UIJ UroToday International Journal®

www.urotodayinternationaljournal.com
Volume 2 - April 2009

Successful Early Prostate Cancer Screening by Three-Dimensional Color Doppler Imaging-Transrectal Ultrasound: A Prospective Study

Walter Merkle
Dept. of Urology, German Diagnostic Clinic, Wiesbaden, Hessen, Germany
Submitted on January 14, 2009 - Accepted for Publication on February 2, 2009

ABSTRACT

INTRODUCTION: Prostate-specific antigen (PSA) screening has been used successfully for the early detection of prostate cancer, but it does not localize the cancer area inside the prostatic gland. Conventional transrectal ultrasound imaging can be used for positioning of the biopsy needle. However, proper targeting is almost impossible when cancers are small. Therefore, overlooked cancer or over-biopsy is a permanent risk. Biplane color Doppler imaging (CDI), a technique that is currently emerging due to improvements in cancer detection, cannot be used to differentiate between different types of hypervascularized lesions such as prostatitis or cancer. Three dimensional (3D) CDI transrectal ultrasound (TRUS) was developed to solve many of these problems.

METHODS: In a prospective and histologically verified study, 418 patients with slightly elevated range of PSA-levels and/or hereditary risk for prostate cancer were screened by 3D CDI-TRUS. Patients were then classified into *benign* or *malignant* according to ultrasound criteria and afterwards biopsied.

RESULTS: 3D CDI-TRUS was used to diagnose these patients correctly, with a sensitivity of 0.82 and good specificity (0.91).

CONCLUSION: 3D CDI-TRUS may be used for prostate cancer screening while reducing unnecessary biopsies in men with elevated PSA levels.

KEYWORDS: Prostate cancer screening, Prostate cancer detection, Transrectal ultrasound, Three dimensional transrectal ultrasound, Prostate biopsy

CORRESPONDENCE: Walter Merkle, M.D., Dept. of Urology, German Diagnostic Clinic, Aukammallee 33, Wiesbaden, Hessen, Germany 65191. merkle.uro@dkd-wiesbaden.de

INTRODUCTION

Prostate cancer is responsible for the second most cancer deaths in men and an increase is expected [1]. Therefore, many efforts are undertaken regarding screening [2]. The detection of PSA as a tumor marker made the screening process easier, but unfortunately led to many unnecessary biopsies on the grounds of the increased serum levels of this marker [3-5]. Although sensitivity is high, specificity is limited. Additional screening by digital rectal examination improves specificity [6,7]. However, too many false positive PSA levels remain, leading to unnecessary biopsies.

doi:10.3834/uij.1944-5784.2009.04.08
http://www.urotodayinternationaljournal.com
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

Transrectal ultrasound (TRUS), the third examination technique for prostate cancer screening, also has sensitivity and specificity that are too limited to make it a reliable technique [7,8]. Therefore, currently TRUS is only useful for biopsy. There is only limited improvement in using the grey-scale 3D-TRUS technique [9].

Parallel to the present study, many investigations were performed with biplane Doppler analysis in transrectal ultrasound. The Doppler analysis improved sensitivity but still remains problematic in clearly addressing hypervascularized areas as cancer [10-12]. On the other hand, color Doppler-guided biopsy was superior to the conventional biopsy technique [13-15].

The aim of the present study was to find a technique with sufficiently high sensitivity and specificity in prostate cancer screening that it would not overlook cancer of the prostate or over-biopsy patients.

METHODS

The author first focused upon the ultrasound technique of transrectal color Doppler imaging (CDI) [10,11,15,16-18]. Sensitivity and specificity improved from the biplane technique, yet still had limitations for clinical purposes. The main problem is that a biplane image might show pathological vascular processes, but they cannot be differentiated. This may be an effect of vessel image summation (one behind the other) or hypervascularization in cancer, so biopsy remains mandatory for further diagnosis [19,20]. However, biplane CDI reduces the overall amount of biopsies [21].

A 3-dimensional (3D) analysis seems to be able to solve the structural imaging problem. Recently, 3D CDI-TRUS became available. After a first study for reproducibility of 3D-CDI-TRUS verified by histological specimen [22], the present prospective study was undertaken for screening of prostate cancer.

