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Magnetic Resonance Imaging/Transrectal Ultrasonography Fusion Prostate Biopsy Significantly Outperforms Systematic 12–Core Biopsy for Prediction of Total Magnetic Resonance Imaging Tumor Volume in Active Surveillance Patients

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Abstract

Objective: To correlate the highest percentage core involvement (HPCI) and corresponding tumor length (CTL) on systematic 12-core biopsy (SBx) and targeted magnetic resonance imaging/transrectal ultrasonography (MRI/TRUS) fusion biopsy (TBx), with total MRI prostate cancer (PCa) tumor volume (TV).

Patients and Methods: Fifty patients meeting criteria for active surveillance (AS) based on outside SBx, who underwent 3.0T multiparametric prostate MRI (MP–MRI), followed by SBx and TBx during the same session at our institution were examined. PCa TVs were calculated using MP-MRI and then correlated using bivariate analysis with the HPCI and CTL for SBx and TBx.

Results: For TBx, HPCI and CTL showed a positive correlation ($R^2 = 0.31$, $P < 0.0001$ and $R^2 = 0.37$, $P < 0.0001$, respectively) with total MRI PCa TV, whereas for SBx, these parameters showed a poor correlation ($R^2 = 0.00006$, $P = 0.96$ and $R^2 = 0.0004$, $P = 0.89$, respectively). For detection of patients with clinically significant MRI derived tumor burden greater than 500 mm^3, SBx was 25% sensitive, 90.9% specific (falsely elevated because of missed tumors and extremely low sensitivity), and 54% accurate in comparison with TBx, which was 53.6% sensitive, 86.4% specific, and 68% accurate.

Conclusions: HPCI and CTL on TBx positively correlates with total MRI PCa TV, whereas there was no correlation seen with SBx. TBx is superior to SBx for detecting tumor burden greater than 500 mm^3. When using biopsy positive MRI derived TVs, TBx better reflects overall disease burden, improving risk stratification among candidates for active surveillance.

Introduction

Prostate cancer (PCa) tumor volume (TV) has been directly correlated with histopathologic stage and biochemical recurrence after radical prostatectomy (RP), and therefore is an important prognostic factor.[1,2] During initial evaluation, tumor quantification with percent of positive cores and/or core length involvement on prostate biopsy is used to infer burden of disease and subsequently risk stratify patients. The percent of tumor involvement in positive cores and core tumor length on systematic transrectal ultrasonography (TRUS)-guided prostate biopsy (SBx) have been correlated with TV as well as pathologic and oncologic outcomes.[3–8] Accurate assessment of core involvement by percent core and core length is therefore critical in stratifying PCa patients, particularly those being considered for active surveillance (AS) versus local and/or definitive treatment.

Advances in multiparametric prostate magnetic resonance imaging (MP-MRI) have allowed for better visualization of the intraprostatic anatomy and identification of potentially malignant lesions. MP-MRI derived TV is positively correlated with and accurately predicts histopathologic TV from RP specimens, making it a reliable surrogate for PCa TV calculation.[9–11] The targeted MRI/TRUS fusion biopsy (TBx) platform directly

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targets and more accurately samples intraprostatic lesions.[12–14] This improved targeting may allow for better assessment of tumor burden and more accurate risk stratification in patients with PCa when compared with 12-core SBx.

The aim of this study was to determine the correlation of highest percentage core involvement and corresponding core tumor length, obtained with SBx and TBx, with total MRI PCa TV.

Patients and Methods

Study population

This prospective study assessing TBx with electromagnetic tracking at the National Cancer Institute (NCI) of the National Institutes of Health (NIH) was approved by the Institutional Review Board (ClinicalTrials.gov identifier: NCT00102544). Patients were prospectively enrolled and provided written informed consent. Patients who underwent MP-MRI with SBx and TBx at the NCI between January 2007 and June 2013 were reviewed and retrospectively analyzed.

