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Role of Multiparametric Magnetic Resonance Imaging in Predicting Pathologic Outcomes in Prostate Cancer

Niklas Harland[1] , Arnulf Stenzl[1,2] , Tilman Todenhöfer[2,3]

[1]Department of Urology, University Hospital Tübingen, [2]Medical School, Eberhard-Karls-University Tübingen, Tübingen, [3]Clinical Trial Unit, Studienpraxis Urologie, Nürtingen, Germany

Multiparametric magnetic resonance imaging (mpMRI) and the introduction of standardized protocols for its interpretation have had a significant impact on the field of prostate cancer (PC). Multiple randomized controlled trials have shown that the sensitivity for detection of clinically significant PC is increased when mpMRI results are the basis for indication of a prostate biopsy. The added value with regards to sensitivity has been strongest for patients with persistent suspicion for PC after a prior negative biopsy. Although enhanced sensitivity of mpMRI is convincing, studies that have compared mpMRI with prostatectomy specimens prepared by whole-mount section analysis have shown a significant number of lesions that were not detected by mpMRI. In this context, the importance of an additional systematic biopsy (SB) is still being debated. While SB in combination with targeted biopsies leads to an increased detection rate, most of the tumors detected by SB only are considered clinically insignificant. Currently, multiple risk calculation tools are being developed that include not only clinical parameters but mpMRI results in addition to clinical parameters in order to improve risk stratification for PC, such as the Partin tables. In summary, mpMRI of the prostate has become a standard procedure recommended by multiple important guidelines for the diagnostic work-up of patients with suspicion of PC.

Keywords: Biopsy; Diagnostic imaging; Early detection of cancer; Magnetic resonance imaging

INTRODUCTION

For a long time, the urological community has been on a quest to find the best means for early detection of prostate cancer (PC). An important milestone was the introduction of prostate-specific antigen (PSA)-testing. While initial results regarding a structured screening were controversial, with longer follow-up of the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial [1] and more detailed assessment of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial [2,3] the advantage is increasingly evident, with the number needed to screen dropping below the levels of the widely accepted breast cancer screening [4].

A variety of markers have since been introduced with improved "sensitivity" and specificity, but low availability and high cost have prevented their wide

adoption.

The most significant progress in the diagnosis of localized and metastatic PC has been achieved in the field of imaging. In the past, the only relevant option for an imaging the prostate has been trans rectal ultrasound but due to its low sensitivity and specificity it has mainly been used for guidance in systematic biopsy (SB) and has not been considered as a major independent tool for diagnostic assessment of PC.

In the last decade magnetic resonance imaging (MRI) was introduced as a diagnostic tool in PC and a standardized protocol which defined image acquisition and reporting was developed and refined by the Prostate Imaging-Reporting and Data System (PI-RADS) versions 1, 2, and 2.1 [5-7]. In addition to detection of PC, MRI has been investigated as relevant tool for differentiating between indolent and aggressive PC [8].

In recent years more emphasis has been placed on defining clinically significant PC (csPC) to reduce over diagnosis and concomitant overtreatment. In most studies clinically insignificant PC is defined as Gleason Group (GG) 1, conterminous to Gleason score 6. In this context, improved imaging is urgently needed.

In this article we will discuss the effect that multiparametric magnetic resonance imaging (mpMRI) has had on PC diagnostics by examining recent literature and providing an outlook to possible future developments.

MAIN BODY

1. Material and methods

To identify current relevant literature on the role of mpMRI in predicting pathological outcomes in PC, a systematic literature search was conducted in January 2020 using PubMed (https://www.ncbi.nlm.nih.gov/pubmed/). Search terms used included 'mpMRI', 'prostate cancer', 'multiparametric MRI', 'targeted biopsy', 'prospective', 'randomized controlled', 'detection rate', 'extracapsular extension', 'seminal vesical invasion', 'pathologic stage', 'PI-RADS'. Additionally, references of included articles were screened for further relevant publications. To be included, manuscripts had to be original articles written in English and manuscripts older than 10 years were excluded to ensure topicality.

