MRI – ultrasound fusion guided biopsy of the prostate: lesion volume as a predictor of cancer in patients with repeat biopsies

Scott Alan Blaine*, Haidar M. Abdul-Muhsin, Nicholas J. Jakob, Paul E. Andrews, Robert G. Ferrigni, Stephen S. Cha[1], Ashkahn Golshani[2], Alvin C. Silva[2], Akira Kawashima[2], Mitchell R. Humphreys

Departments of Urology, [1]Research Biostatistics and [2]Radiology, Mayo Clinic, Phoenix, Arizona, USA
*E-mail: scottblaine1108@gmail.com

ABSTRACT

Introduction: The objective was to analyze the diagnostic value of multiparametric magnetic resonance imaging (MRI) prostate lesion volume (PLV) and its correlation with the subsequent MRI–ultrasound (MRI-US) fusion biopsy results. **Materials and Methods:** Between March 2014 and July 2016, 150 men underwent MRI-US fusion biopsies at our institution. All suspicious prostate lesions were graded according to the Prostate Imaging Reporting and Data System (PIRADS) and their volumes were measured. These lesions were subsequently biopsied. All data were prospectively collected and retrospectively analyzed. The PLV of all suspicious lesions was correlated with the presence of cancer on the final MRI-US fusion biopsy. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. **Results:** There were 206 suspicious lesions identified in 150 men. The overall cancer detection rate was 102/206 (49.5%). The mean PLV for benign lesions was 0.63 ± 0.94 cm^3 versus 1.44 ± 1.76 cm^3 for cancerous lesions ($P < 0.01$). There was a statistically significant difference between the PLV of PIRADS 5 lesions when compared to PIRADS 4, 3, and 2 lesions ($P < 0.0001$, < 0.0001, and 0.006, respectively). The area under the curve for volume in predicting prostate cancer (PCa) was 0.66. The optimal volume for predicting PCa was 0.26 cm^3 with a sensitivity, specificity, PPV, and NPV of 80.7%, 42.7%, 41.2%, and 74.6%, respectively. **Conclusion:** PLV may serve as a useful measure to triage patients prior to MRI-US fusion biopsy and help better understand the limits of this technology for individual patients.

INTRODUCTION

Prostate cancer (PCa) is the most common noncutaneous malignancy in American men.[1] The American Cancer Society estimated that in 2016, there would be 180,000 new cases and 26,000 deaths from PCa in the United States.[1] The diagnosis of PCa has traditionally relied on prostate-specific antigen levels and digital rectal examination findings. These two tests historically have served as useful measures to guide further evaluation with transrectal ultrasound (TRUS)

prostate biopsy, which is needed to confirm or rule out the presence of PCa. Due to the systematic nature of the traditional 12-core TRUS biopsy, false-negative results are prone to occur in up to 15%–34% of patients.[2-4] This specific caveat in PCa diagnostic algorithm resulted in the introduction of the concept of targeted biopsies.

Multiparametric magnetic resonance imaging (mpMRI) has been increasingly utilized for PCa lesion detection, characterization, and staging.[5,6] mpMRI utilizes T2-weighted

Access this article online	
Quick Response Code:	**Website:** www.indianjurol.com
	DOI: 10.4103/iju.IJU_49_19

imaging (T2WI), diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) imaging, and in some cases, magnetic resonance spectroscopy to generate a probability score to differentiate significant PCa from low grade or benign pathology. The Prostate Imaging Reporting and Data System (PIRADS) is a structured reporting system that is based on collective features of each lesion using the above-mentioned advanced imaging modalities. It assigns a (1–5) score for each lesion that reflects the probability of PCa (i.e., higher score and more suspicious of cancer).[7] Multiple studies have demonstrated that MRI-US fusion biopsies are superior to traditional systematic TRUS biopsies in terms of qualitatively defining clinically significant PCa.[8-11] Two recent studies reported PCa detection rates with sensitivities of 80% utilizing fusion biopsy platforms.[12,13]

