Assessing Cancer Risk on Novel 29 MHz Micro-Ultrasound Images of the Prostate: Creation of the Micro-Ultrasound Protocol for Prostate Risk Identification

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Abbreviations and Acronyms

GS = Gleason sum

MRI = magnetic resonance imaging

PI-RADS™ = Prostate Imaging-Reporting and Data System

PPV = positive predictive value

TRUS = transrectal ultrasound

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Purpose: Conventional ultrasound systems operate at 6 to 9 MHz and serve as the standard of care to guide prostate biopsies. We present a protocol using a novel high resolution (29 MHz) transrectal prostate micro-ultrasound system. This protocol includes a scoring system to assess the risk of prostatic carcinoma and enable real-time targeted biopsies.

Materials and Methods: The ExactVu™ system is currently being used in a multisite, 2,000-patient, randomized clinical trial. Cine loops of 400 biopsies from this trial were used to create the PRI-MUS™ (prostate risk identification using micro-ultrasound) protocol and risk scale. Validation was performed in an independent, pathology blinded set of 100 cines. Three of the 5 investigators performing this validation were familiar with micro-ultrasound but naïve to the PRI-MUS protocol and they received only 1 hour of training.

Results: Each increase in risk score demonstrated a 10.1% increase (95% CI 9.3–10.8) in the probability of clinically significant cancer. The risk score also increased with Gleason sum and cancer length with a slope of 0.15 (95% CI 0.09–0.21) and 0.58 (95% CI 0.43–0.73), respectively. Sensitivity and specificity were 80% and 37%, respectively, and the mean ± SD ROC AUC was 60% ± 2%. The protocol was more accurate for detecting high grade disease (Gleason sum greater than 7) with a peak AUC of 74% (mean 66%).

Conclusions: The new resolution of the micro-ultrasound platform paired with the PRI-MUS protocol shows promise for real-time visualization of suspicious lesions and targeting of biopsies. The improved performance of the protocol in more significant disease is consistent with the focus of the field on decreasing insignificant diagnoses and detecting high risk disease early.

Key Words: prostatic neoplasms, biopsy, ultrasonography, diagnostic imaging, clinical protocols

Advances in preclinical ultrasound technology have created new high frequency imaging systems (up to 55 MHz) enabling a new level of spatial resolution with visualization down to 30 μm. The first clinical application of this high resolution ultrasound is transrectal imaging for prostate

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cancer.[1] As in the pilot study these new ExactVu micro-ultrasound devices operate at 29 MHz (21 MHz center) compared to the 8 to 12 MHz (6 to 9 MHz center) of conventional clinical prostate ultrasound systems. This increased frequency provides superior spatial resolution down to 70 μm, leading to 300% improved resolution over existing platforms while maintaining a suitable imaging depth (approximately 50 mm) to visualize the anterior wall of the prostate. These improvements in resolution enable exquisite detail in prostate ultrasound images, which may enable improved visualization and targeting of suspicious regions as well as systematic micro-ultrasound guided prostate biopsy.

TRUS guided prostate biopsy is the current standard of care for the diagnosis of prostate cancer. It may be indicated in the setting of increased prostate specific antigen, abnormal digital rectal examination and/or abnormality of other serum or urinary tests specific for prostate cancer, for example PHI (Prostate Health Index) and PCA3. While hypoechoic areas are often (approximately 50% of cases) seen on conventional transrectal ultrasound,[2–4] their value for predicting biopsy malignancy is poor, providing a positive predictive value of only 18% to 42%.[5,6] More importantly, taking targeted biopsies of only these areas has a high false-negative rate, missing clinically significant cancer in up to 48% of patients with proven disease on radical prostatectomy.[4]

This has resulted in ultrasound being used primarily for biopsy guidance to visualize the prostate borders and midline to appropriately space and extract 8 to 12 systematic biopsy samples. These samples are typically taken systematically with a bias toward the lateral portions of the prostate to preferentially sample the peripheral zone. While they provide some level of consistency and are likely to reveal larger tumors, smaller cancers and atypically located cancers may be missed.

Cancer detection rates using conventional systematic TRUS biopsy range from 20% to 50%,[7–10] indicating that 60% to 80% of men undergo this procedure unnecessarily. The patients frequently undergo repeat or saturation biopsies, often in combination with more costly imaging such as MRI. These further procedures carry increased costs and complexity, and an increased risk of morbidity due to the repeat procedures and potential delays in diagnosis that could decrease the opportunity for treatment.

