



Prostate Contrast Enhanced Transrectal Ultrasound Evaluation of the Prostate With Whole-Mount Prostatectomy Correlation

Edouard J. Trabulsi, Brian P. Calio, Sarah I. Kamel, Leonard G. Gomella, Flemming Forsberg, Peter McCue, and Ethan J. Halpern

OBJECTIVE	To investigate the diagnostic accuracy of contrast enhanced transrectal ultrasound (CE-TRUS) in comparison with whole-mount radical prostatectomy specimens.
METHOD AND MATERIALS	Fifty-eight subjects who underwent CE-TRUS and subsequent radical prostatectomy with whole-mount pathology were included in the study. Each patient underwent evaluation with baseline TRUS and again during CE-TRUS with intravenous infusion of perflutren lipid microsphere (Definity, Lantheus Medical Imaging, N Billerica, MA). A subjective 5 point scale was used to rate each sextant of the prostate in 3 baseline imaging modes and in 5 contrast-enhanced imaging modes. Baseline TRUS and CE-TRUS findings were compared with digitized whole-mount findings. A clustered logistic regression model was computed to compare the area under the receiver operating characteristic curve (A_z) for detection of prostate cancer by various modes of ultrasound imaging.
RESULTS	Among the 58 whole-mount specimens, a maximum Gleason score of 6 was identified in 29 subjects, a score of 7 was identified in 24 and a score of 8 was identified in 5. The A_z for baseline TRUS parameters was 0.55 for grayscale, 0.61 for color Doppler and 0.59 for power Doppler. CE-TRUS parameters demonstrated significant increases in A_z with the highest A_z for CE-power Doppler (0.66) and flash replenishment imaging (0.64) ($P = .04$ for comparison to baseline). The combination of CE-power Doppler and flash replenishment imaging resulted in improved A_z compared with baseline imaging (0.70 vs 0.59, $P = .006$).
CONCLUSION	Contrast-enhanced ultrasonography demonstrates greater diagnostic accuracy than baseline imaging. Diagnostic accuracy is further improved for "clinically significant" tumor volumes >1 cc. UROLOGY 133: 187–191, 2019. © 2019 Elsevier Inc.

Prostate cancer is the most commonly diagnosed visceral malignancy among American men, estimated to affect over 160,000 patients in 2018.¹ With nearly 30,000 projected deaths yearly, accurate diagnosis and staging of prostate cancer is essential. Detection of prostate cancer begins with the assessment of prostate-specific antigen and the digital rectal exam, and culminates with ultrasound-guided needle biopsy of the prostate. Given a positive biopsy rate of 25%-30%, the estimated annual number of TRUS biopsies is close to 1 million.¹

The conventional systematic biopsy includes a minimum of 10-12 cores. Although this biopsy method

samples broadly, it carries significant financial cost involving procedure time and pathologic analysis, as well as risk of procedural morbidity.^{2,3} A 2017 report on the impact of the USPSTF's 2012 recommendations to limit PSA screenings showed that although there has been an absolute reduction in biopsy morbidity since the implementation of new guidelines, the relative morbidity of prostate biopsies has actually risen since the shift in recommendation.⁴ Furthermore, systematic biopsy does not prioritize areas with sonographic appearance suspicious of prostate malignancy. While classically described as hypoechoic, cancerous foci may appear echogenic or isoechoic in more than half of cases. As a result, alternative modalities have been investigated to supplement conventional grayscale imaging. Although some detection benefits have been found with color and power Doppler, currently the combination of these techniques in guiding needle biopsy is not sufficient to eliminate the need for systematic biopsy.⁵ The ideal approach to the diagnosis of prostate malignancy should limit the number unnecessary biopsy cores

From the Department of Urology, Thomas Jefferson University Hospital, Philadelphia, PA; the Department of Radiology, Thomas Jefferson University Hospital, Philadelphia, PA; and the Department of Pathology, Thomas Jefferson University Hospital, Philadelphia, PA

Address correspondence to: Ethan J. Halpern, M.D., Department of Radiology, Thomas Jefferson University Hospital, 132 South 10th Street, Suite 1092A, Main Building, Philadelphia, PA 19107. E-mail: ethan.halpern@jefferson.edu

Submitted: May 30, 2019, accepted (with revisions): July 22, 2019

and provide high likelihood of detecting significant disease with a minimal number of cores. Therefore, improvement of diagnostic imaging in tumor detection and localization is critical in guiding tissue biopsy.

