The influence of prostate volume on prostate cancer detection using a combined approach of contrast-enhanced ultrasonography–targeted and systematic grey-scale biopsy

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INTRODUCTION

In 2006 an estimated 232 090 men in the USA will have a diagnosis of prostate cancer, and 30 350 are expected to die as a result of the disease. This incidence is the highest among all noncutaneous malignancies, and the death rate among men is third only to lung and colorectal cancer [1]. TRUS-guided biopsy is the standard method for diagnosing prostate cancer in patients with either elevated total (t)PSA levels or an abnormal DRE. The sextant biopsy introduced by Hodge et al. in 1989 [2] is a standard technique of TRUS-guided prostate biopsy. Limiting the number of cores to six minimizes the morbidity rate and the possibility of detecting an insignificant cancer, while maximising the detection of large tumours. However, the sensitivity of sextant biopsy might be suboptimal and it has been shown that the technique has a false-negative rate of up to 30% [2]. Of patients with a negative primary biopsy, 13–41% are diagnosed with cancer by repeated biopsy [3]. Therefore, various biopsy strategies have been devised to increase the diagnostic yield of prostate biopsy, including sampling of visually abnormal areas, more lateral placement of biopsies, anterior biopsies and obtaining more cores [4–6].

Colour Doppler ultrasonography (US) is another tool that might be used to improve biopsy performance [7]; especially when combined with a contrast-enhancing agent, Doppler US is a reliable, sensitive and noninvasive method to show tumour blood flow and therefore it has an important role in diagnostic US. Improved cancer detection with US contrast agents is related to better detection of slow flow and flow in small vessels, i.e. tumour vascularity, through a higher signal-to-noise ratio than conventional colour Doppler US. Recently it was found that contrast-enhanced (CE) colour Doppler US-targeted biopsy (CEUS) allows for the detection of lesions that cannot be found on grey-scale TRUS, and that the combined use of CEUS and systematic biopsy (SB) allows for maximum detection of prostate cancer in patients with a PSA level of 4–10 ng/mL. As prostate volume depends on age, and as the widespread use of tPSA screening leads to patients being younger at the time of prostate biopsy, accurate biopsy methods for smaller prostate glands are in use. We devised the present study to evaluate the effect of prostate volume on the cancer detection rate using CEUS-targeted biopsy and a SB approach.

Study Type – Diagnostic (non-consecutive study)
Level of Evidence 3b

OBJECTIVE

To evaluate the influence of prostate volume (PV) on the detection of prostate cancer using a combined approach of contrast-enhanced ultrasonography (CEUS) and grey-scale US-guided systematic biopsy (SB).

PATIENTS AND METHODS

We evaluated 345 patients with prostate cancer and a total prostate-specific antigen (PSA) level of ≥1.32 ng/mL (1.32–35.3, mean 6.6). Biopsies were taken by two independent examiners; one took five CEUS (Doppler) targeted biopsies of hypervascular regions in the peripheral zone, and subsequently the other took 10 systematic prostate biopsies. We assessed the cancer detection rates for the five different subgroups of prostate volumes, i.e. <20, 20–30, 30–40, 40–50 and >50 mL.

RESULTS

Each technique, SB and CEUS, detected 73.4% and 77.1% of all detected cancers, respectively, but there were statistically significant differences in detection rate only in small glands. Only 69.0% and 70.4% of all cancers were detected by SB in glands of <20 and 20–30 mL, respectively, whereas 88.1% and 80.8% were detected by CEUS.

CONCLUSION

The prostate cancer detection rate for CEUS was significantly higher in prostates of <30 mL (48.1% of the study population) than for SB. Therefore the combined approach of CEUS and SB allows improved cancer detection in patients with small glands and low total PSA values.

KEYWORDS

biopsy, colour Doppler, contrast media, prostate cancer, prostate volume, ultrasonography
PATIENTS AND METHODS

We examined 345 consecutive asymptomatic screening volunteers with a tPSA of ≥1.32 ng/mL; a DRE was not part of the screening process, but it was used directly before biopsy. Study exclusion criteria were clinical prostatitis within 1 month of biopsy, active UTI or contraindications to the US contrast agent. The night before biopsy all participants began a 5-day course of a fluoroquinolone antibiotic or 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 5 days before biopsy.

