

Three-dimensional contrast-enhanced power Doppler ultrasonography and conventional examination methods: the value of diagnostic predictors of prostate cancer

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Objective To investigate the value of three-dimensional contrast-enhanced power Doppler ultrasonography (3D-CE-PDU) in the diagnosis of prostate cancer and to compare 3D-CE-PDU with digital rectal examination (DRE), prostate-specific antigen (PSA) levels, grey-scale ultrasonography (GSU) and PDU.

Patients and methods The study comprised 30 patients with localized prostate cancer scheduled to undergo radical prostatectomy and 29 with clinical BPH scheduled to undergo transurethral microwave thermotherapy. The 3D-CE-PDU examinations were carried out using 2.5 g of microbubble ultrasound contrast medium; the images were stored digitally to allow off-line analysis. All the reconstructed 3D images of the prostate were evaluated blindly in random order by two investigators (one expert and one novice). The images were scored according to asymmetry (0–2) and vessel distribution (0–3). Marked asymmetry (2) and/or a focal increase in vascularity (>2) were considered as suspicious for prostate malignancy. Diagnostic predictions using the DRE, PSA level, GSU, PDU, 3D-CE-PDU and their

combinations were investigated using receiver operating characteristic (ROC) curves.

Results True-positive and true-negative rates of the 3D-CE-PDU were 87% (26/30) and 79% (23/29), respectively, for the expert observer. The sensitivity of 3D-CE-PDU was higher than that of DRE, GSU and PDU, but not PSA level, and the specificity was lower, again except for PSA level. However, when compared with those of the other modalities in single-test evaluations, 3D-CE-PDU, and a combination of 3D-CE-PDU and PSA level, had the largest area under the ROC curve (0.830 and 0.933, respectively). The diagnostic agreement between the examiners was 76% (Cohen kappa statistic, 0.5).

Conclusion In this selected group of patients, 3D-CE-PDU alone was a better diagnostic tool than the DRE, PSA level, GSU or PDU alone. The most suitable diagnostic predictor for prostate cancer was a combination of 3D-CE-PDU and PSA level.

Keywords Three-dimensional ultrasonography, contrast-enhanced, power Doppler, diagnosis, prostate pathology

Introduction

Prostate cancer is the most common malignancy in American men, excluding superficial skin cancer [1]. The increase in incidence rates of prostate cancer, particularly in developed countries, has been related to improvements in diagnostic tests, increasing life expectancy and environmental carcinogens [1,2]. Because a DRE is not specific nor sensitive enough to detect prostate cancer, and is unlikely to be improved, many of the studies on the early detection of prostate cancer have focused on further improvement of the two main diagnostic tools, PSA and TRUS.

Although PSA is undeniably the dominant test in evaluating prostate cancer, it is not a cancer-specific marker. Trials have been conducted to increase the diagnostic value of PSA by using PSA-related variations, e.g. PSA velocity, PSA density, PSA transition zone density, age-specific PSA level, and free/total PSA ratio [3,4]. However, even if these studies yield important results, PSA values only give limited information on the extent of prostate cancer and aggressiveness, but not on location. Imaging modalities should be improved to contribute to a more accurate and complete diagnosis of prostate cancer [5].

The traditional imaging method for prostate cancer is grey-scale ultrasonography (GSU). This technique has some disadvantages, e.g. the dependency on transducer

specifications, user experience and visual perception. The size, location and echo texture of the lesion can also influence the result [5]. For this imaging method, the false-positive rates are 40–94% and false-negative rates 7–23% [6–8]. New techniques have been developed to improve GSU, e.g. computer-assisted analysis, three-dimensional (3D) ultrasonography and contrast-enhanced GSU [9–11]. None of these techniques have completely eliminated the need to seek further improvement in imaging techniques; one such is colour Doppler ultrasonography (CDU) and its modifications. Many studies have evaluated the effectiveness of CDU in the diagnosis of prostate cancer. Lavoipierre *et al.* [12] stated that CDU should be a part of the evaluation of the prostate, because 16% of patients with cancer would otherwise be missed. Several studies have reported that CDU is not clearly better than GSU, although some predictive diagnostic values of CDU are higher than those of GSU [8,13].