Prostate cancer is known to exhibit increased microvessel density compared to normal tissue due to proliferation of pathologic neovessels and tumor associated angiogenesis.^{6,7} This neovasculature is typically of small diameter and is below the resolution of conventional Doppler imaging; however, microbubble contrast agents have demonstrated the ability to enhance sonographic visualization.^{8,9} Therefore, contrast imaging allows for accurate guidance of targeted biopsy to areas of increased vascularity.¹⁰ The purpose of this study was to investigate the diagnostic accuracy of contrast enhanced transrectal ultrasound (CE-TRUS) in the detection of prostate cancer and in the guidance of targeted biopsy cores. CE-TRUS and targeted biopsy findings were compared with whole-mount radical prostatectomy specimens to determine the accuracy of tumor location, size, and grade as predicted by CE-TRUS.

METHODS AND MATERIALS

Enrollment

We report a retrospective study of all patients who underwent CE-TRUS at Thomas Jefferson University and who subsequently underwent radical prostatectomy with whole-mount pathologic correlation. This retrospective analysis predominantly included patients who were prospectively enrolled in a National Institute of Health-sponsored protocol to evaluate CE-TRUS (RO1-CA118003; ClinicalTrials.gov identifier: NCT02967458). Over a 5-year period from Nov 2006 to June 2011 subjects with elevated PSA (>4.0 ng/mL) or abnormal digital rectal examination were offered transrectal biopsy at our institution. The 58 subjects in our retrospective study population constitute a subset of our CE-TRUS biopsy patients who were found to have prostate cancer and subsequently opted to undergo radical prostatectomy.¹⁰ PSA in the study population ranged from 1.2 to 64.2 ng/dL, with a mean of 7.1ng/dL. The digital rectal examination was classified as abnormal in 16 subjects.

Imaging

Sonography was performed using the PVT-661VT end-fire endocavitary probe with the Aplio scanner (Toshiba America Medical Systems). Patients were examined in the lithotomy position. The microbubble agent perflutren lipid microsphere (Definity, Lantheus Medical Imaging, N Billerica, MA), was diluted into 50 mL of normal saline (concentration = 49.4 uL/mL) and infused at a rate of 4 mL/min for this study.

Precontrast imaging was performed with conventional gray-scale, color, and power Doppler. Postcontrast images including the aforementioned techniques as well as continuous harmonic imaging, intermittent harmonic imaging and flash-replenishment imaging (FRI) performed during contrast infusion. FRI is a technique that uses high power flash pulses to destroy bubbles, followed by low power pulses which are combined into a single maximum intensity image to demonstrate contrast replenishment and depict vascular architecture. Intermittent harmonic imaging was performed with a 2-second interscan delay. FRI was performed with 3-second duration for the low power pulses.

Table 1. Image scoring system

1	Normal appearance (homogenous, capsular flow only)
2	Probably normal (minimal heterogeneity, symmetrical radial flow from capsular branches)
3	Subtle abnormalities (contour abnormalities, asymmetrical flow patterns)
4	Possible carcinoma (contour bulge or mass, discrete asymmetrical flow in outer gland)
5	Likely carcinoma (hypoechoic mass, asymmetrical flow with disorganized pattern)

The window of visualization for all imaging included the entire gland. To obtain comparable images from both pre- and postcontrast phases, angled axial sweeps through the gland were performed from the base through the apex, each sweep extending over a period of 20-30 seconds. Each examination was recorded on Video Home System tape.