2. Standardization of multiparametric magnetic resonance imaging of the prostate

With the introduction of MRI in the field of PC diagnostics there was a need for a structured approach to image acquisition and reporting. Based on multiple consensus meetings the European Society of Urogenital Radiology created a protocol called PI-RADS [5]. This guideline described the minimum requirements necessary to acquire an mpMRI as well as a standardized interpretation and reporting system. Regions of the prostate are scored from 1 (clinically significant disease is highly unlikely to be present) to 5 (clinically significant cancer is highly likely to be present) (Fig. 1).

This protocol has extensively been validated resulting in version 2 [6].

In this updated version, the required parameters are T2-weighted (T2W) imaging, diffusion-weighted imaging (DWI), and dynamic contrast enhanced (DCE) MRI. Data are assessed depending on the anatomical zone with T2W and DWI being the dominant techniques for the transitional zones and peripheral zones, respectively. However, the benefit provided by DCE images has recently been called in to question [9].

Since significant interreader variability was problematic [10], this led to a second update to version 2.1 with more distinct guidance for scoring DWI between 3 and 4/5 as well as scoring of DCE for non-focal lesions in the peripheral zone [11].

An alternative protocol has been published as a Likert score. Although most recent studies report results according to the PI-RADS classification, Likert has been shown to provide similar diagnostic accuracy [12].

3. The pre-biopsy setting

MpMRI has high sensitivity for PC ≥GG 3. This was shown by Ahmed et al [13] in the prostate MRI Study (PROMIS) trial, which compared the sensitivities of systematic transrectal prostate biopsy and mpMRI with a transperineal mapping biopsy as reference. For the primary definition of csPC (Gleason score ≥4+3 or cancer core length ≥6 mm) mpMRI and SB had a sensitivities of 93% and 48% (p<0.0001), respectively. For the more common definition of csPC (any Gleason score ≥3+4) mpMRI and SB reached respective sensitivities of 88% and 48% (p<0.0001). Although the impact of this study on daily clinical practice was quite significant with most relevant guidelines recommending mpMRI
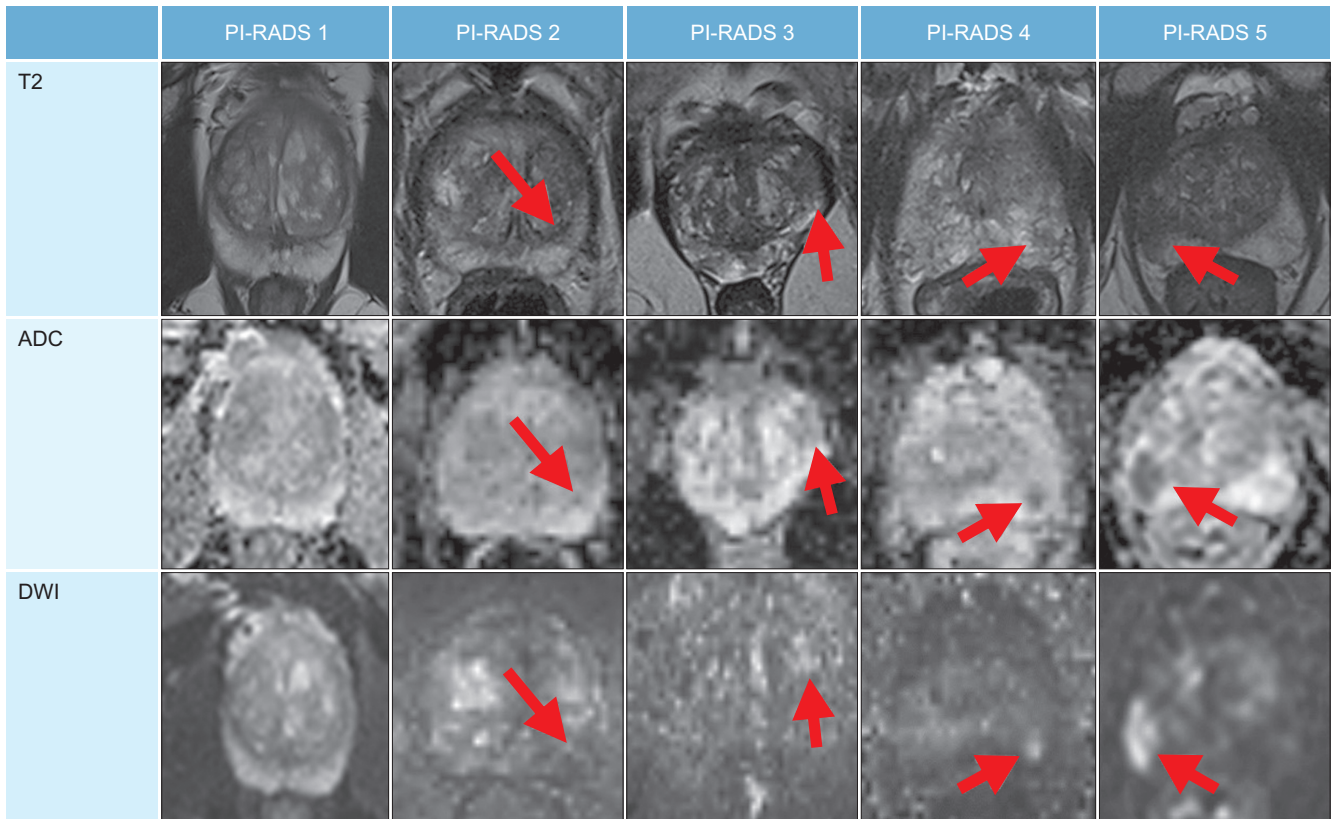
Fig. 1. Examples of lesions (marked by the arrows) graded Prostate Imaging-Reporting and Data System (PI-RADS) 1 to 5 according to PI-RADS version 2.1. ADC: apparent diffusion coefficient, DWI: diffusion-weighted imaging.