At present, the Voluson 730 ultrasound machine from Kretztechnik, Austria (now at GE, Chicago, IL) with RRE6-10 transrectal ultrasound head and 3D CDI software is the only device with this advanced technique. With this device men with PSA ³ 4 ng/mL or positive family history for prostate cancer and/or breast cancer and PSA ³ 3 ng/mL were screened with 3D-CDI-TRUS [23,24].

Prostate lesions were classified into malignant or benign (mostly focal prostatitis) by using criteria derived from the first study [22], as listed in Table 1.

Table 1. Ultrasound Criteria
doi: 10.3834/uij.1944-5784.2009.04.08t1

Classification	Vessel Density
Benign	Little; Similarly distributed all over prostate
Prostatitis	
General	Massively increased; Complete prostate
Focal	Focally increased; Ball Shape
Prostate Cancer	Slightly increased; Ring-formation of vessels

After this classification, patients gave formal consent and then underwent transrectal ultrasound guided biopsies. Biopsies were targeted using the suspect lesion detected through ultrasound as a guideline. Contralaterally, further biopsies were taken in additional suspicious areas if so detected, or randomized in non-suspicious areas for control. Six to 9 biopsies were taken at minimum, because targeting by CDI is more effective than with conventional TRUS [21]. After over 300 patients were tested, the biopsy protocol was modified (see Table 4) to discover how precisely 3D CDI-TRUS can predict the tumor area itself. However, the ultrasound criteria named in Table 1 was still used. All patients received ciprofloxacine prior to and after biopsy.

The pathologists were informed about which region was suspicious, based on the ultrasound criteria. After histological examinations were complete, including immunohistochemic analysis with antibody CK M 903, results were compared with the pre-biopsy ultrasound diagnosis. Cases with negative histology were followed for the next months or years. Only in exceptional cases (n = 4) was the first judgment corrected by a second ultrasound, and a second biopsy was performed. In all 4 patients the new ultrasound image showed new lesions when compared with the first examination.

RESULTS

During the last 4 years, 418 men of the author's outpatient service fulfilled the criteria of suspicious PSA level during routine screening for men over 45 years of age.

PSA levels in primary cancer patients were found between 1.4 and 20 ng/mL. The mean PSA value was 8.2 ng/mL (SD = 6.5). This level is known as the grey zone of PSA. Ratios between free and total PSA were also calculated, but this was more or less not diagnostic. There were patients with reduced ratios without cancer and with normal ratios but significant cancer.

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Figure 1. 3D CDI-TRUS: Typical Circular Vessel Formation of a Prostate Cancer. Small images show different rotation; angle of 45° between both rings, but ring remains stable.

doi: 10.3834/uij.1944-5784.2009.04.08f1

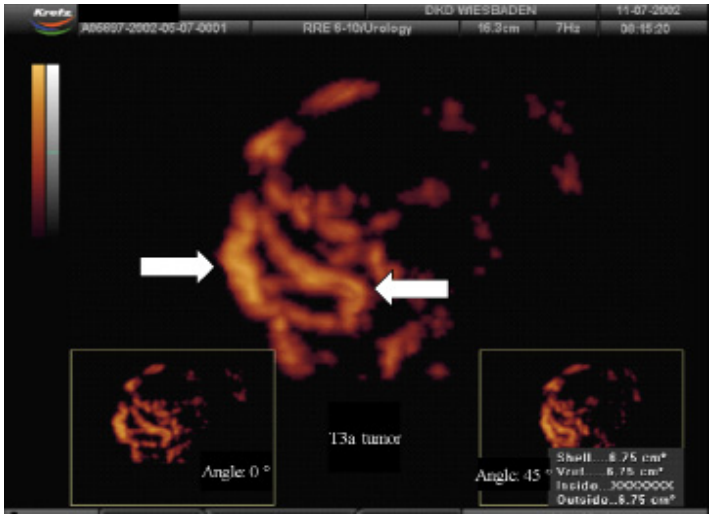
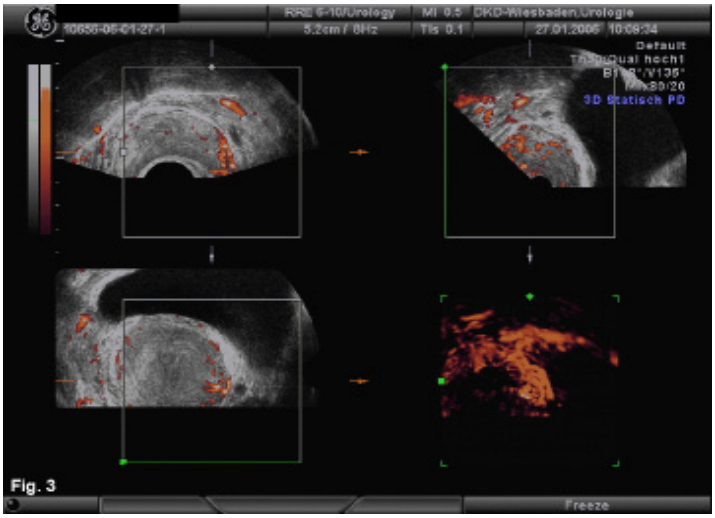