This study aims to provide evidence-based learning to operators for interpreting micro-ultrasound images of the prostate. This should enable more accurate identification of suspicious regions that are now visible at these higher resolutions and subsequently enable real-time targeting of these areas during micro-ultrasound guided prostate biopsy.

In other modalities, such as MRI, protocols (ie PI-RADS) have been developed to help identify common characterizations and manifestations of disease, standardize methodologies and provide consistent imaging based scoring systems to differentiate the risk of carcinoma in each tissue segment. In the same way a novel protocol and risk identification system called PRI-MUS is being developed to provide such a platform with the same intended benefits for micro-ultrasound.

This study represents the development and initial assessment of the PRI-MUS protocol. The study is based on initial findings from a multicenter trial of high resolution transrectal ultrasound vs standard transrectal ultrasound to identify clinically significant prostate cancer. Initial results focused exclusively on interpreting anatomical B-mode images. As functional scan data (eg power flow imaging, elastography and contrast enhancement) become available on micro-ultrasound, the PRI-MUS protocol will be extended to include these multiparametric measures.

METHODS

Image Acquisition

The novel 29 MHz ExactVu transrectal micro-ultrasound system and transducer were used in this study. Investigators acquired cines during each biopsy taken using the high resolution micro-ultrasound platform in patients enrolled in the Multi-Center Trial of High-resolution Transrectal Ultrasound Versus Standard Low-resolution Transrectal Ultrasound for the Identification of Clinically Significant Prostate Cancer (ClinicalTrials.gov NCT02079025). Selected cines from the first half of the trial were used in the development and initial validation of the PRI-MUS technique, which will allow for planned prospective validation in the second half of the trial. The ExactVu research instrument was used under investigational device exemption and has not yet received any regulatory approval for sale.

Pattern Selection Procedure

Whole mount radical prostatectomy slides registered to micro-ultrasound images from a pilot study of 25 men were used as a starting point to suggest useful imaging features.[1] Based on these discussions 200 randomly selected micro-ultrasound cines, each captured during 1 specific biopsy in a total of 121 patients, were analyzed by 3 trial investigators to determine imaging findings along the biopsy needle path indicative of high grade (GS greater than 7) and low-intermediate grade (GS 7 or less) carcinoma as well as normal tissue. Included in the sample were 100 benign, 50 low grade and 50 high grade biopsy proven samples. Investigators were blinded to the pathological findings of each biopsy sample and recorded the variety of features present along the needle path in each image.

These image features were then analyzed to see how often they were associated with biopsy proven cancer.

PRI-MUS Risk Scale

Creation. The RR ratio and the CI were calculated for each feature to determine how often the feature was associated with biopsy proven prostate cancer. Similar features were grouped based on common characteristics to simplify the scale. This final feature set was ranked based on risk level with a preference for features with smaller CIs.

Validation Experiment. Five investigators validated the risk scale in an independent set of 100 biopsy core cines from a total of 93 trial patients. Cines were selected randomly but only 1 core per subject could be used for a given class (benign, GS 6 with core length greater than 50%, GS 7, GS 8 or GS 9-10) to improve the diversity of appearances in each class and reduce bias due to correlation within each subject. The 100 loops were divided among the 5 classes based on per patient occurrence rates in this first part of the study. Of the loops 55 were benign, 2 were GS 6 with a core length greater than 50%, and 29 were GS 7, 9 were GS 8 and 5 were GS 9-10 cores. Three investigators who were not involved in PRI-MUS feature development received 1 hour of training on the PRI-MUS protocol by 2 investigators involved in the original feature analysis and were asked to score each cine loop while blinded to pathology findings. The 2 training investigators (A and E) also scored these cines. Investigators were asked to observe the location biopsied by noting the needle path as it passed through the tissue and only report the risk score of the patch of tissue actually biopsied.

RESULTS

Sonographic Feature RR

Six of the 10 sonographic features identified were found to be significantly associated with benign (values lower than 1) or malignant (values greater than 1) tissue using the RR ratio (table 1 and supplementary Appendix, http://jurology.com/).[11] Regardless of achieving significance in this small data set all features were included in the PRI-MUS protocol. Figure 1 shows an example of each feature to provide a context for the analysis.