We identified 823 patients who had MP-MRI with subsequent SBx and TBx during the study period. Fifty of these patients had a diagnosis of PCa and met criteria for AS, based on outside SBx, defined by clinical stage T_{1c} disease, PSA density <0.15 ng/mL, Gleason score ≤6, two or fewer biopsy cores with cancer, and a maximum of 50% involvement of any core with cancer.[15] These patients were included for analysis. Patient demographics, prebiopsy prostate-specific antigen (PSA) level, PSA density, number of cancer-positive lesions, lesion diameter, and total PCa TV were noted.

MP-MRI and segmentation

Diagnostic MP-MRI using a 3.0T MRI scanner (Achieva; Philips Healthcare, Andover, MA) with a 16-channel cardiac surface coil (SENSE; Philips Healthcare) positioned over the pelvis and an endorectal coil (BPX-30; Medrad Inc., Pittsburgh, PA) was performed. Tri-planar T2 weighted (T2W), axial diffusion weighted (DW) imaging, axial dynamic contrast-enhanced (DCE) and three-dimensional MR spectroscopy were conducted according to protocol as described previously.[16] Images underwent blinded centralized radiologic evaluation by two genitourinary radiologists (BT and PLC) with 8 and 14 respective years of experience with MP-MRI. Screen-positive lesions were identified and assigned PCa suspicion scores (low, moderate, and high) based on the number of positive imaging sequences for each individual lesion in accordance with previously described criteria.[14]

A commercial research software platform (iCAD, Nashua, NH) was used to measure greatest diameter, manually segment, and calculate the TV for each identified lesion on MRI, blinded to the clinical and histopathologic data. TV calculation was standardized by summation of MRI TVs from biopsy positive lesions determined on TBx. For tumor segmentation on MRI, T2W MRI, apparent diffusion coefficient maps of DW-MRI and DCE-MRI sequences were integrated and used in combination. The final regions of interest, however, were drawn on T2W MRI for targeting during fusion biopsy.

Biopsy protocol

After baseline MP-MRI study, patients with identified lesions suspicious for PCa (stratified based on the validated NIH scoring system) subsequently underwent prostate biopsy.[14] All patients underwent SBx, in which the operator was blinded to the suspicious lesions that were identified on MRI. During the same biopsy session, the patients also had a TBx using the prebiopsy MP-MRI images, which were segmented, registered, and fused with the TRUS images using electromagnetic tracking. For each suspicious lesion, a core was taken in the axial and sagittal planes targeting the center of the lesion.[12,17] All biopsies underwent blinded centralized histopathologic evaluation by a single genitourinary pathologist (MJM).

Study design

The highest percentage of a positive core and the corresponding core length in centimeters, for both SBx and TBx, was determined for each patient. Only biopsy results that corresponded temporally with the MP-MRI study used for lesion segmentation were evaluated for this study, irrespective of multiple MP-MRI studies or repeated biopsy sessions. Based on the TBx positive lesions, the individual TVs calculated were summated to obtain a total PCa TV for each patient. Results from SBx and TBx were also compared to assess the detection of MRI derived tumor burden greater than 500 mm^3, a previously identified threshold for low volume disease.[1] The biopsy parameter used was the highest percentage core involvement at a threshold of 50%, a value commonly used in multiple AS criteria.[18]

Statistical analysis

Descriptive statistics were used to report patient demographics. Bivariate analysis was used to determine the empirical relationship, for both SBx and TBx, between the highest percentage core involvement and corresponding tumor length and the total PCa TV. The correlative R^2 value for each of these was also determined. JMP Pro v.10.0 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

Results

Patient-level characteristics of the cohort are outlined in Table 1. The mean age of the patient population was 61.4 years, mean prebiopsy PSA level was 5.34 ng/mL, and the mean prebiopsy PSA density was 0.12 ng/mL^2. The mean number of PCa lesions based on TBx was 1.38 lesions and mean lesion diameter was 1.1 cm.

