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Original article

High-resolution transrectal ultrasound: Pilot study of a novel technique for imaging clinically localized prostate cancer

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Abstract

Objectives: To determine how high-resolution transrectal ultrasound (HiTRUS) compares with conventional TRUS (LoTRUS) for the visualization of prostate cancer.

Methods and materials: Twenty-five men with known prostate cancer scheduled for radical prostatectomy were preoperatively imaged with both LoTRUS (5 MHz) and HiTRUS (21 MHz). Dynamic cine loops and still images for each modality were saved and subjected to blinded review by a radiologist looking for hypoechoic foci $\geq$5 mm in each sextant of the prostate. Following prostatectomy, areas of prostate cancer $\geq$5 mm on pathologic review were anatomically correlated to LoTRUS and HiTRUS findings. The accuracy of LoTRUS and HiTRUS to visualize prostate cancer in each sextant of the prostate and to identify high-grade and locally advanced disease was assessed. The McNemar test was used to compare sensitivity and specificity and paired dichotomous outcomes between imaging modalities.

Results: Among 69 sextants with pathologically identified cancerous foci at radical prostatecomy, HiTRUS visualized 45 and missed 24, whereas LoTRUS visualized 26 and missed 43. Compared with LoTRUS, HiTRUS demonstrated improved sensitivity (65.2% vs. 37.7%) and specificity (71.6% vs. 65.4%). HiTRUS's agreement with pathologic findings was twice as high as LoTRUS ($P = 0.006$). HiTRUS provided a nonsignificant increase in visualization of high-grade lesions (84% vs. 60%, $P = 0.11$).

Conclusions: HiTRUS appears promising for prostate cancer imaging. Our initial experience suggests superiority to LoTRUS for the visualization of cancerous foci, and supports proceeding with a clinical trial in the biopsy setting.

Keywords: Diagnosis; Prostate cancer; Radical prostatectomy; Ultrasound; Sensitivity and specificity

1. Introduction

Imaging modalities have fallen short of expectations for the detection of clinically localized prostate cancer. Despite advances in transrectal ultrasound (TRUS), computed tomography, and magnetic resonance imaging (MRI), the majority of prostate cancers are detected through prostate-specific antigen (PSA) screening or by digital rectal examination (DRE) or both. Dedicated prostate imaging is typically performed during prostate biopsy primarily as a guide to localizing the prostate for accurate needle placement. Even in the face of known prostate cancer (active surveillance cohorts), it is often difficult to identify small, non-palpable lesions [1,2]. Enhanced ultrasound techniques including color and power Doppler have been used in an attempt to enhance prostate cancer detection

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over conventional TRUS (LoTRUS). However, despite modest improvements over LoTRUS these modalities are not in widespread clinical use despite availability [3–6].

Endorectal coil MRI and 3-T MRI are more recent advances that are used primarily to localize and stage known disease for the purposes of guiding therapy [7–9]. However, despite promising reports on their use in cancer detection in at-risk populations [10,11], MRIs are not routinely used to diagnose prostate cancer in the United States. The radiologist expertise required for a precise interpretation of multiparametric prostate MRI and standardization of the technique are among issues affecting widespread adoption of this technology. There is clearly room for urologist-performed, office-based prostate imaging to better identify men with an elevated PSA or abnormal DRE who should undergo a prostate biopsy, and to perhaps target this biopsy more accurately. Ultimately, enhanced urologist-performed prostate imaging in conjunction with MRI may improve anatomic characterization of cancerous foci enough to decrease the number of biopsies performed in both screening and surveillance settings.

Given that TRUS is a standard part of the clinical practice of every urologist that performs prostate biopsy in the United States, where over 1 million prostate biopsies are performed annually, it is of potentially great benefit to improve upon this technology [12]. Conventional prostate TRUS is typically performed at 5 to 9 MHz, frequencies that allow for adequate depth of penetration and fair contrast between the prostate and adjacent structures (bladder and seminal vesicles). Although these low frequencies allow for adequate imaging of the prostate in contrast to adjacent structures, they are suboptimal in delineating intraprostatic architecture. High-resolution (16–21 MHz) ultrasound probes have been available for cutaneous and small animal imaging for some time [13,14], but a high-resolution TRUS (HiTRUS) probe for prostatic imaging was developed only recently. This higher resolution equipment may represent a needed advance in prostate cancer visualization at the clinically localized stage, particularly in the peripheral zone.