Table 1. *RR of ultrasound features on blinded analysis of 100 biopsy proven benign and 100 biopsy proven malignant cine loops*

Feature	No. Loops/No. Ca	RR (90% CI)
Small regular ducts, "Swiss cheese"	7/1	0.28 (0.05—1.72)
Hyperechoic with or without ductal patches	50/14	0.49 (0.31—0.78)
Mild heterogeneity	42/24	1.19 (0.87—1.62)
Bright echoes in hyperechoic tissue	10/4	0.79 (0.37—1.71)
Heterogeneous cauliflower/smudgy/ mottled appearance	32/22	1.48 (1.11—1.97)
Bright echoes	30/18	1.24 (0.89—1.73)
Irregular peripheral zone border	1/1	2.01 (1.75—2.31)
Mixed echo lesions	2/2	2.02 (1.76—2.33)
Irregular shadowing	12/11	1.94 (1.54—2.43)

PRI-MUS Protocol

Based on the results of the unblinded analysis investigators agreed on a certain stepped protocol to guide analysis, including 1) identify the prostate border, noting any irregularities; 2) identify the peripheral zone, noting any irregularities in the border, if visualized; 3) assess the peripheral zone

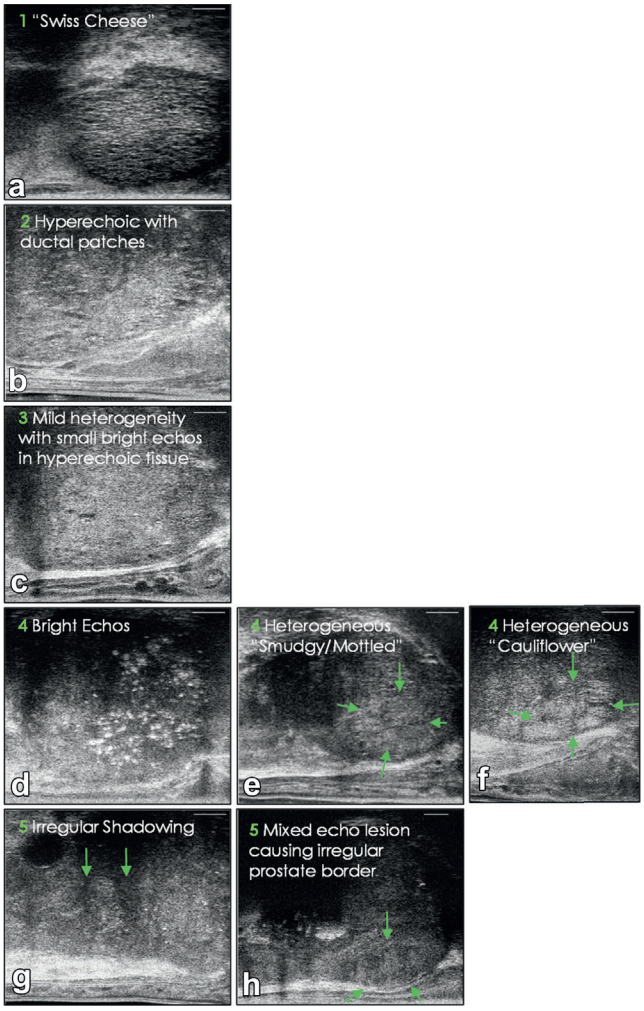

Figure 1. Ultrasound features used in PRI-MUS protocol. *a*, biopsy proven benign tissue shows regular pattern of ductal proliferation termed Swiss cheese appearance. *b*, biopsy proven benign tissue with hyperechoic and ductal regions. Presence or absence of these scattered ducts did not significantly affect risk level. *c*, tissue was benign on biopsy despite mild hypoechoic region (right side). Note mild heterogeneity with small bright echoes (focal bright points) in otherwise hyperechoic tissue. *d* to *f*, higher risk patterns of malignant tissue. *d*, strong bright echoes in hypoechoic GS 8 tissue. *e*, heterogeneous smudgy or mottled GS 7 tissue. *f*, heterogeneous cauliflower or focal nodular hyperplasia-type GS 8 tissue. *g* and *h*, irregular shadowing presenting as vertical hypoechoic regions with no obvious source of attenuation such as calcification or gas bubble. On right side mixed echo lesion with well-defined borders presses on rectal wall, resulting in irregular prostate border with border deflection of only 1.2 mm. Both biopsy samples showed GS 9. *1* to *5*, PRI-MUS risk level. Scale bars indicate 5 mm.

tissue for echogenicity and homogeneity; 4) if suspicious features are identified, analyze the remainder of the image to ensure that no artifacts are present that may have caused the suspicious features; and 5) assign a PRI-MUS risk score based on features (see Appendix).