The PIRADS system has undergone one revision and its updated version still carries a moderate degree of subjectivity in evaluating each one of its elements, and interobserver variability is still of concern. Prostate lesion volume (PLV) is potentially one of the most objective findings that can be measured using accurate software or standardized three-dimensional (3D) measurements in predefined MRI sequences. To date, the value of PLV in predicting PCa and assessing its aggressiveness is not clear, and it has a limited role in assigning the PIRADS score. The aim of this study is to examine the correlation and the diagnostic value of PLV and its correlation with PCa. Lesion volume can provide a simple selection tool for patients considering MRI-US fusion prostate biopsy.

MATERIALS AND METHODS

After institutional board review approval, all patients who underwent mpMRI and subsequently a targeted TRUS biopsy using an MRI-US fusion software between March 2014 and July 2016 at our institution were included. There were three indications to undergo mpMRI: (1) based on high clinical suspicion despite previous negative biopsies, (2) follow-up biopsy in active surveillance of known PCa, and (3) a limited number of patients with high clinical suspicion of PCa and no previous biopsies underwent direct MRI-US fusion biopsy. The data collected included baseline demographics, past medical history, past urological history, previous PCa history (in cases of active surveillance), mpMRI results, and MRI-US fusion biopsy results. All study data were collected and managed using Research Electronic Data Capture clinical database system.[14]

mpMRI of the prostate was performed with a 3T MRI scanner (Skyra, Siemens) with a phased array endorectal coil (Sentinelle, Siemens). T2-weighted series were obtained in axial, coronal, and sagittal planes. Intravenous gadolinium-based contrast-enhanced dynamic T1-weighted and delayed T1-weighted fast gradient-echo series and

diffusion-weighted series were obtained in the axial plane. Whenever a lesion was identified, a PIRADS score was generated using T2WI, DWI, and DCE. Suspicious lesions with a high PIRADS score (score >3) were biopsied. 3D PLVs were calculated by built-in software after outlining the lesion region of interest (ROI) by the radiologist using a free hand function on DynaCAD™ (Invivo Corp, Gainesville, Florida, USA). MRI-US fusion imaging was conducted using UroNav™ Fusion Biopsy System (Invivo Corp, Gainesville, FL, USA). All biopsies were performed under general anesthesia to avoid any movement or registration artifacts. While the patient was placed in the left lateral position, a dual-side/end-firing US probe (BK US, Peabody, MA, USA) was introduced into the rectum, and a systematic US examination of the prostate was performed. Once completed, the UroNav™ device was synchronized to combine the US and MRI images in a conventional manner. In our clinical practice, a sagittal "sweep" is performed for segmentation during this step. However, axial segmentation of the prostate was sometimes used based on the appearance of the prostate and at the discretion of the surgeon. Marked 3D lesion ROIs were biopsied and sent for histopathological examination. We obtained 4–5 cores from each ROI. All targeted biopsies were followed by a standard 12–18-core biopsy. The exact number of cores was determined based on the surgeon discretion and the US findings. Univariate analysis was conducted to compare PLV between lesions with and without cancer. Receiver operating characteristic was used to estimate the area under the curve (AUC) of PLV in PCa diagnosis.