Image Interpretation

Subjective ratings (**Table 1**) were assigned to each sextant of the prostate based upon each of the imaging methods (gray scale, color Doppler, contrast enhanced power Doppler, contrast enhanced continuous gray scale harmonic, contrast enhanced intermittent harmonic imaging, and FRI) at the time of the initial TRUS examination. For baseline grayscale imaging, the suspicion of carcinoma was based on tissue echotexture as well as contour abnormalities. For color and power Doppler, intensity of flow was used to rate the suspicion for neoplasm. Color and power Doppler scores were rated at baseline and again during contrast administration. For contrast enhanced continuous and intermittent imaging, symmetry and intensity of flow were used for rating. For FRI, vessel density and tortuosity were evaluated in addition to symmetry and intensity of flow.

Biopsy Protocol

Following completion of sonographic evaluation, local anesthesia was given with 10 cc 1% lidocaine along the neurovascular bundles at the juxtaposition of the seminal vesicles and base of prostate (5 cc on each side). Focal areas of contrast enhancement or abnormal vasculature were identified prospectively in the transverse plane at the base, midgland, and apex of the prostate. Targeted biopsy specimens were obtained during real-time CE-TRUS imaging. Up to 6 targeted biopsy cores were obtained from each individual patient, directed to areas of abnormal vascular enhancement or morphology. A second physician, blinded to the results of the initial imaging evaluation then performed a systematic 12-core needle biopsy of the prostate. The 12 systematic biopsy included a parasagittal cores on each side of midline and a laterally directed cores on each side of midline (4 cores at each level), obtained at the base, midgland, and apex (×3 levels). Both the initial examining physician who performed the targeted biopsy and the second blinded physician who performed the systematic biopsy were experienced physicians with many years of experience performing prostate biopsy and contrast enhanced studies of the prostate.

Pathologic Evaluation

Following radical prostatectomy, the prostate gland was sliced in 4 mm transverse sections and prepared with standard hematoxylin-eosin staining. The whole-mount slides of each gland were divided into 3 groups classified as apical, midgland, and base. The pathologist mapped all visualized lesions and assigned a