Figure 3. 3D CDI-TRUS: Typical Ball-Shaped Vessel Formation of a Focal Prostatitus

doi: 10.3834/uij.1944-5784.2009.04.08f3



Furthermore, 5 patients of this current series were positively tested with local recurrence after radical prostatectomy, with suspicious lesions in the 3D CDI-TRUS and increasing PSA between 0.3 and 0.5 ng/mL.

As shown in Figure 1, prostate cancer is characterized by circular vessel formation, which is stable in all 3 levels during virtual rotation. This relatively high circulation can be accompanied by broader vessel diameter (Figure 2) and/or faster blood flow, which is a known effect in malignant prostatic tissue [25].

Figure 2. Histological Examination: Broader Vessels in a T3a-Tumor.

doi: 10.3834/uij.1944-5784.2009.04.08f2

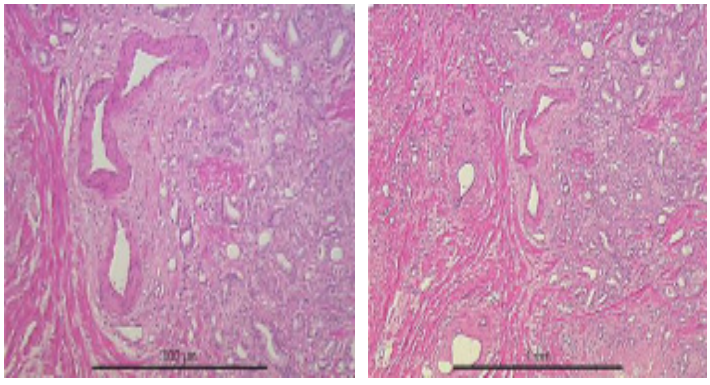


Image courtesy of C. Fellbaum, Institute of Pathology, Hegau Klinikum, Singen, Germany.

Patients with focal prostatitis (Figure 3) show denser vessel formation (ball shape).

Of the 418 men, 211 were sonographically classified as having prostate cancer and then histologically verified. One hundred sixty were classified as having benign lesions, of which 153 were also histologically verified (95.2%).

The sonographic diagnosis was corrected for being malignant in only 7 cases of the total N. Thus, the sonographic diagnosis *benign prostate enlargement* was confirmed in 91.2 % with a probability of 97.5%. The 95% confidence intervals were estimated by the exact method of Pearson-Clopper. The sensitivity of the 3D CDI-TRUS was estimated at 0.82. The statistics are shown in Tables 2 and 3. The correlations hereby are far better than in literature for conventional TRUS-techniques [10-12].