The mean total PCa TV for the cohort was 968.3 mm^3 (Table 1). TBx diagnosed PCa in 50 patients and SBx diagnosed PCa in 37 patients, resulting in a cancer detection rate of 100% and 74%, respectively. Figure 1 illustrates the linear regression model presenting the correlation of the highest percentage core involvement to total PCa TV for SBx and TBx. For the highest percentage core involvement, TBx showed a positive correlation ($R^2 = 0.31$) whereas SBx showed a poor correlation ($R^2 = 0.00006$) with total PCa TV ($P < 0.0001$ and $P = 0.96$, respectively). Figure 2 illustrates the linear regression model presenting the correlation of the tumor length in the core with the highest percentage involvement to total PCa TV for SBx and TBx. For the tumor length of the highest percentage core, TBx showed a positive correlation ($R^2 = 0.37$) whereas SBx showed a poor correlation ($R^2 = 0.0004$) with total PCa TV ($P < 0.0001$ and $P = 0.89$, respectively).

Table 1. Demographics, Multiparametric Prostate Magnetic Resonance Imaging and Biopsy Findings of 50 Men with Prostate Cancer Meeting Criteria for Active Surveillance

Characteristics	P-*Value*
Number of men	50
Age, year, mean ± SD	61.4 ± 7.7
PSA, ng/mL, mean ± SD	5.34 ± 2.6
PSA density, ng/mL^2, mean ± SD	0.12 ± 0.07
Highest cancer suspicion score on MP-MRI, No. (%)[a]	
Low	9 (18)
Moderate	32 (64)
High	9 (18)
Biopsy parameters	*Mean ± SD*
Number of lesions biopsied	2.6 ± 1.4
Number of positive lesions (on targeted biopsy)	1.38 ± 0.6
Lesion diameter of positive lesions, cm	1.1 ± 0.5
Total positive tumor volume, mm^3	968.3 ± 1078.6
Highest % core involvement (on systematic 12-core biopsy)	22.5 ± 22
Highest % core tumor length (on systematic 12-core biopsy), cm	0.33 ± 0.32
Highest % core involvement (on targeted biopsy)	34.6 ± 27.4
Highest % core tumor length (on targeted biopsy), cm	0.49 ± 0.43

[a]Based on appearance of suspicious lesions on four different magnetic resonance imaging parameters as noted in Methods.

PSA = prostate-specific antigen; SD = standard deviation; MP-MRI = multiparametric prostate magnetic resonance imaging.

Of particular clinical relevance is the ability of the biopsy core to reflect clinically significant PCa disease burden. Tables 2a and 2b compare SBx and TBx parameters for the detection of tumor burden greater than 500 mm^3. SBx core percentage did not demonstrate any association with tumor burden greater than 500mm^3 ($P = 0.26$) whereas TBx did demonstrate a significant association ($P = 0.0067$). For detecting tumor burden greater than 500 mm^3, SBx highest percentage core involvement greater than 50% yielded a sensitivity, specificity, and accuracy of 25%, 90.9%, and 54%, respectively. TBx yielded a sensitivity, specificity, and accuracy of 53.6%, 86.4%, and 68%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) for SBx were 77.8% and 48.8% respectively; for TBx, the PPV was 83.3% and NPV was 59.4% (Table 3).

Discussion

Tumor volume is an important prognostic factor in patients with PCa and is associated with histopathologic stage, Gleason grade, lymph node metastasis, and disease progression.[1,19–21] Prostate tumor burden is determined directly from RP specimens or inferred indirectly from SBx, having limited relevance for patients desiring other forms of treatment or who are not surgical candidates. One critical manner in which urologists determine burden of disease preintervention is percentage core involvement and tumor length determined on prostate biopsy. The current study demonstrated that percent core involvement and corresponding tumor length from TBx were significantly better predictors of total MRI PCa TV than the same parameters derived from SBx.

Previous studies, using systematic TRUS-guided prostate biopsies, have demonstrated the correlation of the percentage of tumor involvement in positive cores and core tumor length with PCa TV, pathologic stage, and/or biochemical recurrence.[3–8,22–25] In these studies, patient populations were not limited to AS candidates who have a lower disease burden and likely account for the differences in our findings. In addition, lesions sampled with TRUS-guided biopsy were largely within the more accessible posterior peripheral zone and did not account for lesion location.

