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Contrast-enhanced colour Doppler-targeted prostate biopsy: correlation of a subjective blood-flow rating scale with the histopathological outcome of the biopsy

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Study Type – Diagnosis (exploratory cohort)
Level of Evidence 2b

OBJECTIVE

To correlate a subjective blood-flow rating scale from contrast-enhanced colour Doppler (CECD) transrectal ultrasonography-targeted prostate biopsy with the histopathological outcome of the biopsy.

PATIENTS AND METHODS

In all, 760 men with a serum total prostate-specific antigen (PSA) level of ≥1.25 ng/mL and a free-to-total PSA ratio of <18% were included. CECD-targeted biopsies with five cores were taken only in hypervascular areas of the peripheral zone using a second-generation ultrasonography contrast agent, followed by a 10-core systematic biopsy. Prostate blood flow was scored using a subjective 5-point scale in which 1 indicated 'benign', 2 'probably benign', 3 'indeterminate', 4 'probably malignant' and 5 'malignant'.

RESULTS

Overall 37% (283 of 760) patients had prostate cancer in the biopsy. All 100 patients with a score of 5 had cancer; 153 had a score of 4, of whom 130 (85%) had cancer and 23 had benign histology (15%); 131 had a score of 3, of whom 34 (26%) had cancer and 97 (74%) had benign histology; 284 had a score of 2, of whom 17 (6%) had cancer and 267 (94%) had benign histology; 92 had a score of 1, of whom two (2%) had cancer and 90 (98%) had benign tissue. Statistical evaluation showed that the subjective blood-flow rating scale correlated strongly and significantly ($r = 0.75$, $P < 0.01$) with the histopathological outcome of the biopsy.

CONCLUSION

The present study shows that a subjective CECD blood-flow rating scale is a reliable tool to predict the pathological outcome of biopsy cores.

KEYWORDS

blood flow, rating scale, prostate cancer, biopsy, contrast enhanced

INTRODUCTION

Prostate cancer is recognized as one of the major medical problems facing the male population. In Europe, an estimated 2.6 million new cases of cancer are diagnosed each year. Prostate cancer constitutes ≈11% of all male cancers in Europe and accounts for 9% of all cancer deaths among men within the European Union [1].

The main diagnostic tools used to seek evidence of prostate cancer include a DRE, the serum level of PSA, and TRUS-guided biopsies. The diagnosis depends on the presence of adenocarcinoma in prostate biopsy cores and operative specimens [1]. However, the diagnosis of prostate cancer is far from optimal [2]. Currently, at least 10 biopsy cores are recommended for routine use in the guidelines provided by the European Association of Urology [1]. The positive predictive value of biopsies is low and many biopsies are unnecessary. Furthermore, a significant number of prostate cancer cases are also found in patients with low PSA values [3]. Therefore, the search for improved diagnostic techniques is a necessity.

Microbubble contrast agents enhance the ultrasonographic visualization of the microvasculature associated with prostate cancer. These agents increase the echogenicity of the intravascular space on grey-scale imaging, and provide a dramatic visible increase in Doppler signal. Several clinical trials have shown the efficacy of microbubble contrast imaging for detecting prostate cancer [4–7].

In the present study we used a subjective blood-flow rating scale for contrast-enhanced colour Doppler (CECD) TRUS-guided prostate biopsy and correlated the findings with the histopathological biopsy outcome.

PATIENTS AND METHODS

In all, 760 patients from a prostate cancer screening study, with a PSA level of ≥1.25 ng/

*FIG. 1. Ultrasonograms for scores of 1–5, shown in views **A–E**, respectively.*