The present study was designed to determine how HiTRUS compares with LoTRUS for visualizing prostate cancer. Men who had known clinically localized prostate cancer that were scheduled for radical prostatectomy were recruited and offered LoTRUS as well as HiTRUS preoperatively. Correlations were made between foci of prostate cancer ≥ 5 mm on pathologic analysis and the locations of lesions ≥ 5 mm in maximal diameter on imaging. Pathologists were blinded to any imaging data, and the interpreting radiologist was blinded to all pathologic data. The goal of the study was to define how accurate either imaging modality was for identifying prostate cancer foci ≥ 5 mm.

2. Methods and materials

2.1. Study design

From 2010 to 2011, men with biopsy-proven prostate cancer scheduled for robot-assisted radical prostatectomy (RARP) who had a TRUS-determined volume <60 cc were prospectively recruited into an institutional review board and cancer committee-approved study. Patient recruitment ended after the accrual goal of 25 patients was reached. All patients scheduled for RARP during the study period were offered participation in the study. Volume determination for study inclusion was calculated at the time of diagnostic prostate biopsy by a LoTRUS probe. No further inclusion or exclusion criteria were applied.

After obtaining written informed consent, participating men underwent LoTRUS and HiTRUS imaging in a single setting prior to RARP. Dynamic cine loops and still images were saved during each TRUS examination. All images and cine loops were subsequently reviewed by a radiologist with expertise in diagnostic ultrasonography (J.F.) to identify areas of hypoechogenicity ≥ 5 mm in any diameter within each prostate sextant. The radiologist was aware that each patient had prostate cancer but was blinded to clinical and pathologic data, including cancer location, volume, grade, and stage.

After RARP, actual areas of prostate cancer ≥ 5 mm were identified and localized within a prostate sextant(s). Correlations between pathologic and ultrasound findings were made sextant by sextant such that 6 specific areas of each prostate were assessed for sonographic-pathologic concordance—the right and left apex, mid, and base, respectively, with the sextant areas extending up to the anterior aspect of the prostate (Fig. 1). Ultrasound and pathologic concordance was determined by consensus opinion of reviewing physicians. Sensitivity and specificity analysis for the identification of pathologically confirmed cancerous foci was performed for each imaging modality. The performance of HiTRUS in identifying these cancerous foci was compared with LoTRUS.

Postprostatectomy pathologic data including prostate size, Gleason score, and local tumor extent were recorded for each patient. The ability of each imaging modality to estimate prostate volume, identify high-grade disease (Gleason sum ≥ 7), and identify locally advanced lesions (extraprostatic extension) was assessed.

2.2. TRUS evaluation

LoTRUS and HiTRUS examinations were performed by a single urologist (C.P.P.) with >10 years of experience performing TRUS. All patients underwent DRE followed by TRUS imaging that alternated in order—some underwent HiTRUS first, others LoTRUS first. LoTRUS images were obtained with a conventional 5-MHz end-fire transducer (Hitachi Aloka Medical, Ltd., Tokyo, Japan) and