The Appendix shows the PRI-MUS risk table, which was developed using data from table 1. Features at approximately the same risk level were combined to minimize the number of levels.

The complete PRI-MUS protocol, including a description of the prostate anatomy visible on micro-ultrasound, example images of each sonographic feature and example images of other normal and benign anatomical variants, will be reported separately. This protocol is designed to take advantage of the real-time nature of ultrasound to be applied live during real-time TRUS biopsy.

Validation Experiment Results

Five investigators examined an independent set of 100 high resolution micro-ultrasound biopsy cines, including a mixture of benign and malignant tissue in ratios similar to those in the ongoing clinical trial. Investigators assigned a risk score to each cine based on the set criteria.

Table 2 lists the number of times that each investigator assigned each risk score and the number of those samples that corresponded to biopsy proven cancer. These data were used to calculate ROCs (fig. 2). For each investigator sensitivity and specificity were also calculated as was the ROC AUC.

Accuracy and Consistency. Accuracy was assessed using the AUC under the individual ROC curves (fig. 2), which was a mean ± SD of 0.60 ± 0.02 (range 0.57 to 0.63). For a sensitivity of 80% these curves predicted a specificity of approximately 37%. The concordance correlation coefficient[12] was used to gauge interoperator variability (see supplementary Appendix, http://jurology.com/). It had a mean of 0.36, ranging from 0.23 to 0.57 or fair to moderate. The Cronbach α was 0.76, indicating good consistency. Absolute agreement measured by the Fleiss κ was predictably lower but still indicated slight agreement at 0.15.

To investigate the nature of the disagreement between reviewers a confusion matrix was generated.

Table 2. *Results of blinded verification experiment*

	Investigator (No. samples/No. Ca)				
Risk Level	A	B	C	D	E
1	0/0	0/0	4/2	1/0	1/0
2	13/3	9/4	33/13	45/17	23/7
3	47/20	47/19	27/8	31/15	48/21
4	35/18	31/12	25/13	10/4	19/12
5	5/4	13/10	11/9	13/9	9/5

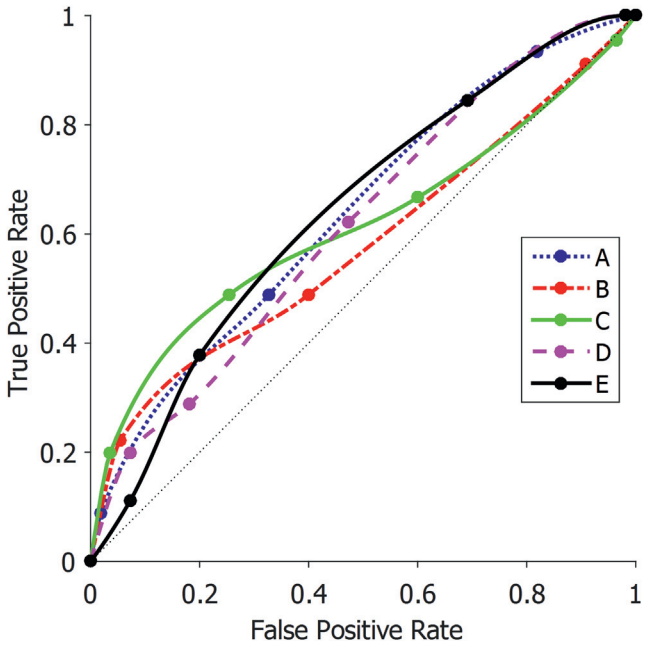

Figure 2. ROC curves to detect clinically significant cancer using PRI-MUS risk score. Mean ROC AUC was 0.60 ± 0.02 (range 0.57-0.63). *A* to *E*, 5 study investigators.

Each (x, y) position in the matrix represented the number of times that any reviewer marked a score of x while another reviewer marked a score of y. The matrix was then normalized by the total number of x and y positions scored. Figure 3 shows that the most common discrepancies occurred when one reviewer scored 3 and another scored 2 or 4. This is consistent with the Appendix since the difference between 2 and 3 or 3 and 4 was a matter of personal judgment about the level of heterogeneity or background echogenicity in the case of the bright echoes feature. Further refining the protocol will provide more guidance on defining these risk levels.