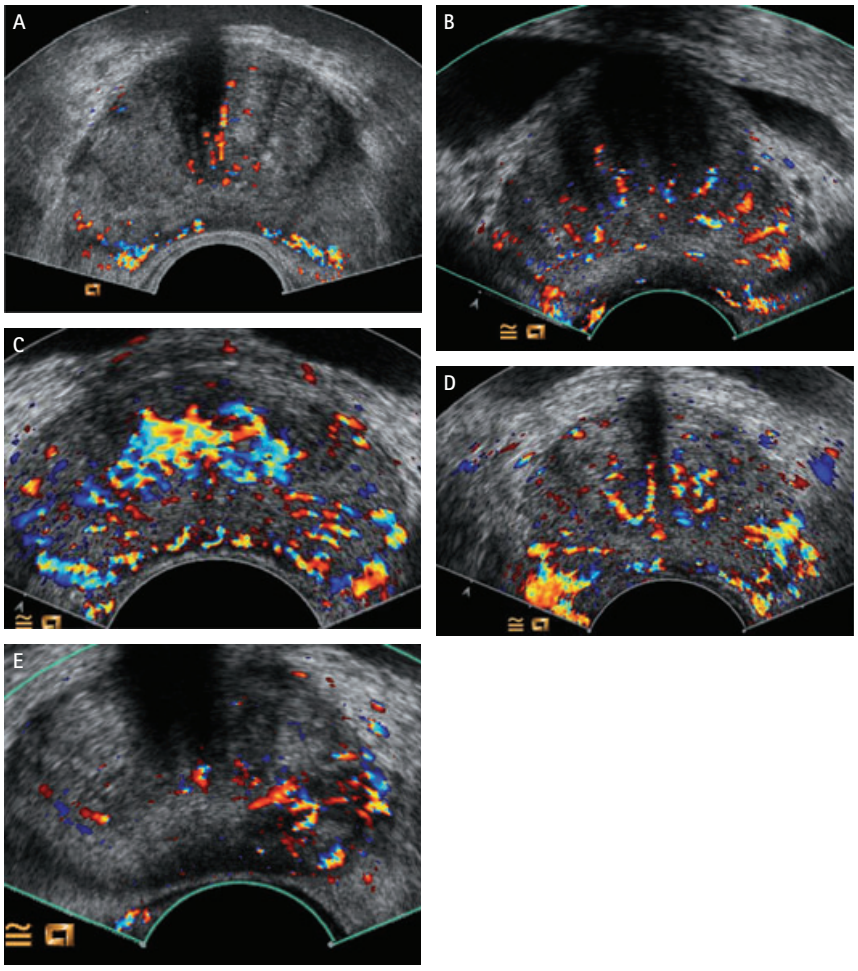

TABLE 1 The five CECD TRUS blood-flow score groups and the corresponding histopathological outcome

	Histopathological finding, *n* (%)		
Score	Benign	Malignant	Total
1	90 (98)	2 (2)	92
2	267 (94)	17 (6)	284
3	97 (74)	34 (26)	131
4	23 (15)	130 (85)	153
5	0	100 (100)	100
All	477 (63)	283 (37)	760

mL and a free-to-total PSA ratio of <18% were enrolled; all had a DRE but it was not part of the study protocol. Study exclusion criteria were clinical prostatitis within 1 month of biopsy, active UTI or contraindications to the CECD-TRUS contrast agent (sulphur hexafluoride). We obtained institutional review board approval and written informed consent from each patient.

The night before biopsy all patient 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 NSAIDs for ≥10 days before biopsy. TRUS was performed with the Sequoia 512 unit (Siemens Medical Systems, Mountain View, CA, USA), fitted with an endorectal end-fire probe operating at a Doppler frequency of 9.0 MHz. To reduce the effect of patient position on prostatic blood flow, all patients were examined in the lithotomy position.

CECD TRUS-targeted biopsies with five cores were taken only in hypervascular areas of the peripheral zone during administration of sulphur hexafluoride; the contrast agent was prepared in a standard fashion. The CECD system presets were optimized based on experience to detect contrast-enhanced flow. Biopsies were obtained transrectally using an 18-G 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 image interpretation a subjective rating score was assigned for each biopsy site on each imaging sequence. Rating scores were assigned by the examining physician, who was an experienced radiologist who had conducted many previous studies with CECD TRUS of the prostate. Biopsy sites were scored for the level of contrast enhancement, using a 5-point subjective scale with the following general guidelines: 1, benign, minimal enhancement (capsular and periurethral flow only); 2, probably benign, mild enhancement (symmetric radial flow from capsular branches); 3, indeterminate, mildly increased enhancement (asymmetric/increased flow in prostate); 4, probably malignant, moderately increased enhancement (asymmetric/increased flow in prostate); 5, malignant, substantially increased enhancement (asymmetric/increased flow in prostate); Fig. 1A–E shows ultrasonograms for each score.