Calculating the specificity of this new method is more difficult than calculating the sensitivity, because 3D CDI-TRUS enables the user to find precursors of malignancy. Meanwhile, the shift from benign tissue with chronic inflammation over post-inflammatory atrophy to manifest cancer is well known [26-31]. Parallel to these histomorphological findings, vessel formation changes and chronic inflammations appear different from premalignant and manifest malignant tissue. However, atrophic lesions and cancer appear very similar in ultrasonographic

Table 2. Sonography Diagnosis (Dx) Compared With Histology Proof (N= 418).
doi: 10.3834/uij.1944-5784.2009.04.08t2

Comparison			
Sonography Dx	**Histology Proof**	**n**	**% N**
Benign	Benign	153	36.6
Benign	Malignant	7	1.7
Malignant	Benign	47	11.2
Malignant	Malignant	211	50.5

Table 3. Sonography Diagnosis (Dx) Compared With Histology Proof (N= 418).
doi: 10.3834/uij.1944-5784.2009.04.08t3

Measure	Value (95% Confidence Interval)*
Sensitivity	0.82
Specificity	0.91
Correlation**	0.753 (0.695-0.812)
False Negatives	1.7% (0.7-3.4)
Correct Diagnosis Benign	95.6% (91.2-98.2)
Correct Diagnosis Total	87.1% (83.5-90.1)

*95% confidence intervals were estimated using the exact method of Pearson-Clopper by M. Wibberg, Datamap, Freiburg, Germany.
**Sonographic diagnosis correlated with histological verification

morphology. Thus, for calculation of specificity, this histological shift has to be taken into account. Consequently, specificity to demonstrate tissue with malignant or premalignant tissue is estimated at 0.74.

This specificity estimation is also supported by the follow-up results, because 5 of the 82 patients with atrophic lesions developed prostate cancer (see Figures 4a, 4b and 5). The period for the evolution from atrophic lesion to cancer was approximately 3 years. This time period also gives the chance for cancer protection, which is done by 200µg of Selenium daily. The results will be presented in another paper.

After the first series with over 300 patients and similar results as presented in this paper (Table 2) a decision was made to find out whether the sonographic prediction of a tumor would be

Figure 4a. 3D CDI-TRUS: Atrophy.
doi: 10.3834/uij.1944-5784.2009.04.08f4a

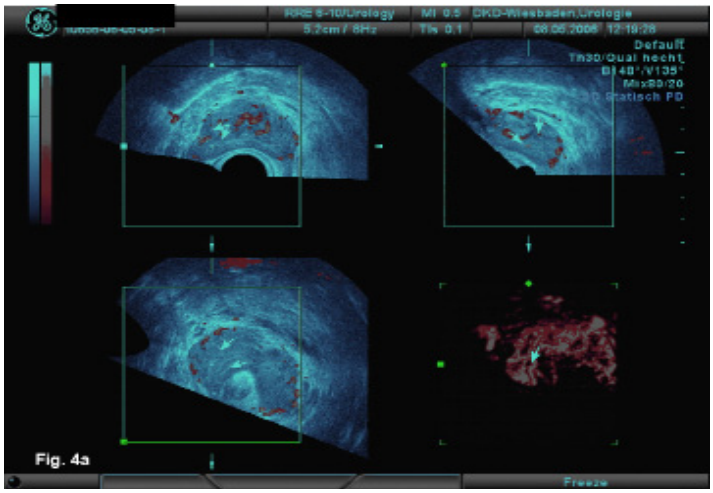


Figure 4b. Histology of Patient in Figure 4a.
doi: 10.3834/uij.1944-5784.2009.04.08f4b

