

Computerized transrectal ultrasound (C-TRUS) of the prostate: detection of cancer in patients with multiple negative systematic random biopsies

Tillmann Loch

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Abstract This study was designed to compare the diagnostic yield of computerized transrectal ultrasound (C-TRUS) guided biopsies in the detection of prostate cancer in a group of men with a history of multiple systematic random biopsies with no prior evidence of prostate cancer. The question was asked: Can we detect cancer by C-TRUS that has been overlooked by multiple systematic biopsies? The entrance criteria for this study were prior negative systematic random biopsies regardless of number of biopsy sessions or number of individual biopsy cores. Serial static TRUS images were evaluated by C-TRUS, which assessed signal information independent of visual gray scale. Five C-TRUS algorithms were utilized to evaluate the information of the ultrasound signal. Interpretation of the results were documented and the most suspicious regions marked by C-TRUS were biopsied by guiding the needle to the marked location. Five hundred and forty men were biopsied because of an elevated PSA or abnormal digital rectal exam. 132 had a history of prior negative systematic random biopsies (1–7 sessions, median: 2 and between 6 and 72 individual prostate biopsies, median: 12 cores). Additionally, a diagnostic TUR-P of the prostate with benign result was performed in four patients. The PSA ranged from 3.1–36 ng/ml with a median of 9.01 ng/ml. The prostate volume ranged from 6–203 ml with a median of 42 ml. Of the 132 patients with prior negative systematic random biopsies, cancer was found in 66 (50%) by C-TRUS targeted biopsies. In this group the median number of negative biopsy sessions was

two and a median of 12 biopsy cores were performed. From literature we would expect a cancer detection rate in this group with systematic biopsies of approximately 7%. We only found five carcinomas with a Gleason Score (GS) of 5, 25 with GS 6, 22 with GS 7, 8 with GS 8 and even 7 with GS 9. The results of this prospective clinical trial indicates that the additional use of the C-TRUS identifies clinical significant cancerous lesions that could not be visualized or detected by systematic random biopsies in a very high percentage. In addition, the results of the study support the efforts to search for strategies that utilize expertise and refinement of imaging modalities rather than elevating the number of random biopsies (f.e. 141 cores in one session) in the detection of prostate cancer.

Keywords Prostate cancer · Prostate biopsy · Computer analysis · C-TRUS

Introduction

The marker most widely used for the diagnosis of prostate cancer is prostate specific antigen (PSA). As a result of its enhanced clinical application, an increasing number of asymptomatic men have become candidates for further prostate cancer work-up. A high PSA value is a good indicator of the presence of prostate cancer. But even in patients with high PSA values in many times prostate cancer can not be identified in systematic biopsies [1–4]. In addition, in patients with a PSA under 4 ng/ml, cancers may be hidden [5].

While PSA is capable of indicating a statistical risk of prostate cancer in a defined patient population, it is not able to localize cancer within the prostate gland or guide a biopsy needle to a suspicious area. This necessitates an

T. Loch (✉)
Klinik für Urologie des Diakonissenkrankenhaus Flensburg,
Lehrkrankenhaus der Christian-Albrechts-Universität Kiel des
Universitätsklinikums Schleswig-Holstein,
Marienhoelzungsweg 2, 24939 Flensburg, Germany
e-mail: lochti@diako.de

additional effective diagnostic technique that is able to localize or rule out a malignant growth within the prostate. It has therefore become routine procedure to perform at least six systematic random biopsies of the prostate under transrectal ultrasound (TRUS) guidance in patients with a suspicious PSA [6, 7]. Some authors even recommend 10, 18, 24 or even more saturation biopsies for this random approach [8–12].

This study was designed to compare the diagnostic yield of computerized transrectal ultrasound (C-TRUS) guided biopsies in the detection of prostate cancer in a group of men with a history of multiple systematic random biopsies with no prior evidence of prostate cancer. Under a strictly limited protocol, serial static TRUS images were evaluated by C-TRUS, which assessed digital signal information independent of visual gray scale information. Interpretation of the results were documented and the most suspicious regions marked by C-TRUS were biopsied by guiding the needle to the marked location.

Materials and methods

Because of either an elevated serum prostate specific antigen (PSA) or an abnormal digital rectal examination (DRE) 540 men were biopsied. The entrance criteria for this study were prior negative systematic random biopsies regardless of number of biopsy sessions or number of individual biopsy cores.

Transrectal ultrasound imaging was performed with a B-K model #2102 ultrasound instrument (B-K Medical) utilizing a 7.5 (5–10) MHz biplane probe model #8808 having a focal point of 2.3 cm and a focal range of 1–6 cm. Standard start-up instrument parameters were employed [near gain 5.7 decibels (db), far gain 50.1 db, slope 9.0 db/cm, contour 3, contrast 3, sizes 1 and 2, frame rate 14/s].