RESULTS

There were 206 suspicious lesions identified in 150 men who underwent MRI-US fusion biopsy of the prostate during the study period. The mean prostate-specific antigen value was 9.7 (SD ± 9.3). Of the 150 men, 79 (53%) had a prior TRUS biopsy that was negative for PCa with persistent high clinical suspicion, 60 (40%) had the previous diagnosis of PCa and were on active surveillance, and 11 (7%) presented with clinically suspected PCa who directly underwent mpMRI and MR-US fusion biopsy. Following evaluation with MRI, there were 105 patients with 1 ROI, 34 patients with 2 ROIs, 8 patients with 3 ROIs, and 2 patients with 4 ROIs. Overall, 93 patients were diagnosed with cancer following MRI-US fusion biopsies (62%). The overall cancer detection rate in prostate lesions was 102/206 (49.5%). The mean PLV for all lesions regardless of the final diagnosis was 1.0 cc ± 1.05. The mean volume for lesions with no evidence of cancer was 0.63 ± 0.94 cm^3, whereas the mean volume for those lesions identified with cancer was 1.44 ± 1.76 cm^3 ($P < 0.01$) [Figure 1]. There was a statistically significant difference between the PLV of PIRADS 5 lesions when compared to PIRADS 4, 3, and 2 lesions ($P < 0.0001$, < 0.0001, and 0.006, respectively) [Figure 2]. No statistical difference could be identified among the PLV for

different Gleason scores, as shown in Figure 3. The diagnostic yield for PLV in comparison to various PIRADS categories are shown in Table 1. Receiver operating characteristic was used to estimate the AUC of PLV in PCa diagnosis [Figure 4] and PIRADS in PCa diagnosis [Figure 5]. The AUC of ROI volume in predicting PCa was 0.66, and for PIRADS, it was 0.72. Using this same model, the optimal volume cutoff for predicting PCa was 0.26 cm^3 with a sensitivity, specificity, positive predictive value, and negative predictive value of 80.7%, 42.7%, 41.2%, and 74.6%, respectively.

DISCUSSION

mpMRI and MRI-US fusion biopsy have greatly increased our ability to detect and properly stage clinically significant PCa using the PIRADS system.[12,13] However, this classification system is not without its drawbacks. The grading is subjective in many ways, often differing between radiologists; it relies on numerous parameters, which often results in a persistently high number of negative biopsies.

Although its cancer-predictive value has been shown in multiple studies, we believe that using it in conjunction with other objective parameters prior to biopsy can help refine its utility. If a lesion was found to be suspicious using the PIRADS, then PLV measurement can be employed as an efficient and accurate practice to determine which lesion can be actually sampled. Moreover, lesion volumes may serve as a surrogate to augment the surgeon's ability to assess a lesion prior to biopsy when no PIRADS is assigned or when no contrast was administered or was contraindicated.

The current role of PLV in the diagnosis of PCa is not yet clear. Although other studies have examined the volume of the prostate as a function of cancer, few studies exist that examine the volume of a specific lesion found on mpMRI. A study by Le Nobin *et al.* determined that volume estimates of PCa using MRI tended to underestimate histopathological volumes, with a wide variability in the extent of underestimation.[15]

Table 1: Diagnostic performance of prostate lesion volume and PIRADS system

Test	Sensitivity	Specificity	PPV	NPV
PIRADS 2	1.000	0.091	0.103	1.000
PIRADS 3	1.000	0.313	0.284	1.000
PIRADS 4	0.936	0.859	0.538	0.944
PIRADS 5	0.487	1.000	0.723	0.712
PLV >0.26	0.807	0.427	0.412	0.746

PPV=Positive predictive value, NPV=Negative predictive value, PIRADS=Prostate Imaging Reporting and Data System, PLV=Prostate lesion volume
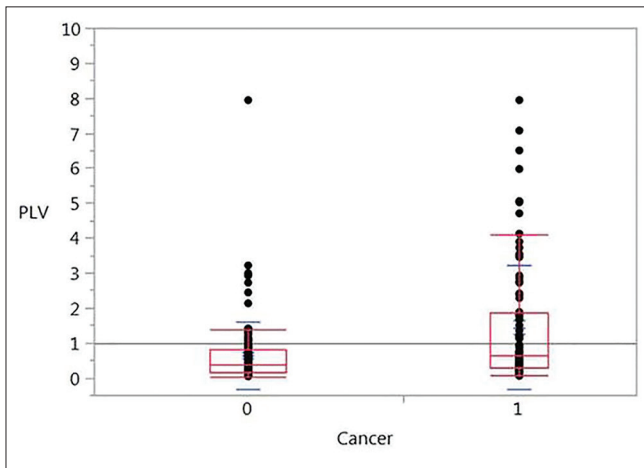