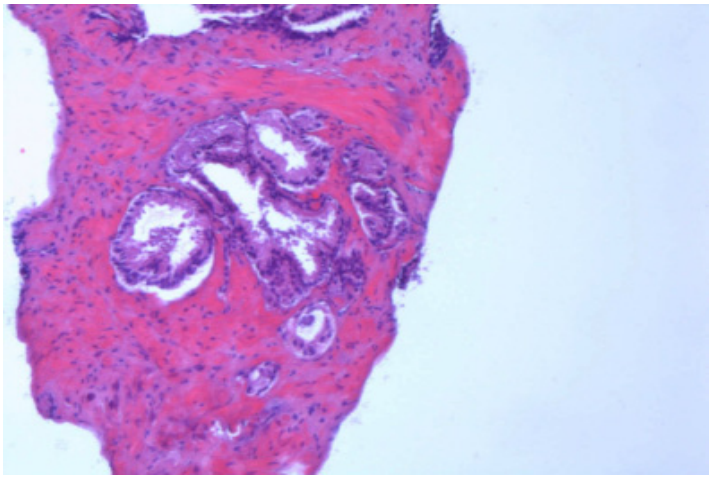


Figure 4b courtesy of A. Fisseler-Eckhoff, Institute of Pathology, Dr. Horst Schmidt-Kliniken, Wiesbaden, Germany

possible by correct indicating of the tumor itself. The biopsy protocol was changed into lesional series as marked by the ultrasound image and additionally to further random biopsies of the ipsilateral lobe and the other lobe thereafter. Thus, at minimum, 9 biopsies were taken. Table 4 shows the histology proof of sonographically predicted tumor location.

Thus, by using 3D FCDS-TRUS, the suspicious tumor inside the prostate (detected sonographically) was correctly verified by

Figure 5. Histological Examination: Prostate Cancer After Atrophy (Same Patient as in Figures 4a and 4b).
doi: 10.3834/uij.1944-5784.2009.04.08f5

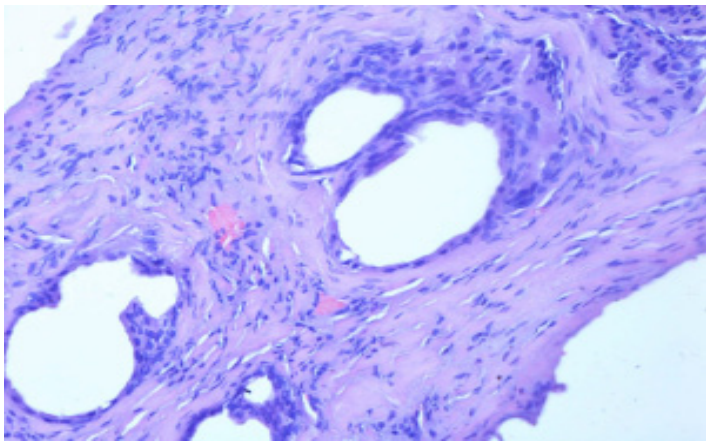


Image courtesy of A. Fisseler-Eckhoff, Institute of Pathology, Dr. Horst Schmidt-Kliniken, Wiesbaden, Germany

histology proof in 50 out of 56 cases. In 5 additional cases the cancer lobe was correctly predicted; only in 1 case was a tumor found contralaterally.

DISCUSSION

Prostate cancer screening is still a major problem in urology and a major concern, because prostate cancer is responsible for the second most cancer deaths in men [2]. Therefore, many efforts are undertaken to find a sufficient screening technique with high sensitivity and good specificity. Large parts of the AUA, EAU and DGU congresses are filled with posters and lectures on improvement of prostate cancer screening.

PSA, at present the best screening method, has good sensitivity but limited specificity. Therefore, debate still is ongoing to find the optimal cut-off value in order not to overlook cancer or over-biopsy men with elevated PSA [32]. At present, only the combination of PSA, digital rectal exam and TRUS render good sensitivity with acceptable specificity [6,7,33,34]. The remaining problem, however, is where the cancer is located inside the prostatic gland in case all diagnostic tools indicate positively. Therefore, strategies are developed for random biopsies so that the cancer is not missed [3,30,35,36]. Unfortunately, these strategies can lead to multiple biopsy protocols hardly tolerable for patients; or, the protocols have to be performed under general anesthesia thus increasing biopsy effort and risk.

Table 4. Histology Proof of Sonographically Predicted Tumor Location (n=56; N=418)
doi: 10.3834/uij.1944-5784.2009.04.08t4

Test Result	n
Tumor lesion isolated positive	25
Tumor and ipsilateral lobe positive	25
Tumor location negative; Ipsilateral lobe positive	5
Tumor lesion negative; Contralateral lobe positive	1

Consequently, a new technique should correctly indicate a suspicious area inside the prostate and enable the urologist to target it sufficiently with only a few punctures. Additionally, cost effectiveness should not be overlooked; thus the method should be possible in an outpatient service with limited costs.