Exclusion criteria were significant gas or stool overlay, shadowing over the region of interest (ROI), reverberation in the ROI. Patients whose prostate volume as determined sonographically by triaxial measurement exceeded 70 ml were included in order to determine the diagnostic yield of C-TRUS in this diagnostically problematic group of men [11].

All scans were performed in the left lateral position. A water balloon stand-off was filled with 5–20 ml of degassed water to optimize focal zone (resolution) orientation (Fig. 1).

Transaxial images were generated at 5 mm intervals beginning at the prostate apex (designated level 00) and proceeding cephalad until the seminal vesicles were reached. Each image was labeled to indicate its level above the apex. All images were stored digitally on a computer hard disk.

C-TRUS evaluation was performed on the digitally stored static images (having no quality loss to the original freeze frame). Transaxial cross-sections were reviewed from the apex to the base of the gland at app. every 5 mm.) Five C-TRUS algorithms, previously described, were utilized to evaluate the information of the ultrasound signal [13, 14]. Although the C-TRUS can objectively utilize and analyze gray scale information, gray level of a lesion was ignored in the automatic analysis [15]. The descriptor data was evaluated by their objective numerical values (Fig. 2) and then displayed in a way that tumor suspicious areas were marked by superimposed red color on the original static image (Fig. 3) [16].

The maximum scan capacity of the C-TRUS system was 65,536 pixels or 32×32 boxes, corresponding to 25% of the monitor screen. Therefore, if the displayed prostate size exceeded this capacity, more than one pass through the stored images was necessary in order for the C-TRUS system to cover all areas of the gland. If an area of suspicion was indicated by C-TRUS interpretation, more precise evaluation was then performed by restricting the region of analysis to a smaller area [15].

For C-TRUS analysis, latero-lateral (*x* axis) and anterior-posterior (*y* axis) locations were coordinated with an overlay grid partitioned into 4×4 mm squares. The center line of the grid was placed over the mid line of the prostate, and the posterior grid line was aligned with the most posterior margin of the gland. Cephalo-caudad orientation (*z* axis) was recorded by noting the location previously recorded on the static images. If an area of suspicion extended through more than one transverse section, coordinates for each section was recorded in order to estimate lesion volume.

Fig. 1 Ultrasound probe with empty and filled water stand off



Fig. 2 C-TRUS: Objective evaluation of the ultrasound image

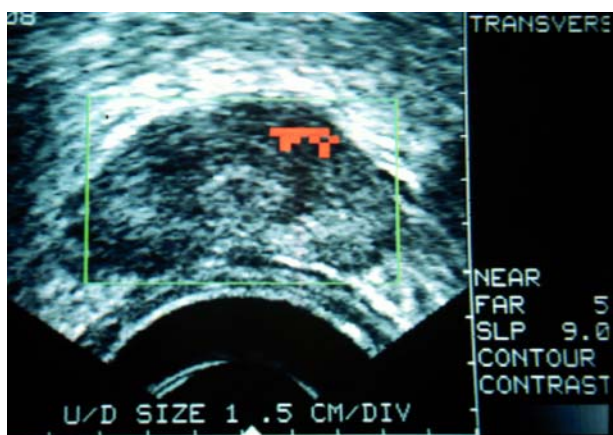
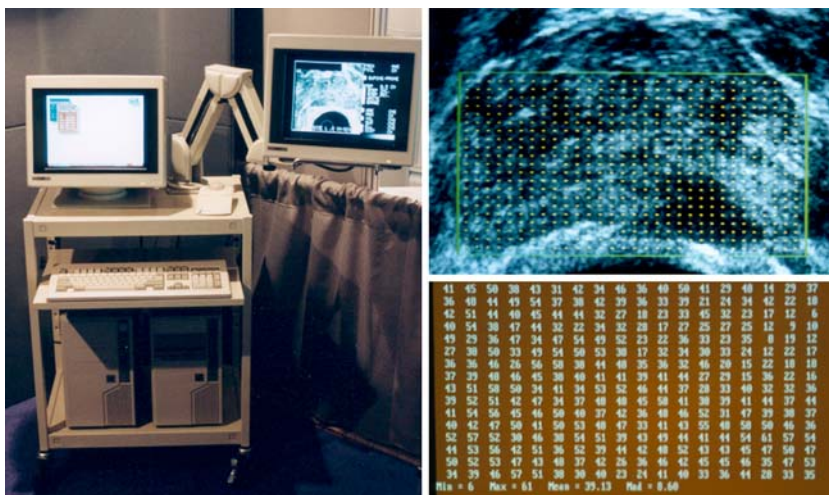
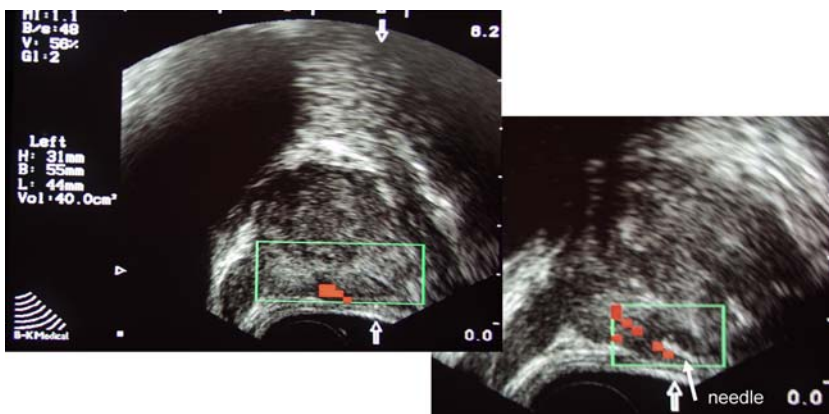