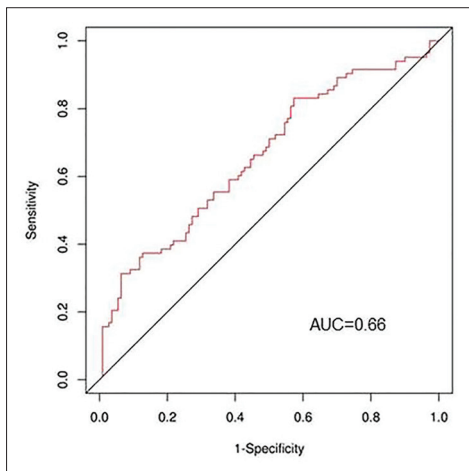**Figure 1:** Comparison of prostate lesion volumes among cancer and noncancer lesions

Figure 2: Comparison of prostate lesion volumes among different Gleason scores

Figure 3: Comparison of prostate lesion volumes among different Prostate Imaging Reporting and Data System classes

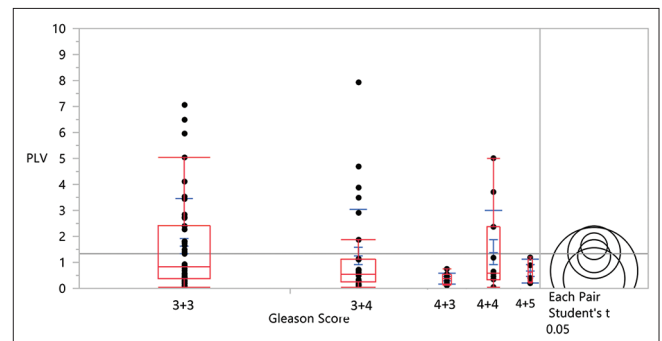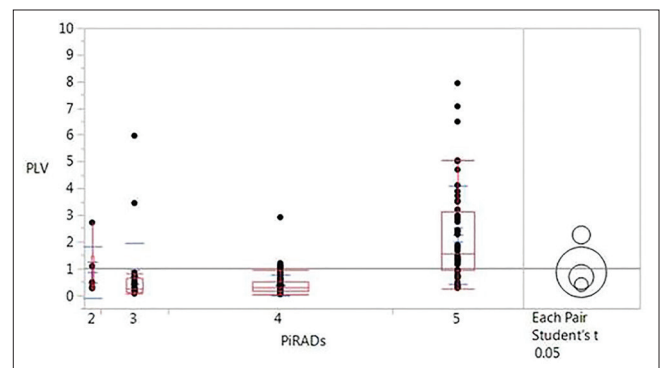**Figure 4:** Receiver operating characteristics analysis for prostate lesion volume
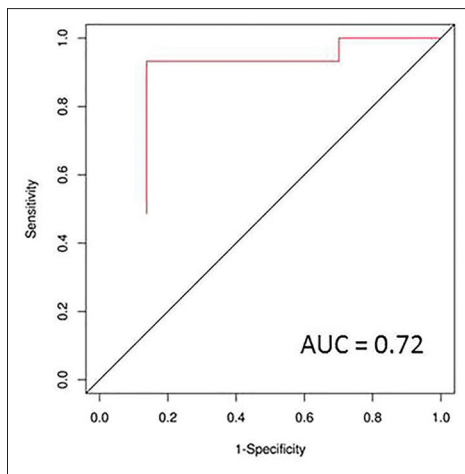
Figure 5: Receiver operating characteristics analysis for Prostate Imaging Reporting and Data System