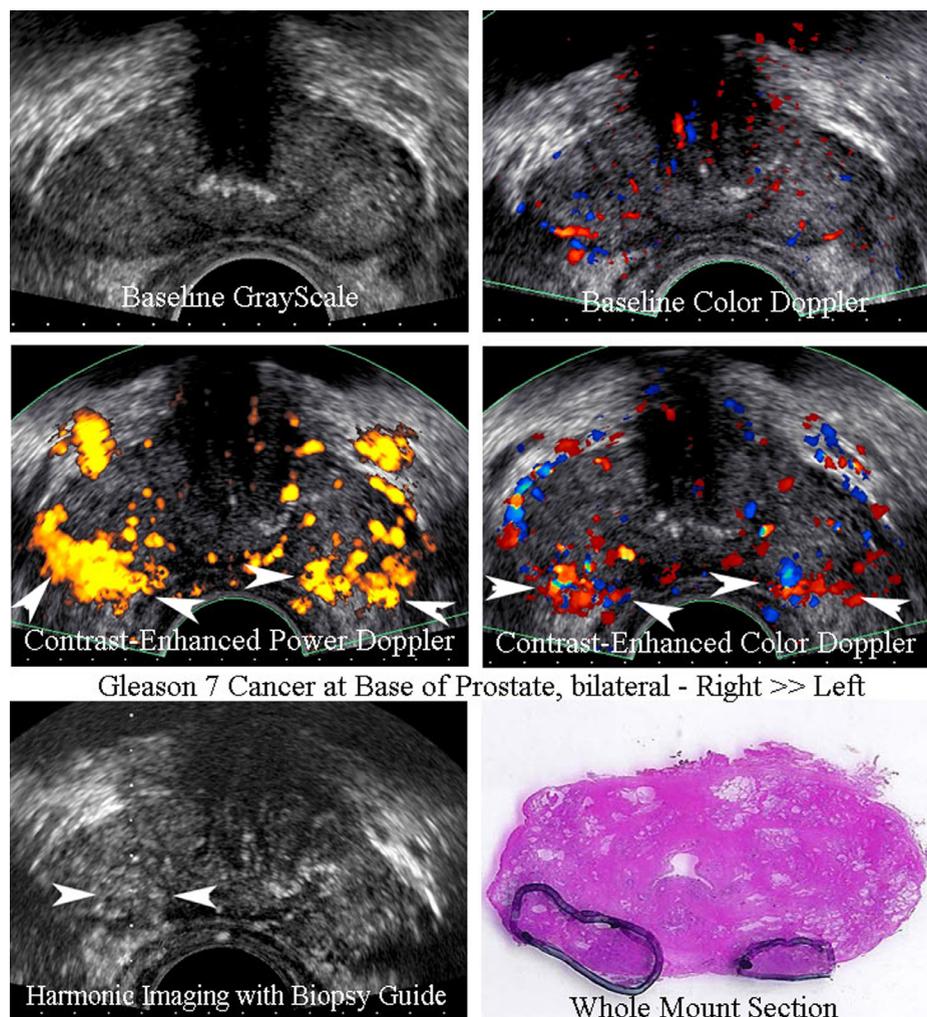


Figure 1. Comparison of various ultrasound imaging techniques to whole-mount pathology. Arrowheads demonstrate increased flow with CE-TRUS corresponding to two areas of Gleason 7 cancer at the base of the prostate. The cancer is not apparent on baseline grayscale and Doppler imaging.

Gleason score as a sum of major and minor patterns. This method is consistent with our previous study regarding whole-mount analysis.² Pathology maps of the prostate were digitized and summations of tumor area and volume were calculated using ImageJ software. Baseline TRUS and CE-TRUS findings were compared with whole-mount findings on a per-sextant basis (Fig. 1).

Statistical Analysis

A clustered logistic regression model was computed to compare the area under the receiver operating characteristic (ROC) curve (A_2) for detection of prostate cancer by various modes of ultrasound imaging. The clustered analysis includes an individual evaluation for each of the 12 systematic biopsy regions in the prostate, but accounts for the lack of true independence of observations within a single patient. For the purpose of receiver operating characteristic analysis, the 5 point imaging scores were treated as an interval scale, with increasing score suggesting higher likelihood of disease. For the calculation of sensitivity/specificity of cancer detection, a score ≥ 3 was considered positive. With regards to the systematic and targeted biopsy results, we retrospectively compared the detection rates of cancers deemed clinically significant (defined as

greater than 0.5 cc tumor volume or a Gleason score ≥ 7 according to whole-mount pathology) by CE-TRUS suspicious targeted cores vs the conventional systematic biopsy. We additionally calculated the potential detection rate of clinically significant cancer if all sextants rated as suspicious by CE-TRUS could be detected. P value $<.05$ was considered statistically significant.

RESULTS

Among the 58 whole-mount specimens, a maximum Gleason score of 6 was identified in 29 subjects, a score of 7 was identified in 24 and a score of 8 was identified in 5. Percent gland involvement was $<2\%$ (less than 1 cc tumor volume) in 8 subjects, 2%-5% in 19, 5%-10% in 14, and $>10\%$ in 17. The A_2 for baseline TRUS parameters was 0.55 for grayscale, 0.61 for color Doppler and 0.59 for power Doppler. CE-TRUS parameters demonstrated significant increases in A_2 with the highest A_2 for CE-power Doppler (0.66) and flash replenishment imaging (0.64) ($P = .04$ for comparison to baseline). When the evaluation was limited to subjects with $>2\%$ gland involvement, A_2 values were slightly higher for CE-TRUS, with the highest A_2 for CE-power Doppler (0.69) and flash replenishment imaging (0.65). The

combination of CE-power Doppler and flash replenishment imaging resulted in improved A_2 as compared with baseline imaging (0.70 vs 0.59, $P = .006$).