Given that TBx can find cancer outside of the established template, it is understandable that SBx would tend to yield results that correlate poorly with TV, whereas TBx would be expected to yield more reliable predictions of TV. TV from radical prostatectomy specimens is difficult to ascertain because it is derived from linear measurements at selected levels of permanent pathology sections. MP-MRI based TV is a

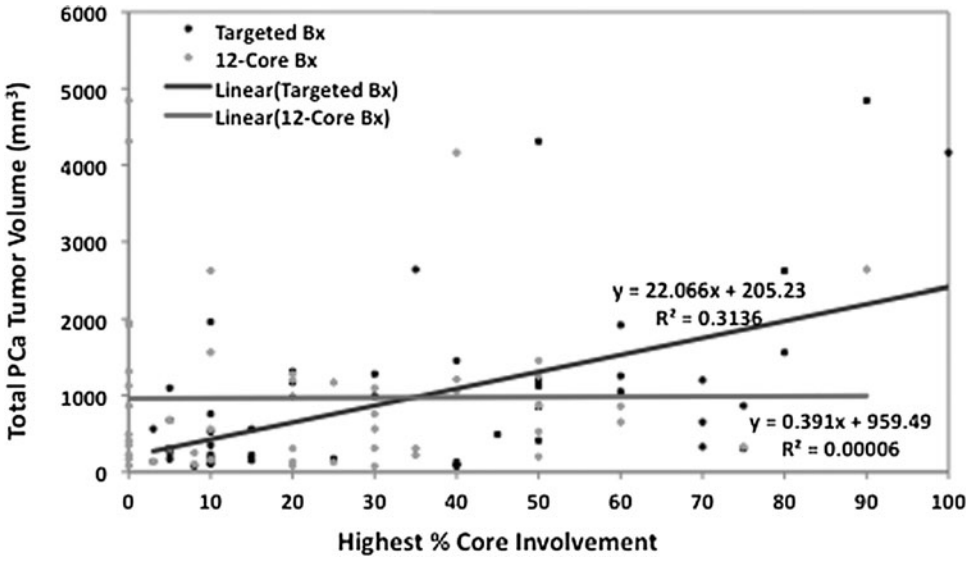

FIG. 1. Correlation of highest percentage core involvement to total positive tumor volume for systematic 12-core biopsy and targeted magnetic resonance imaging/transrectal untrasonography fusion biopsy (Bx). PCa = prostate cancer.

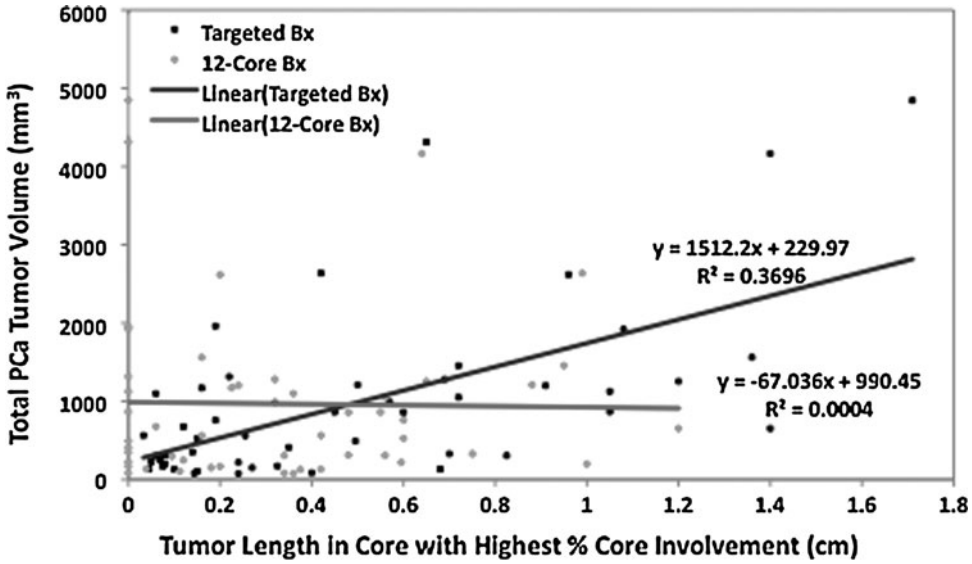

FIG. 2. Correlation of tumor length in core with highest percentage core involvement to total positive tumor volume for systematic 12-core biopsy and targeted magnetic resonance imaging/transrectal untrasonography fusion biopsy (Bx).

reliable surrogate for calculating PCa TV, because volumetric measurements have been positively correlated with and accurately predict actual whole mount histopathologic TVs.