Linearity. Given the objective of making more efficient use of a fixed number of biopsy needles per patient, it is important to recognize the highest risk area in a section of prostate regardless of the overall risk level. This is the same as requiring the PRI-MUS risk scale to be monotonic. Indeed, over the validation data set increasing PRI-MUS risk score was linearly related to an increased probability of cancer with a slope of 10.1% increased risk per PRI-MUS rank (95% CI 9.3–10.8, fig. 4).

More Clinically Significant Disease Prediction. Linear regression analysis showed that the PRI-MUS score was significantly increased by increasing Gleason sum (slope 0.15, 95% CI 0.09–0.21) and by increasing fraction of malignant tissue in the biopsy core (slope 0.58, 95% CI 0.43–0.73). This increase in PRI-MUS score with increasing significance of

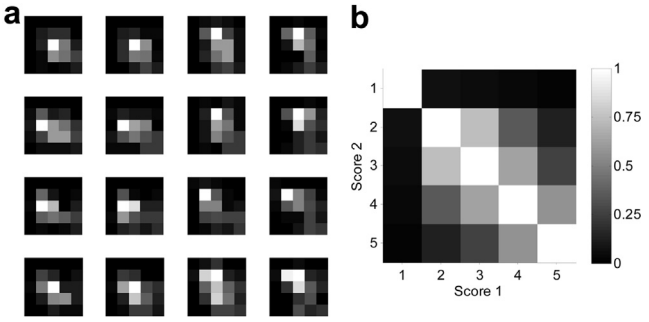

Figure 3. Confusion matrixes plotting fraction of cases in which pairs of reviewers selected particular scores. Diagonal represents cases in which reviewers selected same score. *a*, individual pairs of unnormalized confusion matrices. *b*, normalized overall confusion matrix of all pairs of reviewers shows strong diagonal with decreasing probability off diagonal, suggesting consistent metric. Most mismatched activity occurred between levels 2 and 3 with additional mismatch between 3 and 4, suggesting that distinctions between these levels may not be well defined.

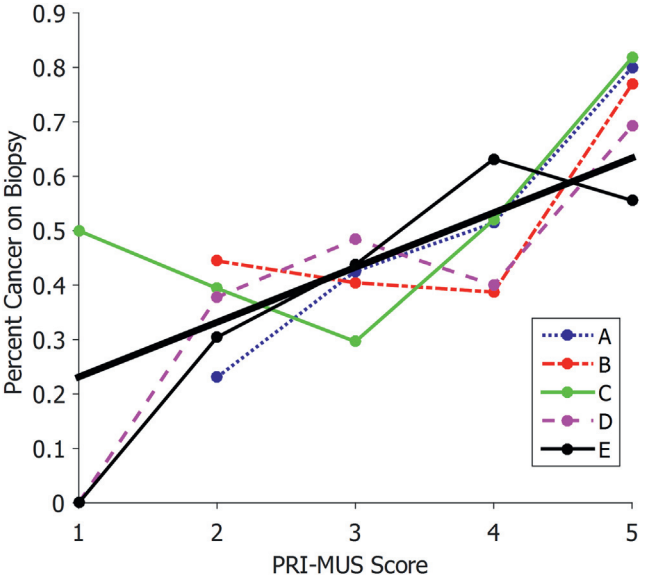

Figure 4. Risk score linearity with cancer probability. PRI-MUS protocol usefulness rests on risk scale monotonicity, in that tissue with higher risk level should be found to be malignant on biopsy more often than lower risk level tissue. Despite high variability of individual investigators, perhaps due to low sample size of some risk levels, overall statistically significant, linearly increasing trend was found that predicted 10.1% increase in probability of detecting cancer on biopsy for each PRI-MUS risk scale level (95% CI 9.3–10.8). *A* to *E*, 5 study investigators.

disease also provided improved detection accuracy. The ROC AUC for high grade disease (GS greater than 7) increased to a mean of 66% with 1 investigator achieving a peak AUC of 74%.

DISCUSSION

The usefulness of B-mode images for targeting biopsy needle placement has been debated for some time with most opting for a combined approach with a fixed systematic set and additional targeted cores when suspicious (often hypoechoic) lesions are seen.[3,13–15] With the new, significantly higher resolution imaging capabilities of micro-ultrasound we now have a basis to create the standardized protocol PRI-MUS, which will guide urologists to achieve accurate, reproducible results.