before any prostate biopsy [14,15], it did receive some criticism. For example transperineal template biopsy was chosen as reference for presence of PC. However, in some patients SB was positive while template biopsy did not find PC leading to a specificity of histological analysis of SB of only 96%, thereby showing the weakness of this reference.

From other studies we now know, that small lesions, even if high grade, can be missed by mpMRI [16]. This shortcoming might have been missed due to the lack of whole-mount-sectioning. Following shortly thereafter was the publication of the Prospective Randomized Evaluation of Celeboxib Integrated Safety *vs.* Ibuprofen or Naproxen (PRECISION) trial. Here, MRI-targeted biopsy (MRI-TB) in cases of suspicious lesions was randomized to SB. Initially set up as a non-inferiority trial, the MRI pathway had a significantly higher detection rate for csPC of 38% compared to 26% for SB [17]. Many prospective studies have compared detection rates of MRI-TB and SB [17-26], and a summary can be found in Table 1. The results of some studies that compared mpMRI to whole-mount section analysis is

shown in Table 2. While sensitivity differs substantially within the cohorts reported here (sensitivities ranging from 74.3% to 100%), an important finding is consistent in all of them, high sensitivity for csPC on a patient basis shows that mpMRI is a relatively reliable pretest before prostate biopsy [16,27-34]. Equally important with the ongoing discussions on overdetection and overtreatment of PC is the limited sensitivity for low grade PC. With growing acceptance of active surveillance as the preferred approach for GG 1 PC the reduced detection rates of mpMRI is often seen as an additional advantage, and therefore omitting SB may be advantageous. On the other hand, Rouvière et al [26] found that SB and MRI-TB equally contribute to the detection rate of csPC. In their study csPC was detected by SB only, MRI-TB only, or by both approaches in 14%, 20%, and 66% of cases, respectively.

4. Patients with negative systematic biopsy and persistent suspicion for prostate cancer

The diagnostic pathway for patients after initial

Table 1. Prospective studies comparing PC detection rates of TB and SB

| First author | Year of publication | Subjects (n) | TB (n) | SB (n) | Detection rate | | | | Techniques of biopsy guidance |
| | | | | | Any PC | | csPC | | |
					SB (%)	MRI-TB (%)	SB (%)	MRI-TB (%)	
Park [21]	2011	85	44	41	9.8	29.5	-	-	Cognitive fusion
Panebianco [22]	2015	1,140	570	570	37.7	73.2	36.8	71.9	Cognitive fusion
Arsov [23]	2015	104	104	104	35	34	25	26	Software fusion
Baco [18]	2016	175	86	89	54	59	49	44	Software fusion
Tonttila [19]	2016	130	53	60	57	64	45	55	Cognitive fusion
Taverna [24]	2016	200	100	100	26	24	12	15	Cognitive fusion
Porpiglia [20]	2017	212	107	105	29.5	50.5	18.1	43.9	Software fusion
Kasivisvanathan [17]	2018	500	252	248	48	46.8	26	38	Cognitive or software fusion
van der Leest [25]	2019	626	626	626	45	39.5	23.3	25.4	In bore
Rouvière [26]	2019	251	251	251	52.2	41.4	29.9	32.3	Cognitive fusion