Although up to 6 targeted biopsy cores were allowed per patient, most patients had 2-4 targeted biopsies (mean of 3 targeted cores/patient). Targeted biopsy based upon CE-TRUS identified 42/58 (72%) of patients with cancer on whole-mount pathologic analysis, and identified multiple foci of high grade (Gleason score >6) cancer that were not detected by systematic biopsy. For patients with clinically significant cancers, CE-TRUS targeted biopsy identified 40/52 (77%). Of the 12 patients with clinically significant cancer who were not detected by CE-TRUS targeted biopsy, 9 had CE-TRUS changes prospectively identified as suspicious for malignancy at the site of cancer demonstrated on the whole mount, though the targeted biopsy cores from these areas did not yield a positive diagnosis. Thus, 49/52 of patients with significant cancers were associated with visible abnormalities on CEUS (sensitivity = 94%), though only 40/52 (77%) were detected on targeted biopsy.

The presence of prostatitis on pathologic evaluation was noted in 4.9% of all biopsy cores, including 4.1% of systematic cores and 7.3% of targeted biopsy cores ($P < .001$ by chi-square analysis). Thus, the presence of prostatitis did impact the targeting of cores within the prostate, and likely decreased the positive predictive value of CE-TRUS based upon the targeting of pathologically benign tissue with prostatitis.

DISCUSSION

Knowledge of tumor grade, size, and location may hold the key to provide better diagnosis, prognosis, and treatment options for patients with prostate cancer. Transrectal grayscale ultrasound-guided needle biopsy of the prostate continues to be the standard-of-care for diagnosis of prostate cancer.³ Prostate cancer misdiagnosis is a concern that persistently plagues systematic biopsy. By blindly sampling the entire prostate, the risk of missing high-risk prostate cancers^{11,12} as well as overdetecting clinically insignificant cancers¹³ is high. Image-guided therapies including MRI-TRUS fusion guided biopsy has demonstrated the capability of detecting high risk prostate cancers at a higher rate than systematic biopsy,¹⁴ however cost remains prohibitive for its widespread use in many centers,¹⁵ and user experience is thought to be influential in its overall effectiveness.^{15,16} Our study demonstrates that CE-TRUS biopsies can provide a cost-effective alternative to MRI-TRUS fusion biopsy. By targeting biopsy cores to areas of suspicion based on vascular dynamics observable on ultrasound, CE-TRUS biopsy can provide improved cancer detection compared to systematic biopsy, with potential for cost savings compared to MRI-TRUS fusion biopsy. A limitation of our study is the relatively small patient population. Nonetheless, our study is the largest to date to evaluate CE-TRUS with whole-mount correlation to define the true sensitivity and specificity of the CE-TRUS technique. Our findings demonstrate that contrast-enhanced ultrasonography demonstrates greater diagnostic accuracy than baseline imaging in diagnosis and prognosis of prostate carcinoma. Since 94% of clinically significant prostate cancers are associated with

findings on CE-TRUS, a normal CE-TRUS study will have high negative predictive value for the absence of clinically significant prostate cancer. In the setting of active surveillance for prostate cancer, CE-TRUS may be useful to allow noninvasive follow-up imaging without biopsy as long as there is no significant contrast enhancement within the prostate, and to limit biopsy to only those areas with contrast enhancement. Our findings also demonstrate the ability of targeted biopsy to detect higher grade cancers and elucidate novel foci of cancer that were not otherwise detected with systematic biopsy.