Fig. 3 C-TRUS: Anterior non palpable cancer marked by red color

As a further control of precise biopsy targeting, a “landmark technique” was also performed. Lesion location was confirmed by relating it to prostatic distinguishing marks (identifiable by TRUS) such as calcifications, cysts, and zonal anatomy [13]. The C-TRUS marked areas were then targeted and biopsied under visual control (Fig. 4).

Fig. 4 C-TRUS: Targeted biopsy of cancer suspicious lesion marked by red



Biopsies were limited to no more than six suspicious areas in each prostate. One or two cores were taken per lesion based on the obtaining of satisfactory tissue. Histopathologically, carcinomas were graded by Gleason primary and secondary patterns [17]. Core length as well as the length and location of cancer in each core were measured. The histo-pathological findings were accepted as representing the true diagnosis of the C-TRUS selected lesions.

Results

Of the consecutive 540 men 132 patients had a history of one thru seven sessions of prior negative systematic random biopsies (median: 2 sessions) and between 6 and 72 individual prostate biopsy punctures (median: 12 cores). A diagnostic TUR-P of the prostate was performed in four patients. Their age ranged between 45 and 78 years of age. The PSA ranged from 3.1–36 ng/ml with a median of 9.01 ng/ml. The prostate volume ranged from 6–203 ml with a median of 42 ml (Table 1, 2).

Table 1 Previous diagnostic procedures in 132 patients with negative systematic random biopsies

	Number	Median
Syst. random biopsies, Sessions	1–6	2
Indiv. biopsies, Cores	6–72	12
Max. biopsies in one session, Cores (under anesthesia)	45	–
Diagnostic TUR-P, patients	4	–

Table 2 Clinical information of the 132 patients with negative systematic random biopsies

	Number	Median
Age (Years)	45–78	64
PSA (ng/ml)	3.1–36	9.01
Volume(ml)	6–203	42

Of the 132 patients 62 had a history of one set of negative systematic biopsies with 6–20 cores. 41 men had two sets of negative biopsies between 10 and 51 cores. 18 patients had three sessions with 17–34 cores. Six men had four sets of negative systematic biopsies between 24 and 40 cores and five patients had five or six sessions with 40 up to 72 cores. All men underwent C-TRUS targeted biopsies of the one thru six most suspicious areas in the prostate. In 24 % (32/132) only 1–3 C-TRUS targeted biopsies were taken [16].

Of the 132 patients with prior negative systematic random biopsies, 66 (50%) were positive for carcinoma by C-TRUS targeted biopsies (see Table 3, 4, 5). In 24 % (32/132) of the patients only 1–3 C-TRUS targeted biopsies were taken because of highly suspicious C-TRUS results. In this group C-TRUS targeted biopsies were positive for prostate cancer in 31 men (97%).

Discussion

Transrectal ultrasound of the prostate is a widely used tool in the diagnostic and management of prostatic disease. Its ability in screening for cancer could not yet be defined, its accuracy in staging is controversially discussed, however, it is an excellent guide for biopsy of palpable and non palpable small lesions [18–22].

The prime criticism of TRUS is its lack of objective criteria for the detection of malignant prostatic tissue [7]. Moreover, experienced examiners doing dynamic scanning are able to achieve a significantly higher diagnostic accuracy in detecting prostate malignancies when compared to clinical evaluation without TRUS [20, 22]. In addition, many TRUS examiners are not using a water stand off

Table 3 Previous history of the 66 patients with prostate cancer identified by C-TRUS

	Number	Median
Syst. random biopsies, Sessions	1–4	2
Indiv. Biopsies, Cores	6–40	12
Max. biopsies in 1 session, Cores	20	–
Diagnostic TUR-P, patients	2	–

Table 4 Clinical information of the 66 patients with prostate cancer identified by C-TRUS