In this first implementation of the standardized PRI-MUS protocol for micro-ultrasound image analysis we achieved a mean accuracy (as measured using the ROC AUC) of 0.60 ± 0.02. This value is comparable to those in several studies performed using the MRI-based PI-RADS protocol when limited (as in the current series) to making judgments based only on anatomical (ie nonfunctional) scans such as T2-weighted MRI.[16,17] The accuracy of PI-RADS has been shown to improve dramatically when functional scans are added. When additional multiparametric micro-ultrasound data become available, as is planned, a further comparison between the 2 protocols will be most instructive.

The lack of similar studies using traditional ultrasound makes comparison more difficult. However, several groups have reported the sonographic appearance of known cancer, suggesting that these lesions appear notably hypoechoic in about 50% of cases and mildly hypoechoic in a remaining 22%.[2] Other sources indicate that when targeted biopsies are performed of hypoechoic lesions, findings are malignant in 42% of cases.[5] This suggests a PPV of 42% and potential sensitivity between 50% and 72%. When selecting a PRI-MUS threshold of 3 or greater for 80% sensitivity, our pooled data suggest a 48% PPV, demonstrating an improvement in sensitivity and PPV. However, without reported specificity or negative predictive values no proper conclusions can be drawn.

Several types of ultrasound based functional imaging have been established to provide significant detection improvements over traditional TRUS. Power/color flow (Doppler) imaging, which has demonstrated sensitivity and specificity values in the 80%[18,19] range, has been shown to provide synergistic information when combined with the standard B-mode.[20] Recent advances in elastography have also demonstrated significant improvements, increasing prostate cancer detection rates in some studies.[21–23] Finally, imaging with microbubble based contrast agents has been a good indicator of prostate cancer[24–28] that was approved for clinical use in Europe. Support for all 3 modes is planned on the micro-ultrasound platform. Future studies will incorporate these data into the PRI-MUS protocol.

It is encouraging to note that the PRI-MUS score increased with increasing disease severity in terms of core length (quantity of cancer) and Gleason sum (severity of cancer). This suggests that the risk score may be useful to improve biopsy accuracy as well as follow the progression of low grade lesions longitudinally as part of an active surveillance management strategy. Higher detection accuracy of up to 74% (mean 66%) was also found for high grade disease (GS greater than 7) compared to less significant disease (GS 7 or less), which may contribute to the clinical usefulness of the protocol.

A limitation in the data set used for this study is the fixed position of the biopsy needle in the image. While reviewing images, in certain cases the reviewers noted a needle that seemed to pass near or on the edge of a high suspicion area. Had the clinician been guiding the needle or if more extensive pathology results were available, we would know whether the area identified was truly malignant. With borderline biopsy locations it is difficult to say whether a score is truly incongruent.

These anecdotal findings of wanting to move a biopsy location are important because they suggest how the PRI-MUS system will be used in practice. A standard 12-core biopsy protocol with 2 cores per sextant still leaves a large volume of tissue available for each individual core. Selecting where to take the sample from is critical, particularly for small lesions. The important issue is whether cores should be spaced evenly to ensure that large lesions are found or to target relatively higher risk tissue in each area. It is beyond the scope of this study to issue a clinical recommendation. However, these data suggest that biasing core locations toward higher risk tissue when it is present is at least a valid strategy when supported by the added resolution capabilities of the micro-ultrasound platform.

Another limitation of this first version of the PRI-MUS system is that it was developed using cognitive image analysis performed after the biopsy using cines of targeted tissue. While this represents an advantage in terms of accurately capturing the exact area sampled by the needle, it is unclear how accurately each sextant would be scored in real time. Clinicians will likely scan each sextant, identify the most suspicious area using the PRI-MUS risk score table and then target a needle. It may be less important to accurately score each biopsied area than to know what image features are associated with malignancy and target those preferentially. Further optimization of PRI-MUS should only improve cancer detection.