The disappointing results of CDU may be explained by the inability to determine the vascularity of the prostate, because of small blood vessels or the low and slow flow in these vessels [5]. Although the prostate is not considered to be a highly vascular organ, improved imaging of prostate cancer is focused on detecting the vascularity of the prostate [5]. Power Doppler ultrasonography (PDU) has been introduced to improve Doppler imaging; PDU is more sensitive at detecting low and slow flow [14–16]. Microbubble ultrasound contrast media may be used to improve the acoustic properties of blood flow and thus enhance the visibility of flow with Doppler methods. The use of contrast-enhanced PDU has been the subject of several studies of prostate vascularity [8,17].

Although unimpressive, some studies showed an increased diagnostic value for PDU and CDU, and of contrast-enhanced CDU [16,17]. Whether 3D image technology can be of additional value in comparing PDU and contrast-enhanced PDU has also been investigated [8,18]. In the first such study, 3D contrast-enhanced PDU (3D-CE-PDU) was a better imaging method than the others [8]. In the present study we assessed the importance of 3D-CE-PDU in diagnosing prostate cancer, compared the diagnostic predictors of 3D-CE-PDU with those of PSA level, DRE, GSU and PDU, and discuss the implications in prostate cancer assessment.

Patients and methods

The study comprised 30 patients with localized prostate cancer scheduled to undergo radical prostatectomy, and 29 patients with BPH scheduled to undergo transurethral microwave thermotherapy (TUMT). All evaluations, including the DRE, PSA test, GSU, PDU and 3D-CE-PDU, were carried out before both treatments. The PSA

level was considered abnormal if >4.0 ng/mL (Tandem-R-assay, Hybritech Corp., San Diego, CA, USA). Abnormalities either on DRE, GSU or an elevated PSA level (>4.0 ng/mL) were indications for taking prostate biopsies to evaluate possible prostate cancer.

3D-CE-PDU was carried out using 2.5 g of Levovist microbubble ultrasound contrast agent (Schering AG, Berlin, Germany) in a 7 mL solution administered via an antecubital vein of the right arm, using an 18 G intravenous cannula (Venflon 2, Ohmeda AB, Helsingborg, Sweden). Immediately after administering the contrast agent, 10 mL of 0.9% sodium chloride solution was injected to clear the intravenous cannula.

All ultrasonography was conducted using a Kretz Voluson 530D ultrasound scanner (Kretz Technik AG, Zipf, Austria) with a 3D S-VDW 5–8 MHz end-fire probe. The mechanical probe can scan a 3D volume at an angle of 95° , enabling the examiner to image the prostate from apex to base in one 3D volume scan. A baseline 3D grey-scale, 3D PDU and contrast-enhanced 3D PDU scan were taken 1 min after injecting the contrast agent. The 3D scans were stored digitally in the Kretz system to allow off-line analysis (Fig. 1). Vascular images were retrospectively evaluated in random order by an expert (J.P.M.S.) and by D.U. (a novice ultrasonographer), both unaware of the values of the other clinical variables. Marked asymmetry and/or a focal increase in vascularity were considered as suspicious for prostate cancer.

The diagnostic predictors (DRE, PSA, GSU, PDU and 3D-CE-PDU) and their combinations were evaluated using ROC curves, obtained by plotting sensitivity against 1 – specificity, and the values of the area under the ROC curve (AUC) calculated. From the AUC the diagnostic value of a test or combination was graded worst (0) to best (1) [19]. Inter-observer variation was assessed using Cohen's kappa statistic and the other analyses conducted using standard methods.

Results

The patients with prostate cancer treated with radical prostatectomy were younger than those with BPH treated with TUMT. The PSA level was significantly higher but prostate volume lower in men with prostate cancer than in those with BPH (Table 1). The relationship between PSA level and age for each diagnosis is shown in Fig. 2.