	Number	Median
Age (Years)	45–78	65
PSA (ng/ml)	3.6–36	10.01
Volume (ml)	6–160	33

Table 5 Gleason score found in 66 patients with prostate cancer identified by C-TRUS

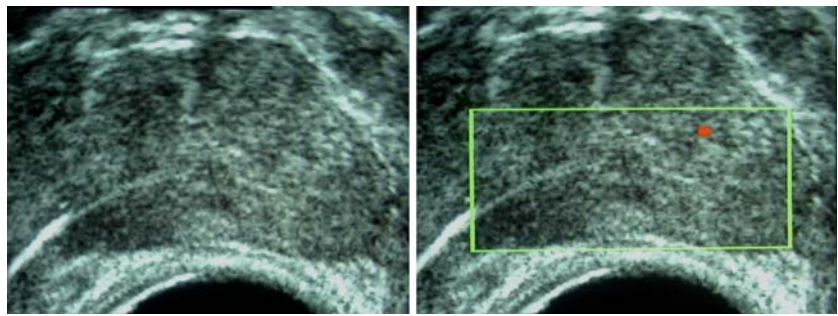
	Number
Gleason score 5	4
Gleason score 6	25
Gleason score 7	22
Gleason score 8	8
Gleason score 9	7

which improves image quality significantly [23]. TRUS has a high learning curve-meaning that the examiner needs a large series of cases with histo-pathological follow up to be able to realize a high diagnostic yield.

To objectify and increase the diagnostic accuracy of TRUS, a computerized image analysis method named C-TRUS was utilized. Previous studies on radical prostatectomy specimens correlating in vivo ultrasound and in vitro histo-pathological morphology showed promising results [14, 15]. In the present prospective study the diagnostic yield of computerized transrectal ultrasound (C-TRUS) guided biopsies in the detection of prostate cancer in a group of men with prior multiple systematic random biopsies with no evidence of prostate cancer was analyzed. The question was asked: Can we detect cancer that by C-TRUS that has been overlooked by even multiple systematic biopsies?

A typical urological patient population (Table 1, 2) was surveyed for which a test with a high positive and negative predictive value should be available [24]. The entrance criteria a positive DRE and/or an elevated PSA were chosen to investigate a group of patients with a high prevalence of small prostatic cancers. Most of the curable lesions (smaller than 4 ml) are hidden in this group [25]. As DRE and PSA

Fig. 5 C-TRUS: most suspicious region marked by red an undetectable by visual interpretation



alone are of low specificity, TRUS or any other diagnostic test is challenged to improve the diagnostic accuracy [24, 26].

Comparing the methods, C-TRUS could identify a dramatic high number of prostate malignancies (66 out of 132) leaving the question of how reliable systematic random biopsies are (Table 3). The previously performed systematic biopsies did not detect 15 cancers that had a Gleason Score of eight and nine. As Table 5 indicates there were only five tumors with a Gleason Score below six. The results demonstrate that diagnosing insignificant tumors were not a concern (Table 5). Moreover, we operated on 21 of the 66 patients and there was no insignificant cancer in that group. The pT-stage was between pT2a and pT3a. Gleason Score correlated well with the preoperative findings.

Of more practical concern is the positive and negative predictive value being the likelihood with a positive test result of having disease or not-after a negative test result. The considerably high positive predictive value of C-TRUS is surprising because it is affected by the prevalence of cancer in this study (Table 3). Up to this date current opinion is that in a population of men with a median of 12 negative random biopsies, there should be a low prevalence of prostate cancer [27]. Furthermore, many studies so far assumed, that if two sets of systematic random biopsies were negative the prevalence of cancer in this group had to be close to zero [9, 25].

This study suggests that the incidence of clinical significant prostate cancer in this group is much higher than expected (see Tables 3, 5). Furthermore, the results of the study support the efforts to search for strategies that utilize expertise and refinement of imaging modalities rather than elevating the number of random biopsies (f.e. 141 cores in one session had been performed to one of our later patients) in the detection of prostate cancer.

Conclusions

The results of this prospective clinical trail indicate that the additional use of the C-TRUS is able to improve the

diagnostic accuracy of conventional TRUS. It is apparent, that C-TRUS can detect cancerous lesions that could not be detected by multiple systematic random biopsies.

By statistical analysis of the digitized ultrasound image an objective, reproducible and a less operator-dependant evaluation is possible. The C-TRUS algorithms provide data that are visually not obtainable (Fig. 5), being different from the gray-level information. Moreover, the C-TRUS is able to obtain gray-level information and could use it in conjunction to the subvisual information.

Especially its benefit in the detection of anterior lesions and lesions in large glands should be further examined being a problem area in the conventional diagnosis. Its benefit for the experienced TRUS operator should be meaningful and the learning curve of new or inexperienced TRUS user in the evaluation of prostatic disease should be shortened.

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