As a reference, the mean difference in prostate volumes between T2WI and registered histopathology was 0.37 mL, indicating that overall prostate volume measurement between the two modalities is concordant. In another study, Mazaheri *et al.* compared histopathology tumor specimens to preoperative mpMRI and concluded that concordance was high between ellipsoid volume formula, volumetric measurements, MRI measurements, and histopathology.[16] In a study of 89 patients who underwent mpMRI prior to prostatectomy by Cornud *et al.*, histology revealed that 99 clinically significant tumors with a volume of >0.2 cc and/or a Gleason score >6.16 (16.2%) of the 99 tumors were undetected by mpMRI.[17] In this study, the tumor volume correlated significantly with pathological volume. Volume underestimation was significantly higher for tumor foci <0.5 cc. In one recent study by Salami *et al.*, diffusion coefficient and lesion volume were examined as a function of cancer. They found that the median volume for a lesion identified as benign after biopsy was 0.25 cm^3, whereas a cancerous lesion was 0.37 cm^3 ($P = 0.016$).[18] In addition, 47.6% of lesions >1 cm^3 were cancerous on biopsy. Our study found that the mean volume of biopsied benign lesions was 0.64 cm^3, whereas the mean volume of cancerous lesions was 1.44 cm^3. In another study by Donati *et al.*, the authors found that the mean ADC value of a lesion was an independent predictor of aggressiveness and that tumor volume (as measured on ADC maps) approached, but did not reach, statistical significance.[19] Collectively, these data suggest that there may be clinical utility in measuring lesion volume, as well as using other measurements obtained with mpMRI.

Theoretically, the PLV value in diagnosing PCa in MRI can be explained by the assumption that a PCa lesion should reach a certain size before declaring itself clinically, and if it is biopsied during this period of time, it can be caught before progression. To assess the utility of volume as a predictor of cancer, we generated a ROC curve using PCa as a function of lesion volume, which yielded an optimal cut point of 0.26 cm^3 and an AUC of 0.66, which was 81% sensitive and 43% specific. Although an AUC value of 0.66 suggests only marginal predictive value, the AUC for PIRADS as a function of PCa in our cohort was only 0.70 which is the current standard in grading mpMRI images prior to biopsy. Given that the AUC of lesion volume was similar to the AUC for PIRADS (the accepted standard), it is likely that both parameters may serve as useful indicators to predict cancer on biopsy.

Despite the growing body of knowledge suggesting utility in MRI-US fusion-guided biopsy, much work remains to be done, and our study is not without limitations. First, this was a retrospective study with relatively small size ($n = 206$ lesions analyzed). Second, our results reflect the learning curve of multiple surgeons in using this technology. Third, results of this type should also be taken with the proper amount of discretion, as there is no direct evidence that a prostate lesion is actually sampled (i.e., small lesions were not found cancerous because they were not actually sampled in contrast to large lesion that were easy to sample). Fourth, the results may potentially differ using different imaging techniques such as 1.5T versus 3T and use of endorectal coil versus not. These factors were not comparatively assessed in this study. There are several practice-specific changes that can potentially affect the results such as performing the biopsy under local versus general anesthesia in addition to the specific technique of the imaging used. The accuracy of the biopsy system is limited naturally, and this may be more prominent in lesions with small volume which can theoretically impact the results.

CONCLUSION

Our study demonstrated that PLV can have a predictive role in the diagnosis of PCa on biopsy in conjunction with the PIRADS scoring system. Both PIRADS and PLV can assist the surgeon in making a clinical assessment of the aggressiveness of a prostatic lesion based on the results of mpMRI. This offers the benefit of making a clinical assessment prior to performing a biopsy, which in theory should help reduce the rate of false-negative biopsies by better selecting which lesions should and should not be biopsied to begin with.

