Prebiopsy Magnetic Resonance Imaging and Prostate Cancer Detection: Comparison of Random and Targeted Biopsies

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Purpose: We compared the accuracy of visual targeted biopsies vs computerized transrectal ultrasound-magnetic resonance imaging registration using a rigid (Esaote®, nondeformable) or elastic (Koelis®, deformable) approach.

Materials and Methods: A total of 391 consecutive patients with suspected localized prostate cancer were prospectively included in analysis. All patients underwent prostate magnetic resonance imaging, followed by 10 to 12-core random prostate biopsies. When magnetic resonance imaging detected suspicious findings, targeted biopsy was performed, including visual, rigid system and elastic system targeted biopsies in the first 127 patients, the next 131 and the last 133, respectively. Cancer detection rates were assessed by conditional logistic regression. Targeted biopsies alone and random biopsies were further compared for the amount of tissue sampled and microfocal cancer detection, the latter defined as a single core with 5 mm or less of Gleason 6 cancer.

Results: Patient characteristics and random biopsy detection rates were similar among the groups. Magnetic resonance imaging detected at least 1 suspicious area in 54 (42%), 78 (59%) and 82 patients (62%) in groups 1, 2 and 3, respectively. The cancer detection rates of rigid and elastic system targeted biopsies were significantly higher than the random biopsy rate (p = 0.0065 and 0.0016, respectively). Visual targeted biopsy did not perform better than random biopsy (p = 0.66). Rigid and elastic system targeted biopsies allowed for decreasing the number of cores and the detection of microfocal cancer, while increasing the detection of high grade cancer.

Conclusions: When performed with computerized magnetic resonance imaging-transrectal ultrasound image registration, targeted biopsy alone improved cancer detection over random biopsies, decreased the detection rate of microfocal cancer and increased the detection rate of cancer with a Gleason score of greater than 6.

In the last decade the trend among urologists has been to perform more prostate biopsies to detect more prostate cancers.[1,2] Sextant biopsies have been all but abandoned and most groups recommend extended biopsy protocols with 12 cores.[1] Some urologists perform even more extended

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protocols in nonselect patients.[3] Although these efforts have undoubtedly led to increased cancer detection, they have also led to important adverse effects. Up to 30% of detected tumors are small and well differentiated,[4] and considered clinically insignificant.[5,6] Over diagnosis of these potentially indolent tumors has led to patient over treatment, as suggested by the results of the ERSPC (European Randomized Study of Screening for Prostate Cancer).[7] Also, the number of unnecessary biopsies has increased along with procedure morbidity.[8]

Multiparametric MRI, which combines T2W, DW and DCE MRI, has recently gained popularity. It has value for detecting, localizing and characterizing prostatic tumor foci larger than 0.2 cm^3.[9–11] As a result, the MRI-TB strategy alone without additional RBs was suggested to decrease the detection rate of insignificant tumors, while increasing detection of potentially aggressive tumors.[12] Thus, it can be hypothesized that biopsy could be deferred in patients with no evidence of lesion on multiparametric MRI.

Performing TB under MRI guidance is expensive, time-consuming and not widely available. On the other hand, despite its limited ability to delineate prostate cancer, TRUS guided prostate biopsies have the virtues of speed, ease, lower cost and wider availability. Therefore, TB under ultrasound guidance with the visual help of prebiopsy MRI is currently the most widely used technique (visual registration of MRI and TRUS images).[12] More recently, computerized MRI-TRUS image registration, which consists of an overlay of MRI detected foci on the corresponding TRUS images, has allowed clinicians to perform TB using these co-registered images.[13,14] Compared to a visual guidance strategy, this newer approach was developed to increase the reproducibility of the technique and improve its accuracy. Previous studies showed the feasibility of computerized MRI-TRUS image registration based TB but to our knowledge none has compared its performance with that of visually guided TB.

In this prospective study we evaluated the performance of MRI-TB compared to standard RB. In this setting we started by performing TB under visual guidance. We consecutively changed our protocol to MRI-TRUS image registration based TB using the rigid (nondeformable) Esaote and the elastic (deformable) Koelis systems. The aim of the current analysis was to assess the value of each TB protocol compared to RB for cancer detection.

PATIENTS AND METHODS

Patient Inclusion
Between January 2011 and March 2012 we prospectively included in analysis 391 consecutive patients with PSA greater than 4 ng/ml, and/or suspicious digital rectal examination and no previous prostate biopsy. All patients underwent endorectal MRI before prostate biopsy. The study was approved by the institutional review board, which issued a waiver of informed consent for the review of clinical, biological, histological and MRI data.

