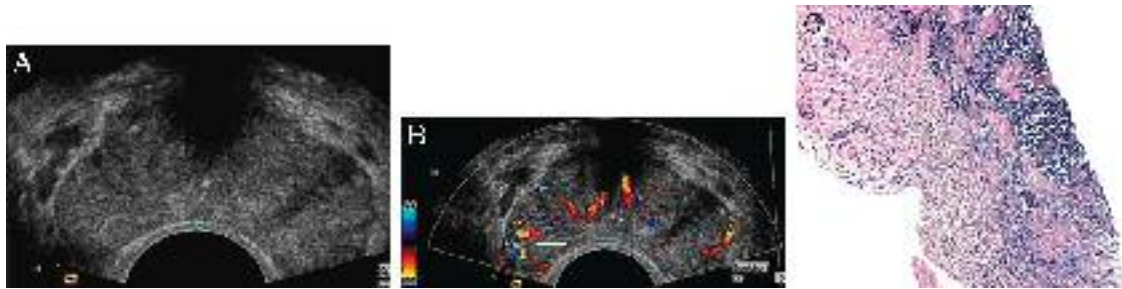


FIG. 1. B-mode transrectal ultrasound (A) vs CECD (B) in 53-year-old man with biopsy proven prostate cancer. Two positive biopsy cores were obtained from right mid gland only on CECD. Corresponding histopathology (reduced from $\times 10$) reveals Gleason score 9 prostate cancer (C).

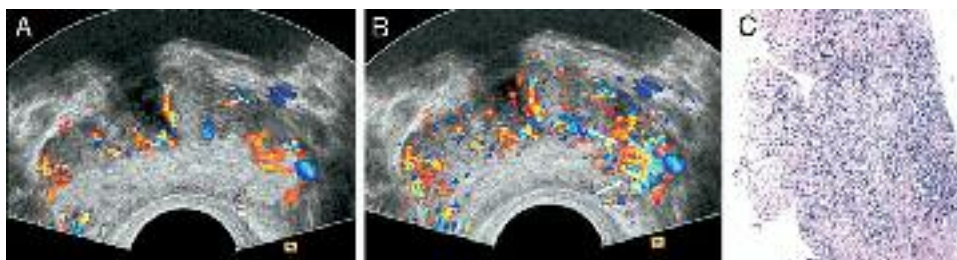


FIG. 2. Color Doppler ultrasound (A) vs CECD (B) in 49-year-old man with biopsy proven prostate cancer. Three positive biopsy cores were obtained from left mid gland only on CECD. Corresponding histopathology (reduced from $\times 10$) reveals Gleason score 9 prostate cancer (C).