PC: prostate cancer, TB: MRI-targeted biopsy, SB: systematic biopsy, n: number of patients included in the study, MRI: magnetic resonance imaging, csPC: clinically significant prostate cancer.

Table 2. Sensitivity of mpMRI of the prostate with whole-mount-sectioning as reference

| First author | Year of publication | Patients (n) | Histologic lesions (n) | Sensitivity | | | |
| | | | | Any prostate cancer | | csPC | |
				Patients (%)	Lesions (%)	Patients (%)	Lesions (%)
Bratan [27]	2013	175	362	-	53–59	-	85–88
Le [34]	2015	122	283	80	47	-	72
Chung [29]	2018	455	-	46.8	-	-	-
Borofsky [30]	2018	100	162	-	-	99	84
Kim [32]	2018	730		73.2		74.3	
Asvadi [33]	2018	425	425	76	-	-	-
Kido [28]	2019	95	136	-	-	83.2	72.1
Lee [31]	2019	107	237	100	46	100	75.5
Ito [16]	2020	136	274	89.7	39.4	95.6	56

mpMRI: multiparametric magnetic resonance imaging, n: number of patients included in the study, csPC: clinically significant prostate cancer.

negative SB has been a matter of intense discussion and controversy. Prior to the era of mpMRI, saturation biopsy in cases of persistent suspicion had been the preferred approach due to lack of alternatives. Since the introduction of mpMRI and MRI-TB, many studies have been performed in this clinical setting. The largest retrospective analysis was published by Hansen et al [35]. In 70.4% of all patients (343/487) where there was at least one lesion of PI-RADS ≥3, using 24 core SB as the reference, MRI-TB had a negative predictive value of 92% and 99% for csPC defined as GG ≥2 or GG ≥3, respectively [35]. These results have been confirmed by several studies [36-40], ans a summary can be found in Table 3.

Many clinical societies have since included a recom-

mendation for performing mpMRI after an initial negative SB and persistent suspicion for PC [14]. Furthermore, while the role of additional SB during MRI-TB as an initial biopsy is still unclear, MRI-TB after a previous negative SB seems to be sufficient for the detection of csPC. Studies on this issue have shown that tumors found exclusively by SB were mostly GG 1 and not considered clinically significant, and SB added only 2.3% to the detection rate by SB according to a Cochrane meta-analysis [41].

This data resulted in a strong recommendation by most guidelines to perform an mpMRI after negative SB and persistent suspicion for PC [14].

Table 3. Studies evaluating the diagnostic accuracy of mpMRI in patients with prior negative prostate biopsy

First author	Year of publication	Patients (n)	Suspicious MRI	Histological reference	Sensitivity of MRI-TB	PPV of MRI	NPV of MRI	Definition csPC
Abd-Alazeez [36]	2014	54	54 (100%)[a]	Transperineal template	76%		92%	≥GG 2
Hansen [38]	2016	295	204 (69%)[a]	24 core systematic	-	91%	91%	≥GG 2
Hansen [35]	2017	487	343 (70.4%)[b]	24 core systematic	-	40%	92%	≥GG 2
Tsivian [40]	2017	50	41 (82%)[b]	Transperineal template	-	51%	100%	≥GG 2
Mortezavi [39]	2018	86	50 (58.1%)[b]	Transperineal saturation	53.90%	42%	86.1%	≥GG 2
Dal Moro [37]	2019	123	101 (82.1%)[a]	Saturation biopsy	100%		100%	≥GG 2

Suspicious findings on mpMRI were compared to histological findings on biopsy to calculate sensitivity, PPV and NPV for mpMRI.
mpMRI: multiparametric magnetic resonance imaging, n: number of patients included in the study, MRI: magnetic resonance imaging, TB: MRI-targeted biopsy, PPV: positive predictive value, NPV: negative predictive value, csPC: clinically significant prostate cancer GG: Gleason Group.
[a]Suspicion defined as Prostate Imaging-Reporting and Data System 3–5. [b]Suspicion defined as Likert score 3–5.