Turkbey and associates[9] retrospectively evaluated 135 patients, 65% of whom had index tumors with Gleason score ≤3 + 4, and reported a correlation coefficient of 0.401 ($P < 0.00001$) for T2W MRI, DW MRI, and DCE MRI at 3T used in combination.[9] Similarly, Mazaheri and colleagues[10] reported a correlation coefficient of 0.6 for T2W MRI-DW MRI at 1.5T in a cohort of 45 patients, 76% of whom had a Gleason score ≤3 + 4 on final pathologic evaluation. Total PCa TV was used for analysis because it best represents total burden of disease in each patient.

Poulos and coworkers[19] demonstrated that the highest percentage of adenocarcinoma at any biopsy site correlated poorly with TV in RP specimens that were whole mount sectioned and analyzed using the grid method ($R^2 = 0.041$, $P = 0.012$). Similarly, our data confirmed that for SBx, the highest percentage core involvement and corresponding tumor length had poor correlation with total PCa TV. Furthermore, SBx missed the diagnosis of PCa in 26% of the patients, whose disease was ultimately diagnosed on TBx. The poor correlation of highest percent core and corresponding tumor length with total PCa TV persisted when these 13 patients were removed from the analysis ($R^2 = 0.077$, $R^2 = 0.056$, respectively; data not shown).

The current standard of care TRUS-guided prostate biopsy is not a sufficiently accurate means of sampling PCa, resulting in significant pathologic upgrading of low-grade disease when compared with RP specimens.[26,27] Although office based, TRUS-guided prostate biopsy inadequately samples the peripheral zone and neglects anterior lesions.[28] Of the 15 tumors that were missed by SBx in our cohort, 8 were located in the posterior peripheral zone, 6 in the anterior central gland, and 1 in the anterior peripheral zone.

Advances in MP-MRI have allowed for the identification of tumor foci within the prostate and the fusion of MRI with real-time TRUS using computer registration, which allows for the office-based targeted sampling of suspicious prostate lesions.[29] The use of this TBx platform has been shown to improve detection of PCa lesions, clinically significant disease, and improve detection in patients with previous negative TRUS biopsy.[12,14,27,30–35] The use of the TBx platform may therefore represent a more accurate means to detect and characterize cancer and thus alter the treatment of patients with PCa.

In the AS population where disease burden dictates the treatment, it is essential to have the most accurate estimate of

TABLE 2. COMPARISON OF BIOPSY RESULTS FROM (A) SYSTEMATIC 12-CORE BIOPSY AND (B) TARGETED MAGNETIC RESONANCE IMAGING/TRANSRECTAL ULTRASONOGRAPHY FUSION BIOPSY FOR DETECTION OF TUMOR BURDEN GREATER THAN 500 MM^3

A

12-Core Biopsy Highest % Core Involvement	Total Prostate Cancer Tumor Volume ≥ 500 mm³	Total Prostate Cancer Tumor Volume < 500 mm³
≥ 50%	7	2
< 50%	21	20

B

Targeted Biopsy Highest % Core Involvement	Total Prostate Cancer Tumor Volume ≥ 500 mm³	Total Prostate Cancer Tumor Volume < 500 mm³
≥ 50%	15	3
< 50%	13	19

Numbers in table represent ''n.''

