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Comparative efficiency of contrast-enhanced colour Doppler ultrasound targeted versus systematic biopsy for prostate cancer detection

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Abstract *Objective* To compare the efficiency of contrast-enhanced colour Doppler ultrasound (CECD-US) targeted biopsy versus systematic biopsy (SB) for PCa detection in 1,776 men. *Methods* Retrospective, single-centre, diagnostic accuracy study from 2002 until 2006 in 1,776 male volunteers with a serum total PSA of 1.25ng/ml or greater. In each patient five CECD-US targeted biopsies were performed in hypervascular areas in the peripheral zone during intravenous injection of a second-generation microbubble US contrast agent. Subsequently, another examiner performed ten SBs. The PCa detection rates for the two techniques were compared. *Results* Of 1,776 patients, cancer was detected in 559 patients (31%), including 476 of the 1,776 patients (27%) with CECD-US and 410 (23%) with SB ($p<0.001$). The detection rate for CECD-US targeted biopsy cores (10.8% or 961 of 8,880 cores) was significantly better than for SB cores (5.1% or 910 of 17,760 cores, $p<0.001$). Among patients with a positive biopsy for PCa, cancer was detected by CECD-US alone in 149 patients (27%) and by SB alone in 83 (15%) ($p<0.001$). *Conclusion* This study represents the largest clinical trial to date, demonstrating a significant benefit of CECD-US targeted biopsy relative to SB.

Keywords Prostate cancer · Prostate biopsy · Ultrasound · Contrast agents

Introduction

Prostate cancer (PCa) is one of the major public health issues facing the male population worldwide. In the US, PCa is the most common cancer in men, with 192,280 new cases every year and 27,360 deaths a year [1, 2].

In patients with increased prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE), grey-scale transrectal ultrasound (TRUS)-guided biopsy is the standard method to diagnose PCa. TRUS-guided biopsy was first described by Holm et al. in 1981, and since then only the number and locations of cores have been increased with controversial results [3, 4]. Several studies suggest that a biopsy with 12 laterally directed cores may detect a comparable number of clinically relevant cancers when compared with a saturation biopsy with 24 cores [4–9]. Attempts to improve PCa detection by increasing the number of biopsy cores result in a substantial overdiagnosis of clinically insignificant tumours while up to 35% of clinically relevant cancers are missed [4–9].

Transrectal ultrasound technology has limited specificity and sensitivity for PCa detection. Researchers have

investigated a number of alternatives, including colour or power Doppler imaging, elastography and MRI [10–13]. Although Doppler imaging can detect vascularity within the prostate, the sensitivity of clinical Doppler ultrasound systems is too low to detect the slow flow velocities within microvessels of PCa [14]. However, the flow signals within the microvasculature of prostate cancer can be amplified by the use of intravenous microbubble ultrasound contrast agents, allowing selective visualisation of neovessels associated with PCa foci. Mitterberger et al. and others showed the potential of contrast-enhanced colour Doppler ultrasound (CECD-US) in smaller series with different ultrasound contrast agents [15–18]. Our hypothesis was that a targeted biopsy procedure based upon imaging of contrast-enhanced microvascularity could improve the detection of PCa and would be superior to an increased number of systematic biopsy cores for PCa diagnosis.

The goal of this study was to compare the efficiency of contrast-enhanced colour Doppler ultrasound (CECD-US) targeted biopsy versus systematic biopsy (SB) for PCa detection in the largest clinical trial to date including 1,776 men.

Materials and methods

This study was performed from January 2002 to June 2006 and included 1,776 male volunteers (white Caucasian) with a serum total PSA of 1.25 ng/ml or greater. Written patient informed consent was obtained before examination, and institutional review board approval was received. Patients were excluded from the study if they had had clinical prostatitis within 1 month of biopsy, active urinary tract infection or contraindications to the microbubble US contrast agent (like known coronary artery disease, myocardial infarction, unstable angina, etc.). DRE was not part of the study protocol. Of the 1,776 patients 57% had their first prostate biopsy during this study, 30% had undergone previous prostate biopsies, and in 13% previous biopsy history was not known. All participants began a 5-day course of a fluoroquinolone antibiotic (or an appropriate alternative antibiotic if there was a fluoroquinolone allergy) the night before biopsy. On the morning of biopsy, a cleansing enema was administered, and biopsies were performed with the patient in the lithotomy position using an 18-gauge biopsy needle with TRUS guidance. Prostate biopsy was performed under a local anaesthetic in 84% of the patients and under a general anaesthetic in 16%.