5. Planning of focal therapy

The promising results of mpMRI in the pre-biopsy setting have led to a wide adoption of local staging. In the field of focal therapy which is still mostly considered experimental, several consensus statements have underlined the importance of mpMRI in planning focal therapy and during follow-up [42,43]. This has led to the inclusion of mpMRI in many protocols of studies investigating focal therapy for PC [44]. While this adoption is supported by the high detection rate of MRI-TB and SB, sensitivity on a lesion basis is not comparably high. In recent studies, detection rates on a lesion basis for any PC and csPC vary between 39% to 59% and 56% to 88%, respectively [16,27-34]. A summary of studies on this issue can be found in Table 2. The most important predictors of detection were size ≥0.5 mL and GG ≥3, while tumor location within the prostate did not show a significant difference [16]. The assessment of whether the treatment of mpMRI visible lesions is sufficient depends on which definition of csPC is applied. GG 2 is most commonly defined as intermediate risk and is therefore recommended for treatment. An mpMRI seems insufficient for single treatment guidance and should be supplemented by a template biopsy. Additionally, Le Nobin et al [45] reported, that mpMRI underestimates the size of lesions especially for higher cancer grades.

6. Prediction of locally advanced stages

To ensure satisfactory functional outcomes without limiting the oncological results a thorough assessment of the local disease stage is mandatory. The tools that are best evaluated to predict extracapsular extension (ECE) or seminal vesical invasion mostly rely on PSA-values and biopsy results. The Partin tables provide probabilities based on Gleason score, serum PSA levels and digital rectal examination (DRE) [46]. The reliability of these tools has repeatedly been assessed. For example Augustin et al [47] showed that the accuracy of the Partin tables for organ-confined disease depends upon the biopsy approach with an area under the curve (AUC), estimated by the receiver operating characteristic curve, in the initial biopsy setting of 0.73 and saturation biopsy (≥20 cores) of 0.585.

Yu et al [48] validated the Partin table tool for ECE in 11,185 patients resulting in an AUC of 0.62, while Bhojani et al [49] evaluated a cohort of 3,105 patients showing an AUC of 0.789. In summary a tool that relies solely on biopsy results, PSA and DRE does not seem to provide a satisfactory prediction of ECE.

These results have led to many studies which evaluated the use of mpMRI in this setting [50-54], which are summarized in Table 4.

For ECE Martini et al [54] found an AUC of 0.688 using mpMRI in their cohort of 561 patients. Radiographic assessments always depend on high quality images and the experience of the interpreter. Zanelli et al [55] showed that this applies to local staging for PC as well with a difference in sensitivity between any two radiologists that differs between 0.583 to 0.667 for pathological stage T3 disease. Ma et al [56] attempted to circumvent this limitation with an automated analysis after contouring of the prostate. Each half of the prostate was investigated separately with an AUC of 0.821 in the validation cohort of 90 prostate lobes. An external validation of these promising results has yet to be performed.

Counterintuitively, Zanelli et al [55] found that add-

Table 4. Studies evaluation sensitivity, specificity and AUC for local staging with multiparametric MRI in prostate cancer

First author	Year of publication	Subjects (n)	Extracapsular extension			Seminal vesical invasion			Any pT3 stage		
			Sensitivity	Specificity	AUC	Sensitivitiy	Specificity	AUC	Sensitivity	Specificity	AUC
de Rooij [50]	2016	5,681	0.57	0.91	-	-	-	-	-	-	-
de Rooij [50]	2016	5,677	-	-	-	0.58	0.96	-	-	-	-
de Rooij [50]	2016	4,001	-	-	-	-	-	-	0.61	0.88	-
Rayn [53]	2018	532	-	-	0.78	-	-	0.86	-	-	0.78
Martini [54]	2018	561	-	-	0.688	-	-	-	-	-	-
Gandaglia [51]	2019	614	0.25	0.93	-	0.21	0.98	-	-	-	-
Mehralivand [52]	2019	553	0.30	0.96	-	0.10	0.99	-	-	-	-