Only a transrectal ultrasound technique has the potential to meet the stated criteria [14,21]. However, neither grey scale TRUS nor biplane CDI-TRUS [12,16,18,34] were able to show sufficient sensitivity, so that many cancers might elude detection. As the presented data demonstrate, 3D CDI-TRUS is the technique with sufficiently high sensitivity that cancer in the prostate is not overlooked.

As virtual post-processing is possible, irregular grey scale areas and highly vascularized areas in the CDI mode can be examined perfectly. Summation effects – circular vessels indicating cancer (see Table 1) – can be ruled out when viewed from another angle (eg, 90° from the side). From this angle, an apparent ring might be revealed as two *C-forms* of vessels, one behind the other, which is a non-suspicious vessel formation in benign prostate. However, a stable ring form clearly visible from whichever side indicates prostate cancer (see Figure 1, small images). Therefore, 3D CDI-TRUS offers the crucial technique for correct classification of suspicious areas within the prostate. Increased vascularization [25], as caused by angiogenesis of tumors (so-called feeder vessels), can also be seen in the histological specimen (Figure 2).

Second, *hot spots* not only appear as a circle but also as ball shaped. Histologically this is different, as it indicates the high blood flow of an inflammation. Thus, focal prostatitis can also be classified correctly even in cases with negative semen culture. To the author's knowledge, there is no other CDI study published showing that a transrectal ultrasound technique can be used to differentiate highly vascularized lesions in cancer and infection.

Third, because hot spots can be seen easily, transrectal ultrasound-guided biopsy is simple and shows which kind of tissue it contains without necessity of multiple blind random punctures [14,21]. Decreasing the number of punctures lowers bacterial intake, thus reducing the entire risk of prostate biopsy [37-40].

Improvement of prostate cancer detection by CDI-TRUS was also found by Strohmeyer et al. [41]. Therefore, at the beginning of this study additional random biopsies were performed not only in the contralateral prostatic lobe, but also next to the suspected lesion. Accumulated experience showed that randomized biopsies in the contralateral lobe could be conducted without change in sensitivity.

Almost no cancer was overlooked. Three of the 6 falsely classified patients were classified as atypical adenomateous hyperplasia (AAH), a possibly pre-malignant lesion [42,43], and would have been biopsied regardless. Therefore, it is more or less formalistic to count these 3 of 418 cases as overlooked cancer. In one of the remaining 3 men, cancer was found in the contralateral lobe not detected by ultrasound; in the other 2 men, cancer was found by random biopsies only. This new ultrasound technique is therefore a valuable screening instrument in cases with PSA levels in the so-called grey zone and in cases with elevated PSA levels that differentiate between benign and malignant lesions. Furthermore, Table 4 shows how precisely prostate cancer can be visualized by 3D CDI-TRUS, with 50/56 correct lesion biopsies.

The 3D CDI-TRUS technique is superior to random biopsies with 12 cores, but with much less risk of infection and bleeding (no inpatient was seen due to bleeding; one inpatient was seen for infection). Proper targeting reduces the number of blind (random) punctures and the percentage of necessary biopsies in men with elevated PSA. Consequently, future patients with benign lesions detected through ultrasonography will be spared biopsy entirely. The risk to overlook prostate cancer patients compared with the risk and the costs of routine over-biopsy can be negated.

CONCLUSION

3D CDI-TRUS is a new technique with excellent sensitivity (0.82) and specificity (0.91) for detecting prostate cancers, even if PSA levels might not be elevated or are within the grey zone. This new technique is a valuable tool in prostate cancer screening. It reduces unnecessary biopsies in men with elevated PSA levels without violating cancer detection.

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TO CITE THIS ARTICLE: Merkle W. Successful early prostate cancer screening by three-dimensional color Doppler imaging-transrectal ultrasound: a prospective study. *UIJ*. 2009 Apr;2(2). doi:10.3834/uij.1944-5784.2009.04.08