CECD-US biopsy technique

Contrast-enhanced colour Doppler-US targeted biopsy was performed before SB in order to avoid errors related to biopsy-induced hyperaemia. A Sequoia 512 unit (Siemens Medical, Mountain View, CA) fitted with an endorectal end fire probe (EC10C5) operating at a Doppler frequency of 9.0 MHz was used, which enables a single-plane approach. Five targeted biopsy cores were obtained from hypervascular areas in the peripheral zone (PZ) during intravenous injection of a second-generation microbubble US contrast agent [sulphur hexafluoride (SF6), Sonovue® (Bracco) Italy] using a maximum dose of 2.4 ml. Hypervascular areas were defined as areas with asymmetrically increased or diffusely increased colour flow signals. As shown in previous studies in a low PSA population the contrast enhanced technique is not sensitive for detection of cancer in the transition zone (TZ) [15]. The current study therefore concentrated on detection of cancer in the PZ. Targeted biopsies were not performed in the TZ. (Figs. 1 and 2).

Systematic biopsy (SB) technique

After targeted biopsies were obtained, a second, investigator who was blinded to the contrast-enhanced findings performed ten SBs in standard spatial distribution. For grey-scale US, an endorectal probe unit fitted with a biplane probe (8808) operating at a grey-scale frequency of 7.5 MHz (BK-Med, Copenhagen, Denmark) was used. SBs were obtained without regard to prostate US appearance. In the systematic approach, ten biopsies of the prostate were taken, five from each prostate side (one core from the base, PZ from each side; one core from the mid-gland, PZ from each side; one core from the apex, laterally directed, PZ from each side; one core from the apex, medially directed, PZ from each side; and one core from the TZ from each side).

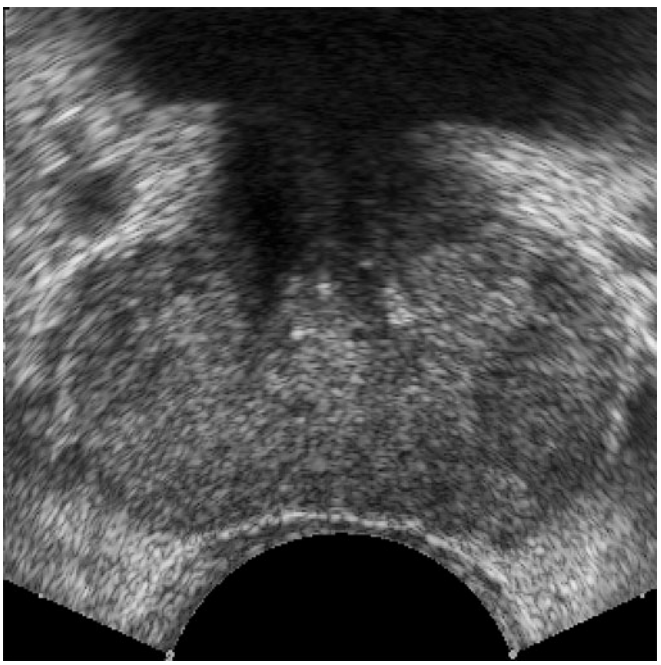

Fig. 1 Grey-scale transrectal ultrasound of the prostate: the US image of the prostate does not show any suspicious lesions

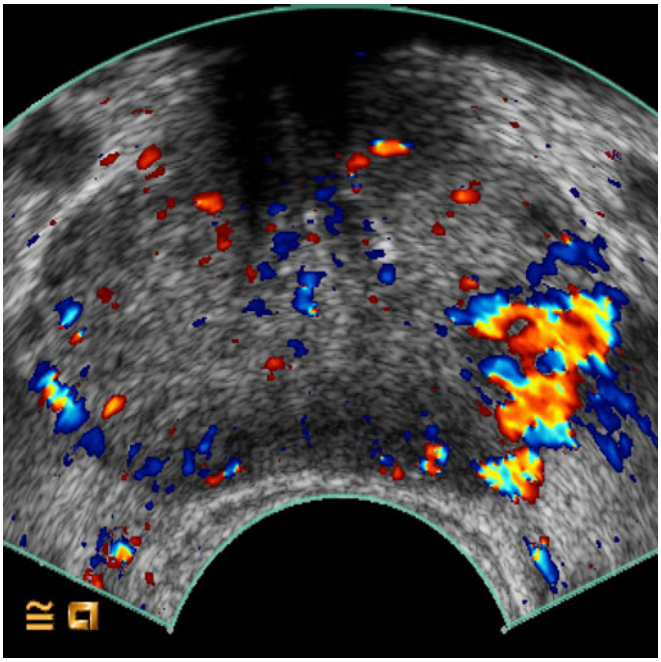

Fig. 2 Transrectal contrast-enhanced colour Doppler ultrasound (CECD-US) shows an area with increased and asymmetric enhancement of colour flow signals on the left side of the PZ. A prostate carcinoma was confirmed by CECD-US targeted biopsy

Histology

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.