The subjective nature of our grading system for CE-TRUS is a limitation, as it relies upon observer experience with a learning curve to assess the presence of significant contrast enhanced findings, and is associated with interobserver variation. We are currently evaluating objective parameters of contrast-enhancement, including measures of perfusion, peak enhancement, time to peak enhancement, and local variations in enhancement. The development of quantitative techniques for measuring prostate perfusion will create a more objective sonographic examination for diagnosis and characterization of Prostate Cancer, thereby facilitating standardization of results and more widespread adoption of this technology.

CONCLUSION

The ability of CE-TRUS to improve detection of clinically significant disease has the potential to be very useful in stratifying the management of patients with prostate cancer. Vascular enhancement may serve as an ultrasonic parameter reflecting the biologic characteristics of individual prostate disease. Therefore, CE-TRUS should have a future role in routine detection of clinically significant prostate cancer, monitoring of patients of active surveillance or target selection with ablative therapies.

References

1. Cancer Stat Facts: Prostate Cancer <https://seer.cancer.gov/statfacts/html/prost.html>.
2. Borghesi M, Ahmed H, Nam R, et al. Complications after systematic, random, and image-guided prostate biopsy. *Eur Urol*. 2017;71:353.
3. Venderink W, Govers TM, de Rooij M, et al. Cost-effectiveness comparison of imaging-guided prostate biopsy techniques: systematic transrectal ultrasound, direct in-bore MRI, and image fusion. *AJR Am J Roentgenol*. 2017;208:1058.
4. Gershman B, Van Houten HK, Herrin J, et al. Impact of prostate-specific antigen (PSA) screening trials and revised PSA screening guidelines on rates of prostate biopsy and postbiopsy complications. *Eur Urol*. 2017;71:55.
5. Trabulsi EJ, Sackett D, Gomella LG, et al. Enhanced transrectal ultrasound modalities in the diagnosis of prostate cancer. *Urology*. 2010;76:1025.
6. Meyer HJ, Wienke A, Surov A. Correlation between ktrans and microvessel density in different tumors: a meta-analysis. *Anticancer Res*. 2018;38:2945.
7. Halpern EJ, McCue PA, Aksnes AK, et al. Contrast-enhanced US of the prostate with Sonazoid: comparison with whole-mount prostatectomy specimens in 12 patients. *Radiology*. 2002;222:361.

8. Lin H, Chen J, Chen C. A novel technology: microfluidic devices for microbubble ultrasound contrast agent generation. *Med Biol Eng Comput.* 2016;54:1317.
9. Halpern EJ, Ramey JR, Strup SE, et al. Detection of prostate carcinoma with contrast-enhanced sonography using intermittent harmonic imaging. *Cancer.* 2005;104:2373.
10. Halpern EJ, Gomella LG, Forsberg F, et al. Contrast enhanced transrectal ultrasound for the detection of prostate cancer: a randomized, double-blind trial of dutasteride pretreatment. *J Urol.* 1739;188:2012.
11. Fernandes ET, Sundaram CP, Long R, et al. Biopsy Gleason score: how does it correlate with the final pathological diagnosis in prostate cancer? *Br J Urol.* 1997;79:615.
12. Kvale R, Moller B, Wahlqvist R, et al. Concordance between Gleason scores of needle biopsies and radical prostatectomy specimens: a population-based study. *BJU Int.* 1647;103:2009.
13. Brown AM, Elbuluk O, Mertan F, et al. Recent advances in image-guided targeted prostate biopsy. *Abdom Imaging.* 1788;40:2015.
14. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA.* 2015;313:390.
15. Hutchinson RC, Costa DN, Lotan Y. The economic effect of using magnetic resonance imaging and magnetic resonance ultrasound fusion biopsy for prostate cancer diagnosis. *Urol Oncol.* 2016;34:296.
16. Calio B, Sidana A, Sugano D, et al. Changes in prostate cancer detection rate of MRI-TRUS fusion vs systematic biopsy over time: evidence of a learning curve. *Prostate Cancer Prostatic Dis.* 2017;20:436–441.