After CECD-targeted prostate biopsy all patients had a 10 core systematic biopsy, as described previously, but the systematic biopsy results were not part of the present study protocol [6].

Descriptive statistics, and for further statistical analyses Spearman's ρ correlation coefficient, were used, with $P < 0.05$ considered to indicate statistical significance. The blood-flow rating scale during the CECD TRUS-guided prostate biopsy was compared with histopathological findings of the biopsy.

RESULTS

Overall, 37% (283/760) of the patients had prostate cancer in the biopsy. The mean (SD) patient age was 60.9 (9.6) years, with a median (SD) PSA level of 4.5 (4.2) ng/mL and a mean free-to-total PSA of 12.6 (7)%; the mean prostate volume was 43 (23) mL. Table 1 shows the number of patients for each score (1–5) who had cancer or benign findings. The five different blood-flow score groups

showed no statistical differences in age, PSA level, free-to-total PSA, prostate volume and Gleason score. There was a statistically significant correlation ($r = 0.751$, $P < 0.01$) comparing the blood-flow rating score with the findings on histopathology, showing that the subjective blood-flow rating score was strongly correlated with the findings on histopathology.

DISCUSSION

Studies of microvessel density within the prostate show a clear association of increased microvessel density with the presence of carcinoma, with metastases, with the stage of disease, and disease-specific survival [8]. The microvessels which proliferate in prostate cancer are below the resolution of conventional TRUS. Microbubble ultrasound contrast agents represent one approach to detect these microvessels. Recently developed ultrasound contrast agents have intravascular residence times of several minutes, pass through the pulmonary circulation, and can be used for parenchymal organ enhancement [9].

The aim of the present study was to evaluate a subjective blood-flow rating scale for CECD-targeted prostate biopsy, and to correlate it with the histopathological outcome of the biopsy. The subjective CECD blood-flow rating score correlated strongly with the histopathological outcome. If there was an asymmetrical substantially increased enhancement of the prostate during CECD TRUS, the probability that the biopsy showed prostate cancer was very high. If there was a capsular and periurethral flow with minimal enhancement on CECD TRUS, the pathology probably showed benign tissue. The aim of the present study was not to compare CECD TRUS with the systematic biopsy, as this has been extensively investigated in previous studies [10]. As stated in a recent meta-analysis by Wink *et al.* [2], there is a clear association between contrast enhancement in the prostate and the diagnosis of clinically significant prostate cancer. Further, the sensitivity of diagnosing prostate cancer was increased, the overall detection rate was improved and fewer biopsies were needed to obtain the same detection rate as conventional prostate biopsy.

The main issue of the present study is the subjective 5-point rating scale and the use of only five CECD-targeted prostate biopsy cores. Halpern *et al.* [11] reported a similar but comparative study and concluded that CECD TRUS is superior to conventional prostate biopsy for cancer detection. By contrast with the solitary, well-defined spherical tumours present in many solid organs, prostate cancer is multifocal in 85% of cases, and the individual sites of tumour are often oblong and irregular in shape [11]. Prostate cancer also often grows along the capsule of the prostate. Furthermore, the normal radial vascular pattern of the prostate is often distorted by the presence of BPH. For these reasons, the hypervascularity associated with prostate cancer might not present as a round mass, and can be difficult to differentiate from normal capsular vascularity on CECD TRUS.

The main limitations of the present study are that blood-flow rating was subjective and analysed for each patient. An objective blood flow measurement is needed but not yet available. The next step in the blood-flow scoring system approach would be an objective evaluation using a computer-based method, e.g. colour pixel counting. Further, the pathological evaluation in the present study was limited by the lack of correlation with whole-mount prostatectomy specimens. Therefore, additional sites of malignancy within the prostate might not be detected by needle biopsy. However, the primary goal of the study was to correlate imaging findings with the histopathology of the needle biopsy cores, and not to compare CECD TRUS with systematic biopsy. Furthermore, all studies were done by one investigator and therefore we have no data on inter- and intra-observer variability. The DRE information was not used because of the low PSA threshold value.