Statistics

The by-patient cancer detection rate for the two techniques was compared using McNemar's test. To compare the diagnostic yield of individual biopsy cores with the two techniques, a generalised estimating equations (GEE) Poisson regression model for repeated measures was applied. Differences in the Gleason score obtained by the two biopsy techniques were assessed using the Wilcoxon test. All statistical calculations were performed using SPSS® 16.0 software with $p<0.05$ considered statistically significant.

Results

The study population characteristics are summarised in Table 1. Mean patient age was 60±9.4 years (standard deviation, SD). The median PSA value was 4.2 ng/ml with a 25th percentile of 2.6 ng/ml and a 75th percentile of 7.4 ng/ml. Mean free-to-total PSA ratio was 13.5±7.1% (SD), and mean prostate volume was 42.7±22 ml (SD).

Overall, PCa was detected in 559 of the 1,776 patients (31.4%). PCa was detected in 476 of the 1,776 patients (26.8%) during CECD-US targeted and in 410 (23.1%) during SB (Table 2). Among patients with a positive biopsy for PCa, cancer was detected by targeted biopsy alone in 149 patients (27%) and by systematic biopsy alone in 83 (15%). The by-patient cancer detection rate was significantly higher with CECD-US ($p<0.001$ using McNemar's test). Comparison of the cancer detection rate stratified by age group showed improved detection rates by CECD-US in all age groups, though this finding was statistically significant only in patients over 50 years. Comparison of cancer detection stratified by total PSA levels revealed improved detection by CECD-US in all PSA groups, though this finding was statistically significant only for patients with a PSA≤2.5 or >4 ≤10 ng/ml. The cancer detection rate was also improved by CECD-US in all prostate volume groups, and was statistically significant for prostate volumes between >20 and 60 ml. Comparison of the cancer detection stratified by the number of previous biospies showed a statistically significant improvement with CECD-US (Table 2).

The detection rate for CECD-US targeted biopsy cores (10.8% or 961 of 8,880 cores) was significantly better than for SB cores (5.1% or 910 of 17,760 cores, $p<0.01$). CECD-US in a patient with PCa was 2.1-fold more likely to detect PCa than SB (Table 3). The comparison of the per core detection rates showed significantly improved detection by CECD-US in all age groups, at all PSA level groups, for all prostate volume groups and for patients with different numbers of previous biopsies (Table 3).

Overall, the mean Gleason score was 6.7. Among 327 patients with PCa detected by both CECD-US targeted biopsy and SB, paired comparison showed no significant difference in Gleason score. No significant difference in Gleason score was found with stratification by age or for PSA stratification ($p=0.236$ using the Wilcoxon test). A prostate mapping for cancer location with SB showed the presence of PCa in the following locations: 25% basal, 25% middle, 39% apical and 11% in the TZ. With CECD-US targeted biopsy, the distribution of cancer location showed 28% basal, 34% middle and 38% apical.

Discussion

Our study of 1,776 men demonstrated that CECD-US targeted biopsy detects a significantly higher number of patients with PCa when compared with SB. The advantage of CECD-US is even more striking in the "by biopsy core" analysis. Our results clearly show that CECD-US increases PCa detection, while the number of biopsy cores is reduced.

Transrectal ultrasound-guided biopsy was first introduced in 1981 by Holm et al. [3]. Since that time there has been a trend towards a greater number of biopsy cores with more laterally directed cores, with varied results [7–9].

Table 1 Study population characteristics in mean (median) values, range (25th–75th percentiles), ± standard deviation

No patients = 1,776	Mean (median)	Range (25th–75th percentiles)	SD
PSA (ng/ml)	8.8 (4.2)	1.25–250 (2.6–7.4)	48.7
% PSA	13.5 (14)	1–54 (10.9–16.5)	7.1
Age (years)	60 (60.2)	39–87 (53.7–65.9)	9.4
Prostate volume (ml)	42.7 (38)	13–350 (30–50)	22

Currently, at least 10–12 TRUS biopsy cores are recommended for a first prostate biopsy with additional cores and/or saturation biopsy recommended for repeat biopsy in the setting of continued elevation of PSA [4, 7, 9].

