Editorial

From PROMIS to PRO-MRI in primary prostate cancer diagnosis

Ivo G. Schoots[1], Monique J. Roobol[2]

[1]Department of Radiology & Nuclear Medicine, [2]Department of Urology, Erasmus University Medical Center, Rotterdam, the Netherlands

Correspondence to: Monique J. Roobol. Department of Urology, Erasmus University Medical Centre, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands. Email: m.roobol@erasmusmc.nl.

Provenance: This is a Guest Editorial commissioned by Editorial Board Member Dr. Xiongbing Zu, MD, PhD (Department of Urology, Xiangya Hospital, Central South University, Changsha, China).

Comment on: Ahmed HU, El-Shater Bosaily A, Brown LC, *et al.* Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815-22.

Submitted Apr 03, 2017. Accepted for publication Apr 06, 2017.

doi: 10.21037/tau.2017.04.35

View this article at: http://dx.doi.org/10.21037/tau.2017.04.35

In the emerging field of MRI in prostate cancer (PCa) diagnosis, it has become clear that targeted biopsy with MRI guidance has additional value over systematic transrectal ultrasound-guided biopsies (TRUS-Bx) alone. The targeted biopsy approach driven by a positive MRI increases the diagnostic yield of high-grade [Gleason score (GS) ≥3+4] or clinically significant (cs) PCa, while concomitantly reducing the number of biopsy cores and the detection of low-grade PCa (GS 3+3) (1-3). Consequently, the question arises what the diagnostic accuracy of MRI (with or without targeted biopsies) in current clinical practice would be?

Ahmed and his co-authors have recently published a prospective multicenter-paired validation study, titled the PROstate Mri Imaging Study (PROMIS) (4) that begins to fill this void in the literature. This study, which has a very sound methodology, evaluates the MRI (index test 1) in combination with transrectal ultrasound guided biopsies (TRUS-Bx) (index test 2) in reference with template mapping prostate biopsies (TMP-Bx) in biopsy-naïve men. They started from the hypothesis that targeted biopsies would have similar diagnostic accuracy as compared to TMP-Bx. We need to be aware of that MRI targeted biopsies were not included in this study design.

The authors' main conclusion is that TRUS-Bx performs poorly as a diagnostic test for clinically significant prostate cancer. Prostate MRI, used as a triage test before first prostate biopsy, could identify a quarter of men who might safely avoid an unnecessary biopsy, can also reduce over-diagnosis of clinically insignificant prostate cancer, and might improve the detection of clinically significant cancer.

And yes, we believe that the PROMIS study works in daily clinical practice as advertised if we do not expect to find all significant disease, if we accept that results depend on the current definitions of clinical significance, and if we assure the quality of the diagnostic process (including MRI scanner, MRI protocol, biopsy procedures, MRI scans, interpretation and reporting), and have robust training for radiologists and urologists.

Diagnostic test accuracy for MRI and TRUS-guided biopsies

Looking in more detail to these recently published results, we focused on the most commonly used definition for csPCa; any Gleason sore 7 (3+4) or higher, detected on template mapping prostate biopsy findings.

For TRUS-Bx the sensitivity and specificity were 0.48 and 0.99, respectively (*Figure 1*). This demonstrates that the missed csPCa following the TRUS-Bx pathway is 52% (n=159) of all csPCa (n=308). This might be unacceptable. In contrast, for MRI the sensitivity and specificity were 0.88 and 0.45, missing 12% (n=38) of all csPCa. This might be acceptable.

This is however only half the story of the diagnostic test accuracy, as predictive values are at least as relevant for clinicians. They are mainly concerned with pre-test and post-test probabilities (predictive values) of a diagnostic test, rather than its sensitivity or specificity.