For the diagnosis, PSA level had the highest sensitivity (100%, 30 men), but the lowest specificity (66%, nine men) compared with the other methods. Of 30 patients with prostate cancer, 26 (87%) were correctly diagnosed using 3D-CE-PDU, 23 (77%) with PDU, 21 (70%) with GSU, and 17 (57%) with a DRE. Of 29 patients with BPH, 23 (79%) were correctly diagnosed using 3D-CE-PDU, 25

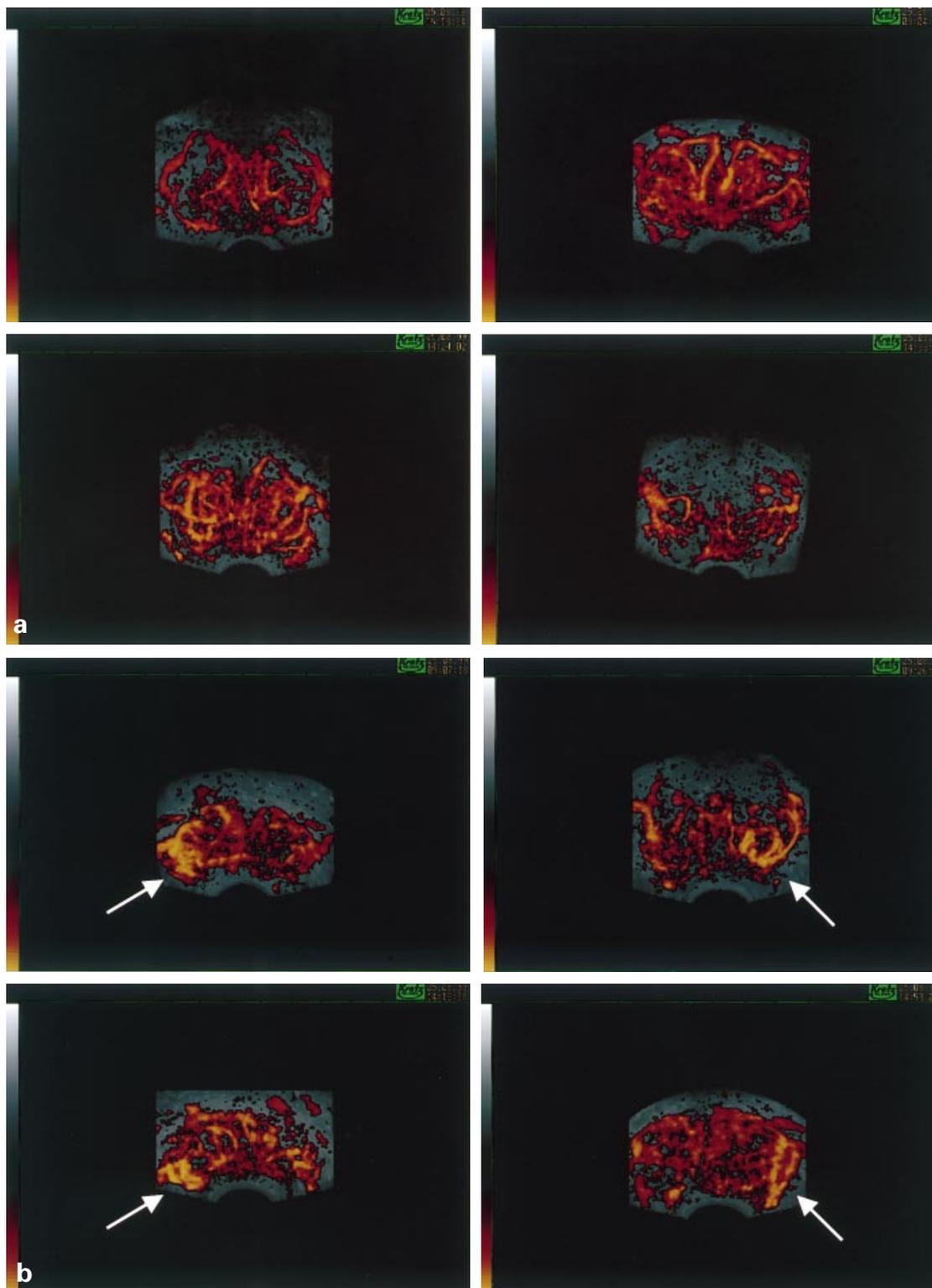


Fig. 1. Four examples of 3D-CE-PDU investigations in patients with (A) clinical BPH and scheduled to undergo TUMT, and (B) prostate cancer and scheduled to undergo radical retropubic prostatectomy. In (A) the vascularity is symmetrically distributed over the whole prostate. The capsular and peri-urethral blood vessels are clearly distinguishable. In (B) all four images show the asymmetrical distribution of blood vessels. The white arrow indicates a lesion with a focal increase of blood vessels. All four lesions were confirmed to be prostate cancer after radical prostatectomy.

Table 1 The characteristics of the patients with BPH and prostate cancer

Characteristic mean (range)	BPH	Prostate cancer	P*
Age	66.7 (49–82)	63.1 (47–72)	0.036
PSA (ng/mL)	7.1 (0.9–63.6)	13 (4.9–62)	0.031
Prostate volume (mL)	54.4 (20–131)	37.4 (11–80)	0.010

*Student's *t*-test.

(86%) using PDU, 26 (90%) using GSU and 26 (90%) using DRE. (Table 2).

Of 13 men with prostate cancer, a normal DRE and an abnormal PSA level, 12 were accurately diagnosed using at least one of the imaging methods. Of seven men with prostate cancer, a normal DRE and GSU, and an abnormal PSA level, six were evaluated as abnormal with one of the PDU methods (PDU and/or 3D-CE-PDU). Of