The cost-effectiveness of saturation biopsy of the prostate is questionable. Recent publications show that 10–12 laterally directed TRUS biopsy cores detect 95% of cancers detected by a 24-core saturation biopsy schema [6]. Saturation biopsy is much more costly because it requires a location and personnel appropriate for the administration and monitoring of conscious sedation. Furthermore, saturation biopsy requires more time, may be associated with increased patient morbidity as a function of the number of biopsy passes, and the pathologist must review two to four times as many prostate cores before arriving at a diagnosis. Ashley et al. estimated that saturation biopsy costs approximately $5,000 more than standard office biopsy [19].

There is urgent need for an intelligent strategy to reduce the number of biopsy cores utilised for the diagnosis of PCa. A simple reduction in the number of systematic cores will likely result in the detection of fewer cancers and may result in decreased detection of clinically significant disease. When the number of systematic biopsy cores is increased, clinically indolent cancer will be identified more often [20]. CECD-US targeted biopsy presents a solution to this dilemma by improving PCa detection with fewer biopsy cores. In prior studies we have shown that CECD-US allows for improved detection of cancers with higher Gleason scores [17]. Results of the current trial do not demonstrate an increased Gleason score in CECD-US targeted cores. Further multicentre trials are necessary to assess the value of CECD-US for detection of higher grade, more clinically significant cancer. Nonetheless, based upon our findings, CECD-US targeted biopsy should improve the evaluation of patients with elevated PSA and/or suspicious DRE.

MRI has recently been proposed as an alternative technique for the detection of PCa. Preliminary results have demonstrated that MR imaging may be used to target suspected lesions in the prostate to facilitate biopsy [21]. However, MRI-guided biopsy is a prolonged procedure that often requires general anaesthesia and is available in only a few centers around the world. In our study CECD-US was shown to be a valuable technique for cancer diagnosis at a cost ($450 per CECD-US study) that is substantially lower when compared with MRI-guided biopsy.

Mitterberger et al. showed in a small prospective, randomised study that CECD-US significantly improves PCa detection when compared with SB [16]. Several other small, non-randomised studies using CECD-US targeted biopsy have failed to demonstrate an improvement in cancer detection rate, though the percentage of positive biopsy cores was higher for CECD-US targeted biopsy in these studies [17, 22–25]. Pelzer et al. demonstrated that a combination of both biopsy strategies on a patient-based level achieved a higher detection rate than either method separately [23]. Our study confirms the complementary nature of CECD-US targeted biopsy and SB. However, in our study, the overall detection of PCa was actually improved with CECD-US versus SB.

Table 2 Overview of cancer detection rate per person of systematic biopsy (SB) vs. CECD-US targeted biopsy with stratification by age groups, by total PSA, by prostate volume (PV) and by number of previous biopsies (using McNemar's test). Note: N is different in the groups stratified by prostate volume and number of previous biospies as not all data were available

Detection rate %				
	Systematic biopsy	Targeted biopsy	N	p value
	23.1	26.8	1,776	<0.0001
Age group	Systematic biopsy	Targeted biopsy	N	p value
≤50	9.9	11.0	282	0.439
>50≤60	17.3	20.1	591	0.041
>60≤70	26.0	30.1	635	0.010
>70	42.9	50.4	268	0.003
PSA total	Systematic biopsy	Targeted biopsy	N	p value
≤2.5	12.4	16.3	380	0.019
>2.5≤4.0	19.8	20.7	459	0.586
>4.0≤10	24.5	30.3	661	<0.0001
>10	40.2	44.2	276	0.052
PV	Systematic biopsy	Targeted biopsy	N	p value
≤20	28.7	29.5	129	1
>20≤40	23.3	27.2	859	0.002
>40≤60	25	28.8	517	0.019
>60	17.7	21.2	226	0.215
Prior biopsies	Systematic biopsy	Targeted biopsy	N	p value
1	23.7	26.9	1,015	0.005
≥2	18.8	23.7	528	0.03

Table 3 Overview of cancer detection rate with by-core analysis of systematic biopsy (SB) vs. CECD-US targeted biopsy. The analysis is stratified by age groups, by total PSA, by prostate volume (PV) and by number of previous biospies (using a GEE Poisson regression model for repeated measures). Note: N is different in the groups stratified by prostate volume and number of previous biospies as not all data were available