Table 3. Diagnostic Accuracy and Predictive Values of Systematic 12-Core Biopsy and Targeted Magnetic Resonance Imaging/Transrectal Ultrasonography Fusion Biopsy for Detection of Tumors Greater Than 500 mm^3

Biopsy method	*Sens (%)*	*Spec (%)*	*Accuracy (%)*	*PPV (%)*	*NPV (%)*
Systematic 12-core biopsy	25	90.9	54	77.8	48.8
Targeted MRI/TRUS fusion biopsy	53.6	86.4	68	83.3	59.4

Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; MRI/TRUS = magnetic resonance imaging/transrectal ultrasonography.

volume, and it is reasonable to assume that TBx may provide a novel pathway to achieve this. Correlation of TRUS biopsy parameters with TV have been reported, but limited data exist with MRI-directed sampling. In our cohort, the highest percentage core involvement and corresponding tumor length on TBx showed a positive correlation with total PCa TV.

Patients with low-risk PCa are assigned a high probability of clinically insignificant disease, defined as PCa volume less than 500 mm^3.[1] We also sought to determine the correlation of SBx and TBx highest percent core measurements with this established threshold. Targeted biopsy was more sensitive and accurate than SBx in detecting tumor burden greater than 500 mm^3 and can therefore better identify patients with clinically significant, larger tumors. Standard SBx appeared to be more specific than TBx for identifying such patients; however, this outcome is confounded by the increased sampling error as evidenced by the 13 missed cancers on SBx. Seven (54%) of these 13 patients had total PCa TVs greater than 500 mm^3, 5 of whom had core involvements ≥50% on TBx. Thus, specificity comes at the cost of sensitivity with missed significant cancers.

Based on these results, TBx significantly outperformed SBx for the prediction of total PCa TV and in the detection of tumor burden greater than 500 mm^3. Having accurate predictors of TV can allow for more confidence when counseling patients regarding AS, focal therapy, radiotherapy, or surgery. This is, however, most important in patients being considered for AS, because correct risk stratification of these patients will allow for the most appropriate course of action in regard to continuing or starting surveillance versus planning for intervention. We propose using MP-MRI and a MRI/TRUS fusion platform as a complementary means of assessing TV and overall disease burden in patients with PCa. As this literature continues to expand, the use and integration of these techniques into current screening and treatment guidelines will be better delineated.

A limitation of this study is that only patients who had MP-MRI visible lesions were subsequently biopsied and included for this study. Although representing a small population of patients, those who had tumors not visible on MP-MRI were therefore excluded from this study. Tumors not visible on MRI tend to be more likely clinically insignificant, and there is a low prevalence of cancer in this subgroup of patients.[36] In addition, all of the patients were enrolled in a prospective trial investigating the use of MP-MRI and performance of the TBx; however, the data were collected and analyzed retrospectively and therefore subject to bias.

Finally, given that all of the patients in the cohort were being followed by AS, whole mount specimens could not be used for tumor volume measurements. Unfortunately, to our knowledge, no study has looked at the correlation of MP-MRI TVs to histopathologic TVs solely in an AS population; however, several studies have shown MRI derived TVs to be an appropriate surrogate for TV calculation in cohorts with a broad disease burden. In addition, MRI derived TVs are more applicable to AS patients or any patient who has not undergone definitive treatment.

Conclusions

The highest percentage core involvement and corresponding tumor length on TBx positively correlates with total MRI PCa TV, in contrast to SBx, which shows a poor correlation. Targeted biopsy is superior to SBx for detecting tumor burden greater than 500 mm^3. When using biopsy positive MRI derived TVs, targeted biopsy better reflects overall disease burden and may aid in improving risk stratification among candidates for AS.

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Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

AS = active surveillance
DCE = dynamic contrast-enhanced
DW = diffusion weighted
MP-MRI = multiparametric prostate magnetic resonance imaging
NCI = National Cancer Institute
NIH = National Institutes of Health
NPV = negative predictive value
PCa = prostate cancer
PPV = positive predictive value
PSA = prostate-specific antigen
RP = radical prostatectomy
SBx = systematic 12-core biopsy
TBx = targeted magnetic resonance imaging/ultrasound fusion biopsy
TRUS = transrectal ultrasonography
T2W = T2 weighted
TV = tumor volume