four men with cancer, a normal DRE, GSU and PDU, and elevated PSA level, three were identified as having prostate cancer with 3D-CE-PDU. However, in three men with prostate cancer, 3D-CE-PDU showed no abnormality despite abnormal results from the DRE, PSA level, GSU and PDU. In one man with BPH and an abnormal DRE, PSA level, GSU and PDU, only 3D-CE-PDU showed the prostate to be benign. However, in four men with BPH, 3D-CE-PDU was the only abnormal indicator and BPH could not be diagnosed using 3D-CE-PDU alone.

In single-test evaluations the most favourable AUC value was that from 3D-CE-PDU; the greatest AUC was that produced by combining 3D-CE-PDU and PSA level (0.933) (Table 2). For combinations of 3D-CE-PDU with other imaging methods, the largest AUC was that with GSU (0.845; Table 2). However, the 95% CI of the AUC values of the all these tests and combinations overlapped (Table 2). The interobserver variability was also calculated; there was agreement between the examiners in 76% of men (Cohen kappa statistic, 0.5; Table 2).

Discussion

The limitations of the diagnostic tools currently used to detect prostate cancer (PSA, DRE and TRUS) have been assessed in many recent studies. Because these methods are unsatisfactory, efforts to improve the early diagnosis of prostate cancer continue. Although PSA, DRE and TRUS lack the diagnostic power to serve as stand-alone tests, their combination remains the 'diagnostic triad' currently used to evaluate prostatic disease. When evaluating a new diagnostic tool, it is therefore justified to compare the capability of such a test with the individual and combined results of the diagnostic triad.