	Systematic biopsy			Targeted biopsy				
	+ scores	Total scores	Detection rate (%)	+ scores	Total scores	Detection rate (%)	Ratio	p value
	910	17,760	5.1	961	8,880	10.8	2.1	<0.0001
Age group	+ scores	Total scores	Detection rate (%)	+ scores	Total scores	Detection rate (%)	Ratio	p value
≤50	53	2,820	1.9	53	1,410	3.8	2	<0.0001
>50≤60	195	5,910	3.3	225	2,955	7.6	2.3	<0.0001
>60≤70	342	6,350	5.4	372	3,175	11.7	2.2	<0.0001
>70	320	2,680	11.9	311	1,340	23.2	1.9	<0.0001
PSA Total	+ scores	Total scores	Detection rate (%)	+ scores	Total scores	Detection rate (%)	Ratio	p value
≤2.5	79	3,800	2.1	109	1,900	5.7	2.8	<0.0001
>2.5≤4.0	152	4,950	3.3	163	2,295	7.1	2.1	<0.0001
>4.0≤10	338	6,610	5.1	400	3,305	12.1	2.4	<0.0001
>10	344	2,760	12.6	308	1,380	22.3	1.8	<0.0001
PV	+ scores	Total scores	Detection rate (%)	+ scores	Total scores	Detection rate (%)	Ratio	p value
≤ 20	95	1,290	7.4	77	645	11.9	1.6	<0.0001
>20≤40	449	8,590	5.2	478	4,295	11.1	2.1	<0.0001
>40≤60	285	5,170	5.5	315	2,585	12.2	2.2	<0.0001
> 60	80	2,260	3.5	96	1,130	8.5	2.4	<0.0001
Prior biopsies	+ scores	Total scores	Detection rate (%)	+ scores	Total scores	Detection rate (%)	Ratio	p value
1	557	10,150	5.5	577	5,075	11.4	2.1	<0.0001
≥2	176	5,280	3.3	245	2,640	9.3	2.8	<0.0001

Numerous factors may account for the variation in results between our study and previous studies dealing with the topic of CECD-US. First, different patient PSA inclusion criteria were used [17, 22, 23]. Second, DRE did not play a role in patient inclusion [17, 24]. Another factor may be the use of different biopsy schemes. Lastly, the various studies used different US probes and US systems, which may have different sensitivities for the detection of PCa.

Prostate volume is a confounder in the cancer detection rate of prostate biopsy [26]. In our study the detection rate of the two approaches was comparable in small and in large prostates (volume≤20 ml and >60 ml). In patients with a prostate volume between 20 and 60 ml CECD-US showed improved cancer detection. Large glands are currently a problem for diagnostic imaging, likely because the enlarged TZ compresses the PZ and interferes with imaging. We feel that prostatic enlargement is a contributing factor to explain why we missed 83 cancers with CECD-US, although our results suggest that CECD-US does provide improved detection of PCa in glands with a volume of up to 60 ml.

The Gleason score is a well-established indicator of prognostic significance in patients with PCa. Published studies suggest that the Gleason scores detected at CECD-US targeted biopsy may be higher than those detected at SB [17, 22]. In the present study, no difference in the Gleason score between CECD-US and SB was found, which might be explained by the small number of paired cases.

There are several limitations to the present study. Different US systems and US probes were used for CECD-US and SB. On CECD-US only PZ targeted biopsies were performed. Currently, CECD-US does not work well in the TZ, and TZ cancers are rare in low PSA patients. We know that the SB is not an "ideal gold standard"—though it is the method of choice for diagnosing PCa. Although we have used SB for comparison purposes, the real number of cancer negative cases cannot be assessed based on our data. PSA follow-up and PSA velocity were obtained, but these tests also fail to provide a true gold standard. Prostatitis is a common cause for false-positive findings since CECD-US techniques are not able to clearly differentiate cancer from prostatitis. New tumor-specific microbubbles may be a solution for the future. Intra- and interobserver variabilities were not studied. We did not assess the learning curve for CECD-US. Furthermore, since all patients in our study had both targeted biopsy and SB, differences in biopsy-related complications cannot be assessed. In order to test the diagnostic accuracy of the two biopsy strategies, multiple subgroup analyses of the patients with different clinical characteristics were performed. The subgroup analysis could theoretically increase the possibility of finding a falsely positive significant result [27]. Consequently, the results of these multiple comparisons should be interpreted cautiously. Although microbubble ultrasound contrast agents have a good safety profile [28], currently FDA approval exists only for cardiac US applications [25].

In conclusion, our trial of 1,776 men—the largest trial to date—demonstrates that contrast-enhanced colour Doppler ultrasound (CECD-US) targeted biopsy provides a significantly higher diagnostic yield in detecting prostate cancer (PCa) compared with systematic biopsy. As compared with saturation biopsy, CECD-US targeted biopsy should provide more cost-effective care for patients with suspected PCa.

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