For MRI the positive and negative predictive values were 0.65 and 0.76, demonstrating the relatively high

Test	Totals	Variables 2x2 tables				Outcomes 2x2 tables					Disease probabilities			Missed disease	Biopsies			
		TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV	Accuracy	Pre-test probability	Post-test probability		missed csPCa	justified biopsy	unnecessary biopsy	potentially avoided biopsy	no biopsy not justified
											(prevalence)	positive (PPV)	negative (1-NPV)	FN/ (TP+FN)	TP/all	FP/all	TN/all	FN/all
TMP-Bx (reference test)	576	308		268							0.53							
MRI (index test 1)	576	270	148	120	38	0.88	0.45	0.65	0.76	0.68	0.53	0.65	0.24	0.12	0.47	0.26	0.21	0.07
TRUS-Bx (index test 2)	576	149	2	266	159	0.48	0.99	0.99	0.63	0.72	0.53	0.99	0.37	0.52	0.26	0.74		

Figure 1 PROMIS results on diagnostic accuracy of prostate MRI and TRUS-biopsy in the detection of clinically significant prostate cancer using the definition of Gleason score ≥3+4 (4). TMP-Bx, template mapping prostate biopsy; MRI, magnetic resonance imaging; TRUS-Bx, transrectal ultrasound guided biopsy; csPCa, clinically significant prostate cancer; TP, true positive; FP, false positive; TN, true negative; FN, false negative; PPV, positive predictive value; NPV, negative predictive value. Blue: beneficial interpretation of the test results; light red: slightly negative interpretation of the test results; red: negative interpretation of the test results.

false positives (35%) and false negatives of MRI: still 1 out of 4 csPCa (24%) is being missed with prostate MRI. In contrast, the negative predictive value of TRUS-Bx was 0.63, showing that even 1 out of 3 men with csPCa is being missed with TRUS-Bx. Hence, we may conclude that MRI performs better in detecting csPCa than TRUS-Bx. However, prostate MRI as a stand-alone cannot yet be considered as the perfect test. When missing 1 in 4, these data shows that csPCa is not equal to visible lesions on MRI. We need to accept the imperfection, and we need to be aware that we miss csPCa if we use MRI as a triage test in biopsy-naïve patients, as suggested by the authors.

We have however lived for decades with the false negative results of systematic TRUS-Bx and we may start accepting this for prostate MRI. Still, it is important to realize that the PROMIS conclusions are based on the assumption that targeted biopsies would achieve similar diagnostic accuracy as TMP-Bx. What is currently lacking is however the assessment of correlation between lesion location on MRI and TMP-Bx, to be able to justify the assumption made.

Avoiding biopsies with the MRI pathway

According to the PROMIS data, a negative MRI (i.e., no suspicious lesions are visible) may potentially avoid unnecessary TRUS biopsies in 28% (*Figure 1*); 21% would be justified based on the true negative results (TN), however 7% would not be justified based on false negative (FN) results. From the published results, it is not possible to assess whether these csPCa's detected by TMP-Bx would have been detected by additional systematic TRUS-Bx.

In addition, the use of multivariate risk stratification in a clinical scenario of opportunistic screening with TRUS biopsies in biopsy-naïve men could potentially avoid 20% to 33% unnecessary biopsies without missing hardly any csPCa (5,6). Although these results are not referenced to TMP-Bx and therefore not comparable with the potential biopsy reduction of 28% in the PROMIS, still a substantial benefit may be hypothesized from (complimentary) multivariate risk stratification. At least, it would be very interesting to further explore this combination.

On the basis of the low specificity of the MRI diagnostic test (45%), we should still accept the fact of considerable overdiagnosis, as most of the men with positive MRI will receive an invasive targeted biopsy. Within the context of further reducing overdiagnosis and biopsy procedures, Alberts *et al.* showed that half of the prostate MRI's could have been avoided by upfront multivariate risk stratification, using the Rotterdam Prostate Cancer Risk Calculator (RPCRC) (7).