REFERENCES

1. American Cancer Society. Vancouver reference style. Key Statistics for Prostate Cancer. Available from: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics. [Last updated on 2016 Mar 11; Last accessed on 2016 Sep 14].
2. Levine MA, Ittman M, Melamed J, Lepor H. Two consecutive sets of transrectal ultrasound guided sextant biopsies of the prostate for the detection of prostate cancer. J Urol 1998;159:471-5.
3. Chen ME, Troncoso P, Johnston DA, Tang K, Babaian RJ. Optimization

of prostate biopsy strategy using computer based analysis. J Urol 1997;158:2168-75.

4. Roehrborn CG, Pickens GJ, Sanders JS. Diagnostic yield of repeated transrectal ultrasound-guided biopsies stratified by specific histopathologic diagnoses and prostate specific antigen levels. Urology 1996;47:347-52.

5. Siddiqui MM, Rais-Bahrami S, Truong H, Stamatakis L, Vourganti S, Nix J, *et al.* Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. Eur Urol 2013;64:713-9.

6. Delongchamps NB, Rouanne M, Flam T, Beuvon F, Liberatore M, Zerbib M, *et al.* Multiparametric magnetic resonance imaging for the detection and localization of prostate cancer: Combination of T2-weighted, dynamic contrast-enhanced and diffusion-weighted imaging. BJU Int 2011;107:1411-8.

7. Turkbey B, Choyke PL. PIRADS 2.0: What is new? Diagn Interv Radiol 2015;21:382-4.

8. Turkbey B, Albert PS, Kurdziel K, Choyke PL. Imaging localized prostate cancer: Current approaches and new developments. AJR Am J Roentgenol 2009;192:1471-80.

9. Turkbey B, Pinto PA, Choyke PL. Imaging techniques for prostate cancer: Implications for focal therapy. Nat Rev Urol 2009;6:191-203.

10. Wang L, Mazaheri Y, Zhang J, Ishill NM, Kuroiwa K, Hricak H, *et al.* Assessment of biologic aggressiveness of prostate cancer: Correlation of MR signal intensity with Gleason grade after radical prostatectomy. Radiology 2008;246:168-76.

11. Turkbey B, Shah VP, Pang Y, Bernardo M, Xu S, Kruecker J, *et al.* Is apparent diffusion coefficient associated with clinical risk scores for prostate cancers that are visible on 3-T MR images? Radiology 2011;258:488-95.

12. Rastinehad AR, Turkbey B, Salami SS, Yaskiv O, George AK, Fakhoury M, *et al.* Improving detection of clinically significant prostate cancer: Magnetic resonance imaging/transrectal ultrasound fusion guided prostate biopsy. J Urol 2014;191:1749-54.

13. Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, *et al.* Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390-7.

14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.

15. Le Nobin J, Orczyk C, Deng FM, Melamed J, Rusinek H, Taneja SS, *et al.* Prostate tumour volumes: Evaluation of the agreement between magnetic resonance imaging and histology using novel co-registration software. BJU Int 2014;114:E105-12.

16. Mazaheri Y, Goldman DA, Di Paolo PL, Akin O, Hricak H. Comparison of prostate volume measured by endorectal coil MRI to prostate specimen volume and mass after radical prostatectomy. Acad Radiol 2015;22:556-62.

17. Cornud F, Khoury G, Bouazza N, Beuvon F, Peyromaure M, Flam T, *et al.* Tumor target volume for focal therapy of prostate cancer-does multiparametric magnetic resonance imaging allow for a reliable estimation? J Urol 2014;191:1272-9.

18. Salami SS, Ben-Levi E, Yaskiv O, Turkbey B, Villani R, Rastinehad AR. Risk stratification of prostate cancer utilizing apparent diffusion coefficient value and lesion volume on multiparametric MRI. J Magn Reson Imaging 2017;45:610-6.

19. Donati OF, Afaq A, Vargas HA, Mazaheri Y, Zheng J, Moskowitz CS, *et al.* Prostate MRI: Evaluating tumor volume and apparent diffusion coefficient as surrogate biomarkers for predicting tumor Gleason score. Clin Cancer Res 2014;20:3705-11.