The assessment of experienced radiologist, blinded to the final pathology, were compared to prostatectomy specimen.
AUC: area under the curve, MRI: magnetic resonance imaging, n: number of specimens included in the study.

ing clinical scoring to mpMRI did not improve results in most combinations. Her group evaluated three different readers of the same images alone and in combination with Partin tables and Cancer of the Prostate Risk Assessment (CAPRA) scores. With an AUC of 0.73–0.75 for mpMRI alone CAPRA scoring improved the AUCs of two readers to 0.76. The remaining combinations did not provide any benefit [55]. Feng et al [57] showed significant improvement of the AUC of clinical assessment tools by adding mpMRI leading to an AUC of 0.92 compared to 0.85 for Partin tables alone.

7. Molecular features of tumors not visible by multiparametric magnetic resonance imaging

Some PC lesions were found to be missed by mpMRI in the aforementioned studies. While some of these cases might be explained by low grade cancer or small tumor volume, some patients presenting with high grade PC do not have visible lesions on mpMRI.

A known reason for reduced visibility is a cribriform architecture found in some PC tumors. In a small cohort of 22 radical prostatectomy specimens, Truong et al [58] found that only 36% of all cribriform lesions (5/14) were visible on mpMRI. However, other studies have provided conflicting evidence. For example Tonttila et al [59] reported a visibility rate of lesions with any amount of cribriform or intraductal histology of 90.5% in a cohort of 95 radical prostatectomies. The sensitivity for lesions with this adverse histology is of utmost importance due to the recently reported worse outcome of these tumors, with higher rates of biochemical recurrence and metastasis after radical prostatectomy [60].

Houlahan et al [61] investigated the genome, transcriptome and histology of mpMRI-visible and invisible tumors. Detectable lesions showed a more aggressive molecular profile. In their study no single underlying factor for visibility could be identified, but rather a combination of several criteria including cribriform architecture or intraductal carcinoma, a higher amount of genomic alterations and overexpression of key noncoding transcripts, such as SCHLAP1 and snoRNAs [61]. A similar combination of different alterations has been described by Chua et al [62]. In their study, these alterations were also associated with higher risk of biochemical failure and metastasis.

8. Limitations of multiparametric magnetic resonance imaging

There are important limitations that must be discussed in the context of mpMRI. A DCE is required for a complete assessment according to PI-RADS, which may represent an issue for patients with decreased renal function. With an aging population more and more patients are receiving hip replacements or pacemakers which often lead to artifacts that limit the accuracy of reporting or represent a contraindication to perform an MRI altogether. Most importantly if an mpMRI becomes a requirement for every man with a suspicion of PC, then availability will become a growing problem.

For these challenges a combination of different solutions will be necessary.

Microultrasound is a new imaging modality that is currently being evaluated as a possible alternative. With a very high frequency and therefore high spatial resolution it has the potential to improve the sensitivity of ultrasound while maintaining high availability,

low cost and few contraindications [63-65].

Additionally, there is growing evidence that support protocols which rely less on mpMRI. Woo et al [9] performed a metanalysis showing that omitting DCE and by performing a biparametric MRI instead had similar sensitivity for csPC (0.87 *vs.* 0.86).

Finally, one should not ignore the power of diagnostic tools that have existed for many years: for a patient with a PSA of 100 ng/mL or cT4 by DRE the harm of postponed diagnosis will probably outweigh the benefit of a pre-biopsy mpMRI.

CONCLUSION

Within the last decade mpMRI of the prostate has become a standard of care method for detection of PC. Numerous studies have shown that the sensitivity for csPC on a patient level is high enough for it to be recommended in all guidelines.

The increasing importance of mpMRI as a diagnostic tool is also the result of the observation that mpMRI findings correlate with features of adverse outcome leading to negative results in many tumors that are considered as insignificant. However, a small proportion of high-grade tumors remain undetected by mpMRI. This is most relevant when considering focal therapy as a treatment option.

Conflict of Interest

Arnulf Stenzl and Tilman Todenhöfer are investigators in trials funded by Bayer AG. Other author has no potential conflicts of interest to disclose.