MR Imaging
MR images were obtained using a 1.5 Tesla scanner with integrated endorectal and pelvic phased array coils (supplementary table 1, jurology.com). The endorectal coil was inserted and inflated with air to a volume of approximately 80 to 100 ml. DW images had the same orientation as transverse T2W images. DCE data were post-processed with pharmacokinetic analysis software (iCAD, Nashua, New Hampshire) based on the model of Tofts et al[15] to estimate tissue physiological parameters, including the transfer constant (K^{trans}) and the efflux rate constant (k$_{ep}$). The initial area under the gadolinium concentration curve for the first 60 seconds after contrast arrival was also calculated. Two experienced radiologists (FC and AS) interpreted MR images by consensus. T2W, DW imaging and each of the 3 parameters calculated from DCE MRI were scaled using a 3-point score of 0 — benign or probably benign, 1—intermediate or 2—malignant or probably malignant (supplementary table 2, jurology.com), as described previously.[10] The scores were added to define a T2W plus DW score of 0 to 4 in the transitional zone and a T2W plus DW plus DCE score of 0 to 10 in the PZ. An area was considered suspicious for cancer if the T2W plus DW score was 2 or greater in the transitional zone and the T2W plus DW plus DCE score was 6 or greater in the PZ.[10]

Prostate Biopsies
All biopsies were performed by an experienced uroradiologist (FC). All patients underwent 10 to 12-core systematic RBs. In case of any suspicious lesion detected on MRI at least 2 additional TBs were done. In the first 127 patients (group 1) image registration during MRI-TB was visual. MRI data were displayed on a work station available in the biopsy room so that the suspicious area on MRI was visually matched with the corresponding location on TRUS. In the next 131 patients (group 2) TB was performed with the rigid navigation system using rigid MRI-TRUS registration, which allows for a dynamic image overlay between real-time ultrasound and pre-acquired MR images (fig. 1). In the last 133 patients (group 3) TB was done using the elastic MRI-TRUS image registration system, which is not a real-time technique since each biopsy is preceded by 3D TRUS volume acquisition (fig. 2).

Histological Evaluation
All biopsy cores were individually labeled. For each biopsy protocol the number of cores involved by cancer, total length of tissue sampled and total length of cancer detected as well as Gleason score were determined. MFC was defined as a single core with less than 5 mm of Gleason 6 cancer.

Measurement and Statistical Analysis
The population was described using proportions for categorical data, the mean ± SEM for normally distributed data, and the median and range for other quantitative
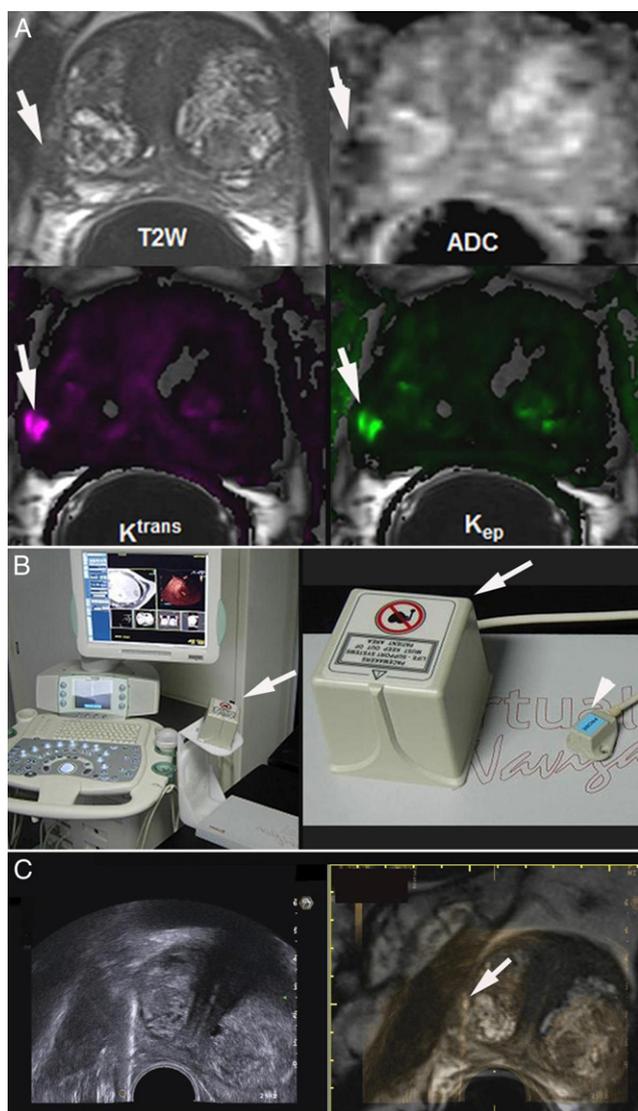
Figure 1. Nondeformable navigation system for MRI-TRUS image registration. Note suspicious area with overall score of 9/10 in right peripheral zone (arrow) on T2W, DW and DCE MRI (*A*). *ADC*, AUC. Transmitter placed close to patient (arrow) and receiver placed on TRUS probe (arrowhead) calculated probe position in real time (*B*). Internal anatomical markers visible on each modality allowed for real-time TRUS and MR image overlay (*C*). Note biopsy tract (arrow) superimposed on MR image.