In the present study the DRE had a high specificity

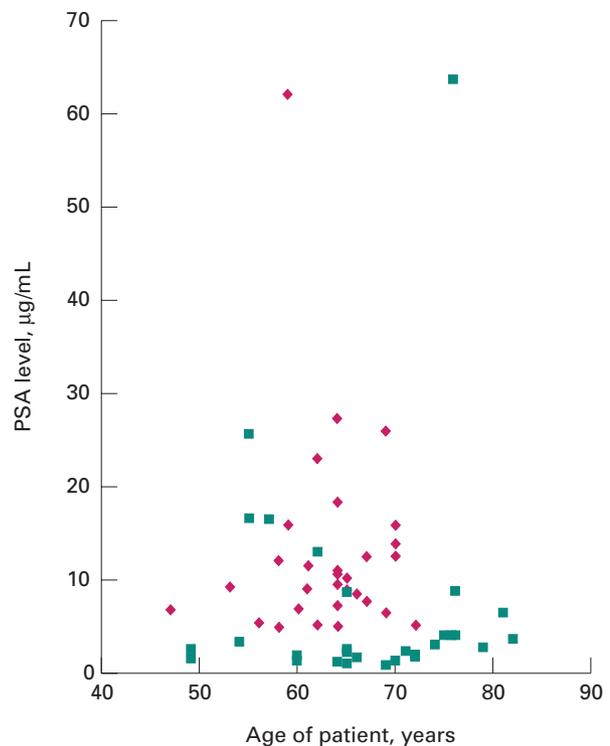


Fig. 2. The relationship between PSA level and patient age, according to diagnosis (BPH, green; prostate cancer, red).

(90%), i.e. only a few men were falsely classified as having cancer. However, the DRE had a disappointing sensitivity (57%), resulting in a relatively high false-negative rate. Thus the DRE is insufficient when used alone for detecting prostate cancer, and is therefore an inadequate method for prostate cancer screening.

To improve the detection rate of prostate cancer, the DRE should be followed by a test with high sensitivity. PSA testing provides such a method, being very sensitive; using the standard threshold of 4 ng/mL, none of the men with prostate cancer were falsely classified as having benign disease. However, the specificity of PSA is low, and it has been reported that PSA in general has higher false-positive rates (73–86%) than false-negative rates (4–9%) [5,13,20]. These results qualify PSA as a screening variable and the introduction of PSA has apparently resulted in an increase in the number of prostate cancers detected. However, screening with PSA is associated with many false-positive diagnoses, because it has low specificity. In addition, PSA cannot provide information on the possible location of a suspected tumour. The limited specificity and lack of spatial information provided by PSA necessitates adding imaging tools to diagnostic testing.

Ultrasonography is the method of choice because it is versatile, used in 'real time', and is readily available. However, reports on the current status of ultrasonogra-

Table 2 Diagnostic predictors of 3D-CE-PDU and the other examinations and combinations used in diagnosing prostate cancer

Method or combination	Diagnostic predictors (%)					
	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC (95%CI)
DRE	57	90	85	67	73	0.732 (0.600–0.863)
PSA	100	66	79	100	86	0.828 (0.715–0.941)
GSU	70	90	88	74	80	0.798 (0.679–0.917)
PDU	77	86	85	78	81	0.814 (0.699–0.930)
3D-CE-PDU	87	79	81	85	83	0.830 (0.718–0.942)
3D-CE-PDU:						
and DRE	47	97	93	64	71	0.716 (0.583–0.849)
and/or DRE	97	72	78	95	85	0.845 (0.737–0.953)
and PSA	87	100	100	88	93	0.933 (0.860–1.007)
and/or PSA	100	52	68	100	76	0.759 (0.631–0.887)
and DRE and PSA	47	100	100	64	73	0.733 (0.603–0.864)
and/or DRE and/or PSA	100	45	65	100	73	0.724 (0.591–0.858)
and GSU	60	97	95	70	78	0.783 (0.661–0.905)
and/or GSU	97	72	78	95	85	0.845 (0.737–0.953)
and PDU	67	97	95	74	81	0.816 (0.702–0.931)
and/or PDU	97	69	76	95	83	0.828 (0.715–0.941)
and GSU and PDU	50	97	94	65	73	0.733 (0.602–0.864)
and/or GSU and/or PDU	97	66	74	95	81	0.811 (0.694–0.928)
Observer 1 (expert)	87	79	81	85	83	0.830 (0.718–0.942)
Observer 2 (novice)	77	76	79	73	76	0.763 (0.636–0.889)