Both the CEUS-targeted and the SB were taken using needle guidance. Five targeted biopsy cores were obtained during an i.v. injection with the US contrast agent (SonoVue,Bracco, Milano, Italy), which amplifies the colour Doppler signal up to 25 dB [8]. The contrast agent was prepared in a standard fashion and administered to a maximum dosage of 4.8 mL. Colour Doppler system pre-sets were optimized based on previous experience to detect CE flow; CEUS was always done before SB to avoid biopsy-induced hyperaemia on the CEUS study. CEUS biopsies were taken in standard spatial distribution in a maximum of two hypervascular areas in the peripheral zone only. No targeted biopsies were taken in the transition zone (TZ). For this biopsy approach we used an endfire probe (Sequoia, ed5 probe, 9 MHz, Acuson, Siemens Medical Solutions USA, Inc., Malvern, PA, USA) which enables a single-plane approach.

Subsequently another investigator unaware of the findings on CEUS took 10 SBs in a standard spatial distribution, guided by grey-scale TRUS using a Hawk unit (Brue & Kjaer, Copenhagen, Denmark) fitted with a biplanar probe operating at a grey-scale frequency of 7.5 MHz. Biopsies were obtained with no regard to the appearance of the prostate on US. Two biopsy cores were obtained per side from the apex area, including one medial and one lateral. Another biopsy core was obtained on each side from the lateral aspect of the mid prostate, one was obtained on each side from the posterolateral area at the base, probably in the central zone, and a final biopsy core was obtained from each side of the TZ. The TZ biopsies were anterior biopsies in the mid prostate [9]. 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, prostatic intraepithelial neoplasia, inflammation or benign prostatic tissue.

For statistical analyses, McNemar’s chi-square test was used with P < 0.05 considered to indicate statistical significance; we assessed cancer detection rates for the different five subgroups of prostate volume, i.e. <20, 20–30, 30–40, 40–50 and >50 mL.

RESULTS

The study population comprised 354 men with prostate cancer, with a mean (range) age of 62.2 (41–75) years, a mean tPSA level of 6.9 (1.32–43.4) ng/mL, a mean free-to-total PSA ratio of 13.6 (5.9–58.2)% and a mean prostate volume of 35.4 (15–130) mL. Based on those prostate cancers detected by biopsy using either technique, the sensitivity for cancer detection was 77.1% (267 of 345) for CEUS biopsy and 73.4% (252 of 345) for SB.

When assessing various subgroups there were differences in cancer detection rates according to prostate volume. In smaller glands CEUS seemed to be better than SB (Table 1); 69.0% and 88.1% of cancers were detected by SB and CEUS, respectively, in prostates of <20 mL. The results were similar in prostates of 20–30 mL (70.4% by SB, 80.8% by CEUS), but there were no statistically significant differences in the detection rate for larger prostates.

Cancer detected in the various subgroups of prostate volume did not differ in Gleason score (6.3–6.6), but patients with cancer detected in small glands had lower tPSA levels (Table 1). Furthermore, patients with cancer detected in smaller glands were younger than those who had a larger prostate (60.9 and 66.6 years in patients with glands of 20–30 and >50 mL, respectively).

DISCUSSION

There are several studies reporting the effect of prostate volume on cancer detection, but the role of prostate volume in guiding the prostate biopsy technique remains a controversial issue. When considering the likelihood of detecting prostate cancer in glands of various sizes using a limited number of random core biopsies, several factors must be considered, e.g. the prevalence of cancer in prostates of different sizes, tumour volume, distribution of the lesion or lesions, and the overall size of the biopsy specimen in relation to that of the gland. Given that sextant SBs can only sample ≈90 mm of prostate tissue (6 × 15 mm cores), a larger prostatic volume might significantly reduce the ability to detect

| TABLE 1 The patient characteristics and cancer detection rates by SB and CEUS according to prostate volume; differences were considered statistically significant at *P < 0.05 (McNemar’s chi-square test) |
|---|---|---|---|---|---|
| Prostate volume, mL | Mean (range) | Detection rate, % |
| age, years | volume, mL | tPSA, ng/mL | Gleason score | SB | CEUS |
| <20 | 42 | 57.5 | 18.1 | 4.3 (1.3–18) | 6.3 | 69.0* | 88.1* |
| 20–30 | 125 | 60.9 | 26.2 | 6.6 (1.5–43.4) | 6.5 | 70.4* | 80.8* |
| 30–40 | 90 | 62.3 | 35.3 | 6.7 (1.8–29.5) | 6.3 | 75.6 | 73.3 |
| 40–50 | 44 | 65.8 | 44.9 | 8.1 (1.8–35.3) | 6.6 | 79.5 | 79.5 |
| >50 | 44 | 66.6 | 69.8 | 9.5 (1.8–41.2) | 6.3 | 72.7 | 63.6 |
| Overall | 345 | 62.2 | 35.4 | 6.9 (1.3–43.4) | 6.4 | 73.4 | 77.1 |

| TABLE 2 The characteristics of cancers detected either by SB or CEUS or both |
|---|---|---|---|---|
| Mean variable | SB | CEUS | Both |
| tPSA, ng/mL | 7.3 | 7.5 | 8.5 |
| Prostate volume, mL | 34.8 | 35.1 | 33.7 |
| Age, years | 62.6 | 62.8 | 63.7 |
| Gleason score | 6.5 | 6.5 | 6.1 |