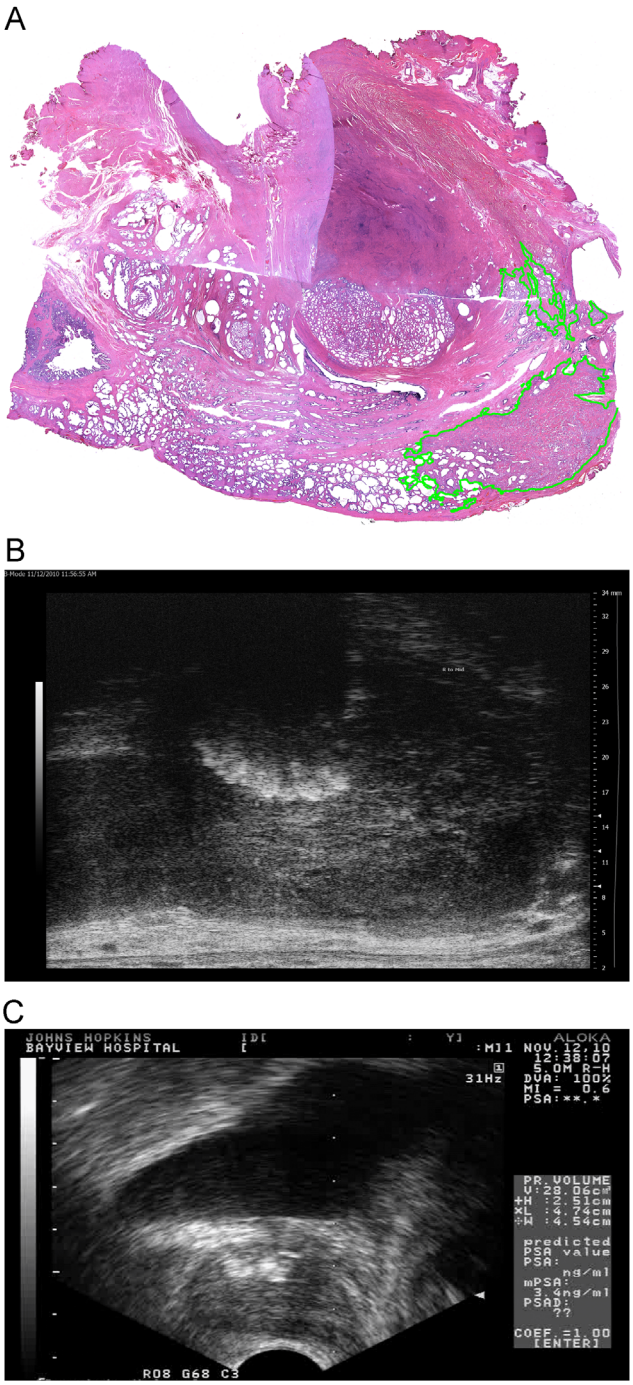

Fig. 1. (A) Reconstructed sagittal prostate section with Gleason 3 + 4 = 7 tumor at left apex outlined in green ink. This corresponds to a hypoechoic lesion most accurately identified on high-resolution transrectal ultrasound (B). The lesion is less clearly defined on low-resolution transrectal ultrasound and could be missed (C). (Color version of figure is available online.)

HiTRUS images were obtained with a 512 element, 21-MHz center-frequency side-fire transducer (Imagistx, Inc., Las Vegas, NV). Dynamic cine loops and still images were saved for both modalities in a standardized fashion (1 right-to-left approximately 15-s entire prostate loop and approximately 7 sagittal images for LoTRUS, and 3 to 5 approximately 5-s cine loops, an approximately 45-s entire prostate loop, and approximately 7 sagittal images for HiTRUS). Prostate volume was calculated using the formula for an ellipsoid using 3 axes for LoTRUS (height, width, and length, formula $V = [W \times L \times H] \times \pi/6$), and using 2 axes (height and length and estimating the third for HiTRUS [formula $V = \{L \times L \times H\} \times \pi \times 1.108 \times 1.108/\{6 \times 1.025\}$]) for HiTRUS as this technique is, at present, sagittal only.

2.3. Pathologic analysis

After RARP, men had their prostates sagittally sectioned and then further sectioned into quadrants as per the pathology department's routine. All specimens were processed by a single histopathologic assistant (R.L.) and the cases were initially evaluated for diagnosis by a single pathologist (F.A.) who was blinded to imaging data.

Resulting glass slides were digitized using an iScan Coreo Au (Ventana Medical System, Inc., Tucson, AZ) slide scanner. An expert anatomic pathologist (T.C.C.) annotated digital images with freehand drawing tools in ImageJ (National Institutes of Health, Bethesda, MD) using a Cintiq 21UX LCD graphics tablet (Wacom Co., Ltd., Vancouver, WA). All foci of prostate cancer were included in the annotation process, and a leading expert reviewed foci in which the diagnosis was uncertain (J.I.E.). The annotated digital images of the sagittal quadrants were then fitted together manually to create seamless (mosaic), digitally reconstructed whole-mount sections.

2.4. Statistical analysis

The McNemar test was used to compare sensitivity and specificity between LoTRUS and HiTRUS for detection of cancers ≥ 5 mm using the excised prostate specimen sections as the reference. Additionally, the McNemar test was used to compare paired dichotomous outcomes between LoTRUS and HiTRUS. The standards for the reporting of diagnostic accuracy (STARD) guidelines were observed when reporting results. Analyses were performed using STATA version 11.0 (Stata Corp LP, College Station, TX) and R 2.14.1 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients

A total of 25 men underwent LoTRUS and HiTRUS followed by RARP. Demographic, clinical, and pathologic data are listed in Table 1. No complications or adverse events occurred during preoperative imaging or RARP. Average estimated prostate volume was 27.3 cc with LoTRUS and 26.6 cc with HiTRUS. Average pathologic

Table 1
Demographic, clinical, and pathologic data of 25 men with clinically localized prostate cancer undergoing high-resolution and low-resolution (conventional) transrectal ultrasound followed by robot-assisted radical prostatectomy