data. The normality assumption was checked by quantile-quantile plots and the Shapiro-Wilks test. Categorical variables were compared by the Pearson chi-square test, when appropriate, and the Fisher exact test otherwise. Quantitative data were compared by the Student t test and ANOVA. Comparisons between groups were assessed by 1-way ANOVA. The comparison of cancer detection rates obtained with each biopsy protocol was assessed by conditional logistic regression. Similarly, logistic regression was performed to compare the ability of each TB protocol to detect a focus undetected by RB. The OR and 95% CI were derived from the regressions. All tests were considered significant at p <0.05 and statistical analysis was performed using R.
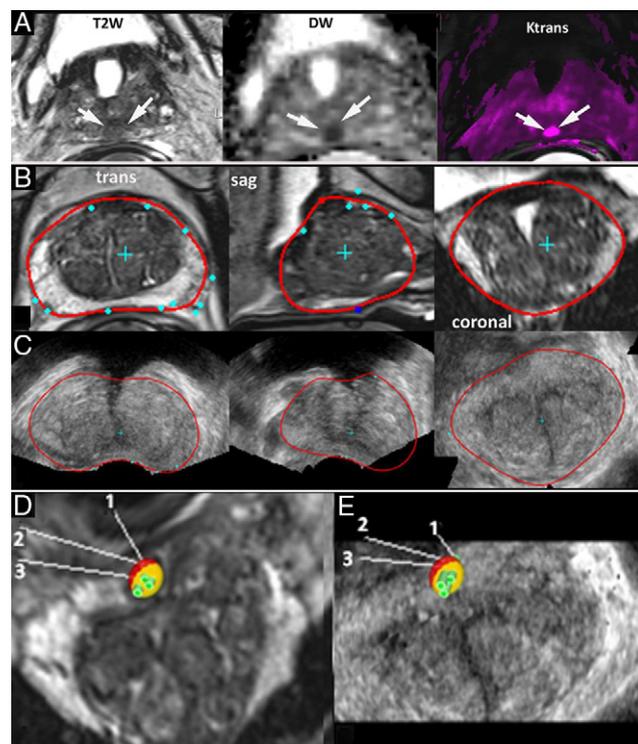
Figure 2. Deformable MRI-TRUS image registration. Suspicious area on median line detected on T2W, DW and DCE (*Ktrans*) MRI (*A*). Prostate segmentation was done on pre-acquired MRI images (*B*) loaded in work station and on TRUS 3D volume (*C*) acquired with 3D TRUS probe. *trans*, transverse. *sag*, sagittal. After MRI-TRUS image registration regions of interest (yellow and red areas) drawn on T2 and DW MRI were shown on MRI (*D*) and TRUS (*E*) images, and biopsies were performed.

RESULTS

Patient characteristics were similar in the 3 groups (table 1). RB detected 55 (43%), 60 (46%) and 44 cancers (33%) in groups 1, 2 and 3, respectively (p = 0.08). Multiparametric MRI detected at least 1 suspicious area for cancer in 54 (42%), 78 (59%) and 82 patients (62%) in groups 1, 2 and 3, respectively (p <0.001). Of these suspicious areas 36 (67%), 50 (64%) and 51 (62%), respectively, were located in the PZ (p = 0.7).