Apart from these limitations, the present study clearly shows that a subjective CECD-based blood-flow rating scale is a reliable tool to predict the pathological outcome of the biopsy cores. Objective measurement, although not yet available, is needed and should further improve CECD TRUS.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Heidenreich A, Aus G, Bolla M *et al.*** EAU guidelines on prostate cancer. *Eur Urol* 2008; **53**: 68–80

2 **Wink M, Frauscher F, Cosgrove D *et al.*** Contrast-enhanced ultrasound and prostate cancer; a multicentre European research coordination project. *Eur Urol* 2008; **54**: 982–92

3 **Pallwein L, Mitterberger M, Gradl J *et al.*** Value of contrast-enhanced ultrasound and elastography in imaging of prostate cancer. *Curr Opin Urol* 2007; **17**: 39–47

4 **Frauscher F, Klauser A, Halpern EJ, Horninger W, Bartsch G.** Detection of prostate cancer with a microbubble ultrasound contrast agent. *Lancet* 2001; **357**: 1849–50

5 **Mitterberger M, Horninger W, Pelzer A *et al.*** A prospective randomized trial comparing contrast-enhanced targeted versus systematic ultrasound guided biopsies: impact on prostate cancer detection. *Prostate* 2007; **67**: 1537–42

6 **Mitterberger M, Pinggera GM, Horninger W *et al.*** Comparison of contrast enhanced color Doppler targeted biopsy to conventional systematic biopsy: impact on Gleason score. *J Urol* 2007; **178**: 464–8

7 **Colleselli D, Bektic J, Schaefer G *et al.*** The influence of prostate Volume on prostate cancer detection using a combined approach of contrast-enhanced ultrasonography-targeted and systematic grey-scale biopsy. *BJU Int* 2007; **100**: 1264–7

8 **Halpern EJ.** Contrast-enhanced ultrasound imaging of prostate cancer. *Rev Urol* 2006; **8** (Suppl. 1): S29–37

9 **Mitterberger M, Pelzer A, Colleselli D *et al.*** Contrast-enhanced ultrasound for diagnosis of prostate cancer and kidney lesions. *Eur J Radiol* 2007; **64**: 231–8

10 **Pelzer A, Bektic J, Berger AP *et al.*** Prostate cancer detection in men with prostate specific antigen4–10 ng/ml using a combined approach of contrast enhanced color Doppler targeted and systematic biopsy. *J Urol* 2005; **173**: 1926–9

11 **Halpern EJ, Ramey JR, Strup SE, Frauscher F, McCue P, Gomella LG.** Detection of prostate carcinoma with contrast-enhanced sonography using intermittent harmonic imaging. *Cancer* 2005; **104**: 2373–83

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Abbreviations: **CECD**, contrast-enhanced colour Doppler.

EDITORIAL COMMENT

The use of CE-based TRUS techniques to improve the diagnosis of prostate cancer is not widespread. This is primarily because there are no US Food and Drug Administration-approved microbubble contrast agents for this use (these agents are approved for echocardiography) and the more labour-intensive and specialized ultrasound equipment needed for proper imaging. Two of the largest centres with significant experience of this method include the Medical University at Innsbruck, and Jefferson Prostate Diagnostic Center of the Kimmel Cancer Center at Thomas Jefferson University in Philadelphia. Most microbubble CE studies to date from these centres have shown a clear association between contrast enhancement in the prostate and the enhanced ability to identify prostate cancer. While there is a promising role for using CE techniques to improve the diagnosis of prostate cancer, this technology might have other practical applications. The vascular abnormalities detected in association with this cancer might provide another measure of the biological aggressiveness of the tumour. The preliminary data from our ongoing Thomas Jefferson University National Cancer Institute-funded trial suggest that cancers visualized with CE techniques tend to be larger and of higher grade, suggesting a potential role for this technology in detecting clinically relevant prostate cancer compared to conventional systematic biopsy. Targeted biopsy of the prostate with CE techniques might allow us to identify men with low-risk prostate cancer who could be ideal candidates for active surveillance programmes. Follow-up CE TRUS might one day allow the non-invasive detection of progression of cancer without invasive repeat needle biopsy of the prostate. By eliminating the need for repeat biopsy, we might potentially be able to provide a low-morbidity, cost-effective strategy for monitoring prostate cancer that will encourage more men with low-risk prostate cancer to participate in active surveillance programmes.

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