PPV, positive predictive value; NPV, negative predictive value.

phy in evaluating prostate disease shows the limitations of standard GSU. The detection of prostate cancer relies mainly on the identification of hypoechoic lesions, especially when compared with surrounding tissue. However, not all hypoechoic lesions seen on GSU represent prostate cancer, and not all prostate cancers present as hypoechoic lesions [6–8,21]. Thus despite developments in GSU, this technology has arguably reached its limit for technical improvements and user experience in prostate cancer detection. This is also shown by the results of the present study in a selected group of patients; the diagnostic accuracy of GSU was 80%, which is lower than all other single tests except (surprisingly) the DRE.

There is renewed interest in Doppler ultrasonography of the prostate because of the developments in 3D techniques and the availability of contrast agents. Although initial results for normal Doppler ultrasonography of the prostate suggested limited advantages over GSU, early reports on contrast-enhanced Doppler for differential diagnosis showed encouraging results [8,12,22]. The first study to combine contrast-enhanced Doppler and 3D ultrasonography showed increased diagnostic accuracy in a few patients who underwent biopsy for suspected prostate cancer [8]. These results formed the basis for the present study.

The final diagnosis for the two groups of patients compared in the present study was obtained from the histology of the prostate as the 'gold standard'.

However, not every patient with clinical BPH had biopsies taken to exclude prostate cancer. The evaluation for TUMT in these patients included a DRE, PSA level and TRUS. Biopsies were only taken in those with suspected prostate cancer, either because of an abnormal DRE and/or TRUS, or an elevated PSA level (>4.0 ng/mL). Although no abnormalities were found in this evaluation, it cannot be guaranteed that no patient with clinical BPH had prostate cancer, although the chance of malignancy with a normal evaluation is very small.

The results indicated that the sensitivity of 3D-CE-PDU was higher than the sensitivity of all other single tests except for PSA level. Furthermore, 3D-CE-PDU had a higher AUC than the DRE, PSA level, GSU and PDU, combining the sensitivity and specificity of the individual tests. The 3D-CE-PDU could also be regarded as an objective test because of the good agreement between the expert and novice observer.

When combining single tests to predict the final diagnosis, PSA and 3D-CE-PDU provided the highest diagnostic accuracy. This is important, as this combination produced the optimal specificity of 100%. Because of the high sensitivity of PSA, the diagnostic accuracy of the combination was very good in this selected group of patients. We acknowledge that the present patients do not reflect the population of patients seen in the urology clinic; thus it is not appropriate to transfer the results to other groups. Of

special interest would be the group of patients with an intermediate PSA level and no abnormalities on DRE, GSU or unenhanced PDU.

The present results rely on the observation of asymmetry and/or a focal increase in Doppler signals in the 3D prostatic blood flow images. The study is based on the assumption that prostate cancer can cause angiogenesis, to allow autonomous growth of the tumour. This assumption has been evaluated in studies of microvessel density, by counting the number of vessels in pathology images and by determining other characteristics of the observed vessels [23–25]. The present study evaluated whether this increased vessel density could also be detected in images of the prostate using 3D-CE-PDU. The encouraging results provide the foundation for a study comparing the results from Doppler images and the microvessel density in pathology specimens. Such a study is currently underway in our clinic; the outcome of this study should establish the real clinical value of these imaging techniques. If it is possible to retrieve similar diagnostic information from Doppler imaging and pathology, a less invasive and more practical method would be available for urologists to obtain important diagnostic and prognostic information in confirmed prostate cancer. If the reliability of obtaining diagnostic and prognostic information is confirmed, the most appropriate application of these techniques should be established. Of special interest are those patients with a PSA level in the intermediate range and with no abnormalities identified by DRE and GSU. Using 3D-CE-PDU for guiding biopsy to the appropriate lesion and comparing the result with standard sextant biopsy, the additional clinical value of this technique could be assessed, and whether it is cost-effective to use this sophisticated but more expensive method.

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