In group 1 visually guided TB alone detected 37 of the 55 cancers detected by RB as well as 3 unde-

Table 1. *Patient characteristics in 3 groups*

	Group 1	Group 2	Group 3	p Value
No. pts	127	131	133	
Mean ± SD age	62.7 ± 7.4	64.6 ± 6.7	64.5 ± 7.9	0.06
Mean ± SD PSA (ng/ml)	8.1 ± 3.7	8.3 ± 4.1	9 ± 3.9	0.05
Mean ± SD gland vol (cm³)	53 ± 25	55.7 ± 35.1	58.3 ± 28.6	0.15
No. Ca stage (%):				0.61
T1c	107 (84)	115 (88)	117 (88)	
T2a	20 (16)	16 (12)	16 (12)	

tected by RB, of which 2 had a Gleason score of greater than 6. Of the 18 cancers missed by TB but detected by RB 16 had a Gleason score of 6 and 15 involved less than 5 mm of the biopsy core.

In group 2 rigid system TB alone detected 46 of the 60 cancers detected by RB as well as 18 undetected by RB, of which 7 had a Gleason score of greater than 6. All 14 cancers missed by TB but detected by RB had a Gleason score of 6, of which 12 involved less than 5 mm of the biopsy core.

In group 3 elastic system TB alone detected 35 of the 44 cancers detected by RB as well as 27 undetected by RB, of which 8 had a Gleason score of greater than 6. All 9 cancers missed by TB but detected by RB had a Gleason score of 6, of which 7 involved less than 5 mm of the biopsy core.

In all groups TBs alone allowed us to decrease the number of cores and the total length of tissue biopsied as well as the detection of MFC (table 2). However, using conditional logistic regression to compare the ability of the 3 TB protocols to detect cancer, rigid and elastic system TB performed significantly better than RB (p = 0.0065 and 0.0016, respectively), whereas visually guided TB did not (p = 0.66, fig. 3). Also, the probability of detecting cancer undetected by RB was significantly higher with rigid and elastic system TB than with visually guided TB (fig. 4). Finally, rigid and elastic system TB detected significantly more high Gleason score (greater than 3 + 3) cancers than RB, while visually guided TB did not (table 2).

DISCUSSION

Over diagnosis of insignificant cancer[4–6] along with poor characterization of cancer on biopsy[2] may be the direct consequences of random targeting and extensively potential lesions that are invisible on TRUS. Indeed, there is accumulating evidence that cancer detection and characterization would be more accurately performed if the lesion could be detected first by imaging. The high reported performance of multiparametric MRI for cancer detection and localization should naturally suggest its use as a first tool before proposing any kind of invasive evaluation. Also, because MRI is associated with tumor size and grade,[9,16] its use as a first screening tool would probably limit the over detection of potentially insignificant tumors by deferring biopsy in case of normal MRI. In a recent study correlating multiparametric MRI findings with those of radical prostatectomy specimens Rosenkrantz et al reported that undetected tumor foci were significantly smaller and more differentiated.[17] As a result, fewer than 10% of Gleason score greater than 6 cancers remained undetected on multiparametric MRI, including T2, DW and DCE weighted sequences.

Table 2. *RB and TB results in 3 groups*

| Group	RB		TB		p Value
1:					
No. pts	127		54		
Median No. cores (range)	12	(10–12)	4	(3–10)	<0.001
Median mm total tissue length (range)	180	(4–280)*	40	(15–180)	<0.001
Median % pos cores (range)	22	(8–100)	67	(20–86)	<0.001
Median % Ca involvement (range)	4.5	(0.4–22)	38	(5–80)	<0.001
No. Gleason score greater than 6 (%)	18	(33)	18	(45)	0.6
No. MFC (%)	12	(22)	0		0.01
2:					
No. pts	131		78		
Median No. cores (range)	12	(10–12)	4	(3–8)	<0.001
Median mm total tissue length (range)	155	(46–198)	39	(4–105)	<0.001
Median % pos cores (range)	16	(8–66)	75	(17–100)	<0.001
Median % Ca involvement (range)	5	(0.5–72)	46	(2–100)	<0.001
No. Gleason score greater than 6 (%)	26	(43)	33	(52)	0.02
No. MFC (%)	15	(25)	6	(9)	0.03
3:					
No. pts	133		82		
Median No. cores (range)	12	(10–12)	3	(2–5)†	<0.001
Median mm total tissue length (range)	154	(39–195)	36	(17–70)	<0.001
Median % pos cores (range)	22	(8–100)	75	(33–100)‡	<0.001
Median % Ca involvement (range)	10.5	(0.5–54)§	31	(4–100)	<0.001
No. Gleason score greater than 6 (%)	19	(43)	27	(44)	0.01
No. MFC (%)	9	(20)	4	(6)	0.04

* For RB p $<10^{-4}$ vs groups 2 and 3.
† For TB p $<10^{-4}$ vs groups 1 and 2.
‡ For TB p = 0.003 vs group 1.
§ For RB p = 0.015 vs groups 1 and 2.