Variable	Median (range) or % (n)
Clinical and demographic data	
Age	59 (50–70)
Race	
Caucasian	84% (21)
African American	12% (3)
Other	4% (1)
PSA, ng/dL	5.5 (2.5–9.9)
Clinical stage	
T1c	84% (21)
T2a	8% (2)
T2b	8% (2)
Biopsy Gleason score	
3 + 3 = 6	12% (3)
3 + 4 = 7	64% (16)
4 + 3 = 7	16% (4)
8–10	8% (2)
Pathologic data	
Prostate and seminal vesicles weight, g	44.4 (23.5–66)
Pathologic Gleason score	
3 + 3 = 6	28% (7)
3 + 4 = 7	48% (12)
4 + 3 = 7	24% (6)
Pathologic Stage	
T2	76% (19)
T3a	12% (3)
T3b	12% (3)

specimen weight was 44.9 g. The mean discrepancy between estimated prostate volume and actual pathologic volume was 17.6 cc (0.7–33.8) for LoTRUS and 18.3 cc (5.8–34.8) for HiTRUS ($P = 0.80$), largely due to seminal vesicle weight.

3.2. Identification of prostate cancer

Cancerous foci ≥5 mm were identified within 69 prostate sextants. LoTRUS identified 26 and missed 43 sextants with cancer foci (38% correct). HiTRUS identified 45 and missed 24 sextants with cancerous foci (65% correct). Benign tissue was incorrectly identified as a cancerous focus within 28 and 23 sextants using LoTRUS and HiTRUS, respectively. Compared with LoTRUS, HiTRUS had higher sensitivity, specificity, positive predictive value, and negative predictive value (Table 2).

In 37.3% of sextants both LoTRUS and HiTRUS were concordant with pathology, and in 16% neither was concordant with pathology. In the 46.7% of sextants where LoTRUS and HiTRUS were not in agreement, LoTRUS and HiTRUS were concordant with pathology in 32.9% and 67.1%, respectively. HiTRUS's agreement with pathologic findings was twice as high as that of LoTRUS ($P = 0.006$).

Table 2
Comparison of low-resolution (conventional) transrectal ultrasound (LoTRUS) and high-resolution transrectal ultrasound (HiTRUS) in the identification of pathologic cancerous foci ≥5 mm detected upon review of complete radical prostatectomy specimens

	Sensitivity, %	Specificity, %	PPV, %[a]	NPV, %[b]
LoTRUS	37.7	65.4	48.1	55.2
HiTRUS	65.2	71.6	66.2	70.7

[a]Positive predictive value.
[b]Negative predictive value.

3.3. Identification of high-grade and locally advanced disease

Pathologic review of the reconstructed digital whole-mount radical prostatectomy specimens demonstrated 43 discrete cancerous lesions ≥5 mm. There were fewer discrete cancerous lesions compared with the number of prostate sextants harboring cancer given that several lesions involved ≥1 sextant. Final pathologic grade was Gleason 3 + 3 = 6, 3 + 4 = 7, and 4 + 3 = 7 in 18, 17, and 8 lesions, respectively. Extraprostatic extension was identified in 6 patients. In total, HiTRUS identified significantly more of the cancerous lesions than LoTRUS (79.1% vs. 51.2%, $P < 0.008$). Furthermore, HiTRUS identified more high-grade (primary or secondary Gleason pattern ≥4) lesions than LoTRUS, though this did not reach statistical significance (84% vs. 60%, $P = 0.11$). HiTRUS and LoTRUS each identified 66.7% of lesions with extraprostatic extension, though seminal vesicle invasion was not specifically evaluated (Table 3).

4. Discussion

Despite numerous advances in prostate cancer imaging over the past 35 years, the ability to reliably image cancerous foci within the prostate remains limited. Hindered by suboptimal sensitivity, few advances in imaging technology have achieved widespread acceptance by the urologic community. Thus, LoTRUS-guided, systematic prostate biopsy remains the predominant means for identifying prostate cancer in men with an elevated PSA or abnormal DRE or both in the United States.

In the present study, we present the first clinical application of a novel 512 element, 21-MHz center-frequency sagittal transducer probe to human prostate cancer. The transducer probe and technology were easy to use for the clinician and well tolerated by patients. Enhanced visualization of intraprostatic architecture resulted in improved detection of significant cancerous foci compared with LoTRUS in a blinded, randomized comparison. As expected, despite improved

Table 3
Comparative analysis of low-resolution (conventional) transrectal ultrasound (LoTRUS)and high-resolution transrectal ultrasound (HiTRUS) in identifying high-grade (any Gleason pattern ≥4), low-grade (Gleason 3 + 3 = 6), and locally advanced (presence of extraprostatic extension) prostate cancer. Lesions characterized upon pathologic analysis of complete radical prostatectomy specimens