In this first statement of the protocol feature definitions were agreed upon after review of only 200 cines. As with any new modality and protocol, time is required to build consensus on how to interpret images. As more procedures are completed, periodic reviews of the PRI-MUS committee will be held to refine our definitions and increase the set as needed. These refinements and standardizations are expected to improve results since in the current validation results the reviewers were generally correct when they all agreed on the PRI-MUS score with a score SD less than 0.6 over the reviewers. Of the cases 30 of 46 (65%) were correct compared to 29 of 54 (54%) in which reviewers disagreed. This improved accuracy for well categorized cases led to an improved AUC of 0.68. Understanding the source of these disagreements and how the analyses of the correct reviewers differed from the others will likely be used to inform updates to this initial version of PRI-MUS.

The PRI-MUS technique described focuses exclusively on peripheral zone lesions while perhaps 20% of cancers are known to have no peripheral zone component.[29,30] Our current data set does not have sufficient examples of proven anterior, transition or central zone lesions to provide useful guidance on their appearance. Future work with a more complete data set, including functional scans and perhaps more detailed histology analysis, may enable us to revise the protocol.

CONCLUSIONS

During the last 6 years the development of PI-RADS for MRI has continuously improved accuracy while also standardizing the complex protocols. We have leveraged this idea of standardization and applied it to a novel micro-ultrasound modality that has the potential to improve biopsy outcomes by improving the current TRUS biopsy procedure tool kit. By following the PI-RADS model we are optimistic that the PRI-MUS protocol applied to affordable, real-time micro-ultrasound imaging can guide new and experienced practitioners to improve overall detection rates of clinically significant cancer, improve false-negative rates and continue to improve these metrics in the coming years.

APPENDIX

PRI-MUS Risk Table

PRI-MUS Risk Score	Ca Risk	Findings
1	Very low	Small regular ducts, "Swiss cheese" with no other heterogeneity or bright echoes
2	Some	Hyperechoic with or without ductal patches (possible ectatic glands or cysts)
3	Indeterminate	Mild heterogeneity or bright echoes in hyperechoic tissue
4	Significant	Heterogeneous cauliflower/smudgy/mottled appearance or bright echoes (possible comedonecrosis)
5	Very high	Irregular shadowing (originating in prostate, not prostate border) or mixed echo lesions, or irregular prostate and/or peripheral zone border

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EDITORIAL COMMENT

The authors report high frequency TRUS to detect prostate cancer in the peripheral zone, which is a new technique. However, do we really need such high frequencies to detect prostate cancer? The use of such high frequencies (29 MHz) allows for the visualization of lesions in the submm range. We assume that detecting such lesions may lead to significant over diagnosis of insignificant prostate cancer.[1]

Currently, the system only offers B-mode. However, we know from TRUS and multiparametric MRI that determining functional

parameters, ie flow parameters, vascularity and diffusion, is important for an exact evaluation of suspicious lesions of the prostate. We strongly believe that the foundation of further improvements are based on a multiparametric approach.[2] Further refinements in TRUS may contribute to better detect prostate cancer. Further studies are warranted to evaluate the success of this technique, keeping in mind a sound methodology of evaluation.

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REPLY BY AUTHORS

The introduction of higher frequencies in any imaging modality is often met with resistance and skepticism regarding how much more detail can actually be visualized, especially when the pixel size is already smaller than any individual visible object. The purpose of increased resolution is not only to see smaller objects but also to see the textures, borders and details of objects more clearly. In prostate cancer diagnosis this amounts to a better appreciation of the microstructures and patterns of the tissue. In the same way that an appreciation of tissue organization informs pathological diagnosis, we believe that such improvements in resolution and newly identifiable tissue microstructures will inform and improve the placement of needle biopsies.

As discussed in the article, one of the key findings of the new PRI-MUS protocol is a linear relationship between PRI-MUS risk score and severity of disease as measured by pathology findings (Gleason sum and size). Contrary to the comment, this suggests that the protocol may lead to a reduction in over diagnosis by helping focus micro-ultrasound based biopsies on more significant disease.

We also agree that functional modes, particularly multiparametric imaging, are extremely promising for micro-ultrasound based prostate cancer detection.[1] The goal of the PRI-MUS protocol is to form an evidence-based platform on which other real-time micro-ultrasound based functional modalities can be synergistically added, similar to multiparametric MRI.[2] We believe that these refinements will increase detection accuracy and help further differentiate disease grade.

Finally, because ultrasound is the standard of care for prostate biopsies, we believe that there is significant potential for micro-ultrasound to eliminate or minimize the need for magnetic resonance-ultrasound fusion biopsies if the morphological changes provided by MRI (on T2-weighted imaging) can be detected in real time on the higher resolution micro-ultrasound platform.

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