In our prospective study TB with computerized MRI-TRUS image registration significantly improved cancer detection over that of RB. This improvement was not the consequence of any kind of over detection of potentially insignificant cancers. Of the cancers detected by RB 22%, 25% and 20% were MFC in groups 1, 2 and 3, respectively. This rate decreased to 0%, 9% and 6%, respectively, for TB alone (table 2). On the other hand, TB alone missed only 2 of the 63 high grade cancers (3%) detected by RB, while it detected an additional 17 with a Gleason score of greater than 6 that were missed by RB. In the 391 consecutive study patients a TB only strategy would have avoided unnecessary biopsy in 45%, while limiting the number of cores in the other 55%. These results confirm the prior retrospective study of Haffner et al, who compared MRI-TB with extended RB in 555 patients.[12] A TB only strategy would have necessitated only a mean of 3.8 cores per patient and avoided unnecessary biopsy in 38% with normal MRI, while avoiding the diagnosis of 13% of
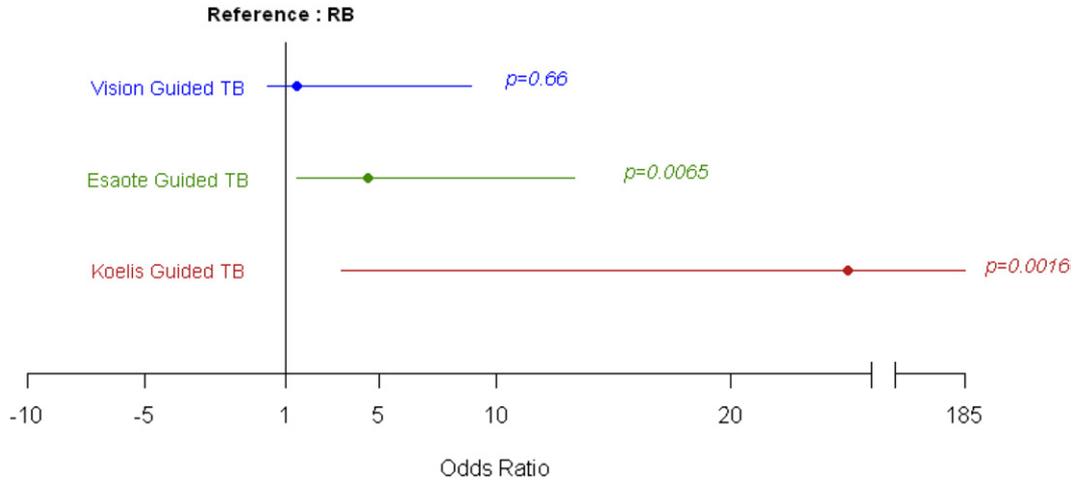
Figure 3. Probability of detecting cancer with RB, vision guided TB alone, rigid system TB alone and elastic system TB alone

the insignificant cancers detected by RB. In another recent study Pinto et al also noted that TB alone detected more cancer per core than standard 12-core biopsy.[18]

After acknowledging the value of TB to improve prostate cancer detection, the next question would be how to choose the most accurate technique to perform these biopsies. We performed MRI-TB using 3 techniques. The first consisted of prebiopsy MRI visual guidance to target the suspicious lesion (visually guided TB, group 1). The limitation of this approach was the difficulty of localizing the corresponding TRUS area with the help of zonal anatomy and internal tissue landmarks. The other 2 techniques in groups 2 and 3, respectively, involved targeting the suspicious lesion with MRI-TRUS computerized image registration. These techniques were developed to allow for more precise biopsy targeting.

The 2 image registration systems that we tested are based on 2 registration methods. The first system uses rigid (nondeformable) image registration.