Variable	Pathologic lesions	LoTRUS	HiTRUS	*P*-value
Total lesions	43	22 (51.2%)	34 (79.1%)	0.008
Dominant lesion[a]	25	15 (60%)	20 (80%)	0.23
High-grade lesion	25	15 (60%)	21 (84%)	0.11
Low-grade lesion	18	7 (38.9%)	13 (72.2%)	0.15
Lesions with extraprostatic extension	6	4 (66.7%)	4 (66.7%)	–

[a]The largest lesion identified upon analysis of radical prostatectomy specimen.

cancer detection, there were false-negative and false-positive results with HiTRUS. This was expected given the novelty of HiTRUS to both the radiologist and urologist involved in the study, the first-generation nature of the probe and imaging station, the lack of any image enhancement techniques such as Doppler flow, and perhaps limitations inherent to ultrasound imaging of prostate cancer. These data should not be interpreted to suggest that HiTRUS replace biopsy for prostate cancer detection, but rather that HiTRUS may be superior to LoTRUS and warrants further investigation, such as for targeting prostate biopsies or cancer monitoring or both in active surveillance populations.

Since its introduction in the 1970s, TRUS-guided prostate biopsy has become the gold standard in the diagnosis of prostate cancer [15]. Unfortunately, at standard low resolutions, the similarly echogenic properties of cancerous foci and noncancerous prostate tissue have limited the ability of TRUS to be used as a singular modality in cancer diagnosis. In fact, up to 40% of cancerous foci are isoechoic to surrounding benign tissue on LoTRUS [16–18]. Therefore, since Hodge's comparison study in 1989, systematic rather than targeted biopsies have remained the standard in prostate cancer detection [19–21].

Discovery of capillary neovascularization and increased microvessel density within prostate cancer lesions has led to new modalities of ultrasonography [22]. Color and power Doppler were introduced to detect increased vascularity within the prostate that may correlate with prostate cancer [3,4,23,24]. More recently, microbubble-enhanced Doppler TRUS has shown improvement over unenhanced LoTRUS in identifying prostate cancer foci [25–28]. However, mixed reports on the utility of such technologies, and modest improvements demonstrated in cancer detection over unenhanced LoTRUS have limited their widespread adoption. Furthermore, increased costs of technology, prolonged examination times, and variability in interpretation of ultrasound results have further hindered dissemination of these advances into routine urologic practice. HiTRUS represents a readily adoptable technology that was well tolerated by patients, and shows significant promise in visualizing cancerous foci in real time without exposing patients to prolonged examinations or injectable agents.

This pilot study was specifically designed to provide an initial assessment of the potential utility of a new technology to image prostate cancer in the clinically localized setting. As such, it was subject to many limitations. Prostate imaging by HiTRUS had not previously been performed by any study investigator, hence the preliminary nature of the data collected. Additionally, ultrasound images and dynamic cine loops for both HiTRUS and LoTRUS were reviewed after TRUS and not in real time by the blinded study radiologist. Although real-time evaluation is acknowledged to be optimal for ultrasonic evaluations in general, this would be unlikely to have introduced bias into the study given that it affected both modalities equally. This study was performed on only 25 patients because of cost and manpower limitations, given how exhaustive the digital reconstruction and pathologic analysis of whole-mount prostates was for purposes of direct comparison with sagittal ultrasound examinations, and preliminary nature of the imaging technology. This pilot study was specifically designed to assess for the presence of small lesions in men with known prostate cancer. The lesion target size threshold decided upon (0.5 cm diameter) was well below an accepted threshold for clinically significant prostate cancer (1 cm diameter, 0.5 cc volume) so as to garner as much information as possible pertaining to this new technology. However, because of post–pathologic processing volume loss some lesions meeting the size criteria may have been overlooked. No conclusions can be made regarding the utility of HiTRUS in the screening/biopsy setting at this time; however, HiTRUS has demonstrated significant promise in terms of identifying small hypoechogenic foci that proved cancerous at radical prostatectomy. The utility of this technology, which trades more limited depth of penetration in exchange for better resolution in the peripheral zone, to identify anterior tumors in larger glands or seminal vesicle invasion still needs to be determined—to date only glands <60 g were imaged [29]. In fact, of the 8 anterior tumors present in our pilot study, HiTRUS identified 1 and LoTRUS did not visualize any of these lesions. Finally, only echogenicity was used to assess the ultrasound images. It is anticipated that additional image features such as Doppler might inform future studies.

Imaging the prostate with sufficient accuracy to identify prostate cancer has long been an elusive goal. HiTRUS provides better resolution of the prostatic peripheral zone and significantly improves the visualization of prostate cancer foci, at the expense of more limited penetration. These promising results justify the refinement and study of HiTRUS, and its assessment on a larger scale in the screening/biopsy setting.

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