Generalizability of PROMIS results

The prevalence of csPCa in the PROMIS study was 53% based on the reference TMP-Bx, with transperineal biopsies at 5 mm intervals. Predictive values are strongly dependent of the prevalence of csPCa in the studied cohort study. To be able to extrapolate the diagnostic test results from the PROMIS to one's clinical practice, an estimate of the

prevalence in your clinical population should be available. This dependency is nicely shown in a recent publication on the negative predictive value of prostate MRI, graphically presenting these values against the prevalence of many reports on MRI and targeted biopsies (8).

Nonetheless, the likelihood of having TMP-Bx results available in biopsy-naïve men will be extremely rare. Therefore, to generalize the PROMIS study results to one's clinical setting, we may use the detection rate of 26% csPCa by TRUS-Bx within this study, instead. This csPCa rate is probably comparable to rates of other clinical biopsy-naïve patient cohorts in Western countries with opportunistic screening, varying from 11% (9), 16% (10), 20% (6), 27% (11) to even 39% (12). Therefore, we believe that the PROMIS results are generalizable to other Western biopsy-naïve patient cohorts, however, we observe a large variability in prevalence, resulting in insuperable differences in MRI predictive values.

The authors should be applauded with this laudable effort. The PROMIS study is based on quality control checks and quality assurance for MR images by independent imaging clinical research organization, blinding of MRI results to biopsy procedures, repeated centralized training for radiologists, and on-site training of TMP-Bx for urologists.

We advocate a policy that each prostate cancer center evaluates their own MRI and biopsy test results, to determine their positive and negative predictive values, and improve in constant dialogue between radiologist, pathologist and urologist.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol 2015;68:438-50.
2. Valerio M, Donaldson I, Emberton M, et al. Detection of Clinically Significant Prostate Cancer Using Magnetic Resonance Imaging-Ultrasound Fusion Targeted Biopsy: A Systematic Review. Eur Urol 2015;68:8-19.
3. Wegelin O, van Melick HH, Hooft L, et al. Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique? Eur Urol 2017;71:517-31.
4. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815-22.
5. Roobol MJ, van Vugt HA, Loeb S, et al. Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators. Eur Urol 2012;61:577-83.
6. Gayet M, Mannaerts CK, Nieboer D, et al. Prediction of Prostate Cancer: External Validation of the ERSPC Risk Calculator in a Contemporary Dutch Clinical Cohort. Eur Urol Focus 2016. [Epub ahead of print].
7. Alberts AR, Schoots IG, Bokhorst LP, et al. Risk-based Patient Selection for Magnetic Resonance Imaging-targeted Prostate Biopsy after Negative Transrectal Ultrasound-guided Random Biopsy Avoids Unnecessary Magnetic Resonance Imaging Scans. Eur Urol 2016;69:1129-34.
8. Moldovan PC, Van den Broeck T, Sylvester R, et al. What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. Eur Urol 2017. [Epub ahead of print].
9. Poyet C, Nieboer D, Bhindi B, et al. Prostate cancer risk prediction using the novel versions of the European Randomised Study for Screening of Prostate Cancer (ERSPC) and Prostate Cancer Prevention Trial (PCPT) risk calculators: independent validation and comparison in a contemporary European cohort. BJU Int 2016;117:401-8.
10. Delongchamps NB, Peyromaure M, Schull A, et al. Prebiopsy magnetic resonance imaging and prostate cancer detection: Comparison of random and targeted biopsies. J Urol 2013;189:493-9.
11. Roobol MJ, Vedder MM, Nieboer D, et al. Comparison of Two Prostate Cancer Risk Calculators that Include the Prostate Health Index. Eur Urol Focus 2015;1:185-90.

12. Pokorny MR, de Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. Eur Urol 2014;66:22-9.

Cite this article as: Schoots IG, Roobol MJ. From PROMIS to PRO-MRI in primary prostate cancer diagnosis. Transl Androl Urol 2017;6(3):604-607. doi: 10.21037/tau.2017.04.35