(Tables 1 and 2). There was no statistically significant difference in overall cancer detection rate between CEUS-guided and SB; the characteristics of each group of cancers detected either by SB or CEUS are shown in Table 2.

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cancer [10–12]. Hence, in smaller glands the sextant prostate biopsy provides a more extensive sampling than in large prostates [13,14]. Several groups have proposed new biopsy strategies in which more cores are taken and more biopsies taken more laterally. However there is no consensus on the real advantage of these new techniques [4,6,15,16]. Recently the influence of the total and TZ prostate volumes on cancer detection was analysed. In a prospective study, Djian et al. [17] prospectively analysed 1018 men using two successive sets of sextant biopsies plus two TZ biopsies. In patients with a total prostate volume of >45 mL and TZ of >22.5 mL, a single set of sextant biopsies was insufficient to exclude cancer and a repeat biopsy was to be considered if the first biopsy was negative. Pelzer et al. [18] concluded that cancer detection by TZ biopsies did not improve, even in patients with a re-biopsy, and there was no correlation between the detection of TZ cancers and prostate volume. However, the question of optimal biopsy sites and number of cores (independent of prostate volume) remains unanswered. To improve further the detection of cancer and limit the number of biopsy cores per patient, microbubble agents were introduced to optimize the diagnostic value of colour Doppler TRUS; conventional colour Doppler US cannot detect flow in a small vessel of <50 µm, as found in the neovasculature of tumours, because of the limited spatial resolution of US equipment and the slow flow in these vessels. However, intravascular US contrast agents can enhance the backscattered echo from blood flow in small vessels [19]. These agents provide clear enhancement of the Doppler signal from human prostate. In the present series CEUS was used in hypervascular areas in the peripheral zone only. No targeted biopsies were taken in the TZ because the changes of BPH often show hypervascularity, which cannot be differentiated from the hypervascularity caused by malignant tissue. In this series cancer was detected in 345 patients; 77.1% of the cancers were detected by CEUS and 73.4% by SB, but differences in detection by either technique were only statistically significant in small glands, i.e. in those <30 mL CEUS was better than SB. Of all cancers in the subgroup of glands of 20–30 mL, 80.8% were detected by CEUS, while only 70.4% were detected by SB.

One important issue in the present study is the way the biopsies were taken; we used 10 SB and five CEUS biopsies, a completely different study design from that comparing 10 and 15 cores. The reason behind this was that in ~80% of men the five CEUS-targeted biopsies were taken in one hypervascular area of the PZ only. In a previous study we showed that multiple cores from one hypervascular area had a higher chance of detecting cancer than had fewer cores from one hypervascular area. Furthermore, since we introduced the ‘Tyrol early-detection programme’, most of our patients with prostate cancer had had only one hypervascular area. Several hypervascular areas are more likely to be associated with prostatitis in our population [20]. The increase in cancer detection rate is mainly related to the use of CEUS, which can detect areas that cannot be seen on greyscale TRUS and are often not included in the SB approach.

The limitations of the present study include different US systems and US probes; thus we cannot definitely exclude that there is an overlap between SB and CEUS biopsies. One advantage of the Bruel and Kjaer probe is that it allows a simultaneous display of both the transverse and sagittal plane; this seems to be helpful in guiding the SB, whereas for CEUS we used a single-plane probe only. Furthermore, the sagittal approach provides better core specimens than a transverse biopsy approach, which was used for the CEUS. The resolution of the endfire probe (Acuson) is higher than the biplanar probe (B&K; 9 vs 7.5 MHz).

In conclusion, the prostate cancer detection rate for CEUS was significantly higher in glands of <30 mL (48.1% of the study population) than for SB. Since the introduction of early detection programmes for prostate cancer results in the biopsy of smaller glands, the combined approach of CEUS and SB allows better cancer detection in patients with small prostates and low tPSA values.  

CONFLICT OF INTEREST

None declared.

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Abbreviations: tPSA, total PSA; (CE)US, (contrast-enhanced) ultrasonography; SB, systematic biopsy; TZ, transition zone.