This technique relies on the matching of internal anatomical markers to activate the TRUS-MR image overlay.[19] However, nondeformable registration does not consider the differences in prostate shape between TRUS and MR images, making a mismatch possible. Also, prostate movements induced by the TRUS probe during TRUS scanning may engender registration errors. The second registration system uses an elastic (deformable) image registration that is performed with a 3D TRUS probe to acquire prostatic volume. Before each biopsy 3D TRUS acquisition is performed to calculate the deformation of the prostate shape on MR images. Thus, it is not a real-time technique but the spatial accuracy of the system after image registration was reported to be close to 1 mm.[14,20]

To our knowledge our study is the first to compare the visual technique and 2 techniques of computerized assisted MR/ultrasound image registration to guide TRUS prostate biopsies. Our conditional logistic regression analysis revealed that only computerized MRI targeted, TRUS guided biopsies signifi-
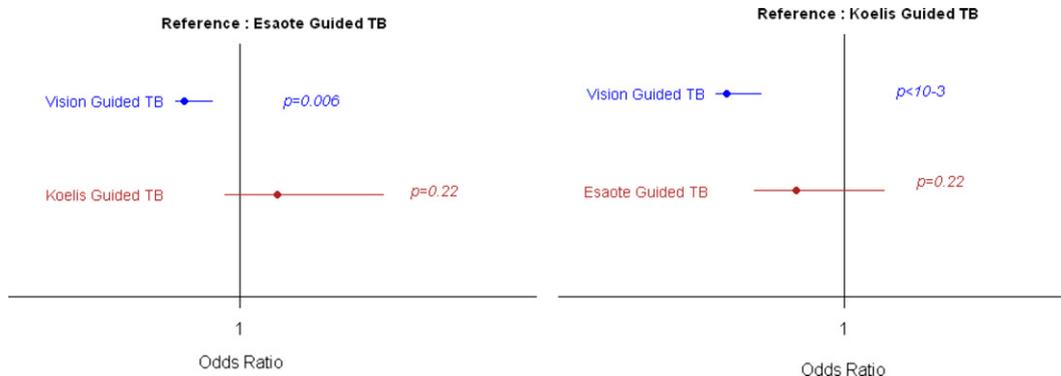
Figure 4. Probability of detecting cancer undetected by RB using VTB alone, ETB alone and KTB alone

cantly increased the cancer detection rate over RB (figs. 3 and 4). These TBs also detected additional high Gleason score tumors and significantly decreased the MFC detection rate. In contrast, TB with the sole use of visual registration did not perform significantly better than RB. The comparison of the 2 techniques of computerized image registration showed a higher increase in the detection rate in favor of elastic system TB (OR 5.5) but the difference was not significant (p = 0.13). This trend may be explained by the lower RB detection rate in group 3, although it was not statistically different than that in the other 2 groups. It may also be explained by potential differences between populations as well as MRI performance. The cancer detection performance of elastic system TB was also associated with significantly fewer cores performed compared to the 2 other TB protocols (table 2). Results suggest that TB should not be done with a visual system but rather with a computerized, possibly deformable MRI-TRUS image registration system to allow for optimal performance with fewer cores.

Our study has some limitations, of which the most important is the absence of a radical prostatectomy specimen as the reference for precise cancer characterization. As a surrogate, we used predictors of nonsignificant features on biopsy, which may have introduced bias in the results. Also, our MRI scoring system is not a generalized approach. It could be argued that incorporating the 3 DCE scores (K^{trans}, k_{ep} and area under the gadolinium concentration curve) separately into the overall score over weighted DCE. This is not in agreement with the scoring system currently reported by Barentsz et al and developed by the European Society of Uroradiology, which is not yet validated.[21] Ultimately, this limitation would probably not significantly modify our results, particularly in regard to the comparison of the 3 TB techniques. Finally, patients were not randomized to the 3 groups analyzed. Further prospective, randomized studies are needed to confirm the value of MRI-TB.

CONCLUSIONS

When performed with computerized MRI-TRUS image registration, MRI-TB alone provided a significantly higher cancer detection rate than RB. Furthermore, TB increased the detection rate of high Gleason score cancer, while decreasing the detection rate of small and well differentiated tumors. In the absence of a MRI detected suspicious area detection rates were low and most cancers detected were potentially insignificant.

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EDITORIAL COMMENT

Previous prospective studies showed that combining a standard random biopsy scheme with an oversampling strategy at sites targeted by multiparametric MRI indications resulted in significantly higher cancer detection rates, particularly in patients with a prior negative prostate biopsy and persistently increased PSA.[1] As reported, matching abnormal MRI regions to TRUS to guide biopsies can present limitations (reference 11 in article).

These authors appropriately assessed the impact of prebiopsy MRI on cancer detection with the ability to increase the detection of high risk tumors and decrease the detection of insignificant tumors, also avoiding a saturation scheme biopsy. This relevant study analyzes possibilities to better ensure the correspondence of TRUS biopsy spatial accuracies with suspicious areas on multiparametric MRI by comparing visual targeting and computerized registration for targeting.

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