Author Contribution

Conceptualization: NH, TT. Data curation: NH, TT. Formal analysis: NH, TT. Funding acquisition: none. Investigation: NH, AS, TT. Methodology: NH, AS, TT. Project administration: TT. Resources: NH, AS, TT. Software: NH, TT. Supervision: TT. Validation: NH, TT. Visualization: NH, TT. Writing – original draft: NH, AS, TT. Writing – review & editing: NH, AS, TT.

REFERENCES

1. Hugosson J, Roobol MJ, Månsson M, Tammela TLJ, Zappa M, Nelen V, et al.; ERSPC investigators. A 16-yr follow-up of the European randomized study of screening for prostate cancer. Eur Urol 2019;76:43-51.

2. Pinsky PF, Prorok PC, Yu K, Kramer BS, Black A, Gohagan JK, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer 2017;123:592-9.

3. Tsodikov A, Gulati R, Etzioni R. Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. Ann Intern Med 2018;168:608-9.

4. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. Br J Cancer 2013;108:2205-40.

5. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al.; European Society of Urogenital Radiology. ESUR prostate MR guidelines 2012. Eur Radiol 2012;22:746-57.

6. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS prostate imaging - reporting and data system: 2015, version 2. Eur Urol 2016;69:16-40.

7. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. Eur Urol 2019;76:340-51.

8. Sathianathen NJ, Warlick CA. The use of magnetic resonance imaging in the prostate cancer primary diagnostic pathway: Is it ready for primetime? World J Mens Health 2018;36:223-9.

9. Woo S, Suh CH, Kim SY, Cho JY, Kim SH, Moon MH. Head-to-head comparison between biparametric and multiparametric MRI for the diagnosis of prostate cancer: a systematic review and meta-analysis. AJR Am J Roentgenol 2018;211:W226-41.

10. Pickersgill NA, Vetter JM, Andriole GL, Shetty AS, Fowler KJ, Mintz AJ, et al. Accuracy and variability of prostate multiparametric magnetic resonance imaging interpretation using the prostate imaging reporting and data system: a blinded comparison of radiologists. Eur Urol Focus 2020;6:267-72.

11. Padhani AR, Weinreb J, Rosenkrantz AB, Villeirs G, Turkbey B, Barentsz J. Prostate imaging-reporting and data system steering committee: PI-RADS v2 status update and future directions. Eur Urol 2019;75:385-96.

12. Khoo CC, Eldred-Evans D, Peters M, Bertoncelli Tanaka M, Noureldin M, Miah S, et al. Likert vs PI-RADS v2: a comparison of two radiological scoring systems for detection of clinically significant prostate cancer. BJU Int 2020;125:49-55.

13. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al.; PROMIS study group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study.

Lancet 2017;389:815-22.

14. Rouvière O, Schoots IG, Mottet N; EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel. Multiparametric magnetic resonance imaging before prostate biopsy: a chain is only as strong as its weakest link. Eur Urol 2019;75:889-90.

15. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management. London: National Institute for Health and Care Excellence; 2019.

16. Ito K, Furuta A, Kido A, Teramoto Y, Akamatsu S, Terada N, et al. Detectability of prostate cancer in different parts of the gland with 3-Tesla multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Int J Clin Oncol 2020;25:732-40.

17. Kasivisvanathan V, Emberton M, Moore CM. MRI-targeted biopsy for prostate-cancer diagnosis. N Engl J Med 2018;379:589-90.

18. Baco E, Rud E, Eri LM, Moen G, Vlatkovic L, Svindland A, et al. A randomized controlled trial to assess and compare the outcomes of two-core prostate biopsy guided by fused magnetic resonance and transrectal ultrasound images and traditional 12-core systematic biopsy. Eur Urol 2016;69:149-56.

19. Tonttila PP, Lantto J, Pääkkö E, Piippo U, Kauppila S, Lammentausta E, et al. Prebiopsy multiparametric magnetic resonance imaging for prostate cancer diagnosis in biopsy-naive men with suspected prostate cancer based on elevated prostate-specific antigen values: results from a randomized prospective blinded controlled trial. Eur Urol 2016;69:419-25.

20. Porpiglia F, Manfredi M, Mele F, Cossu M, Bollito E, Veltri A, et al. Diagnostic pathway with multiparametric magnetic resonance imaging versus standard pathway: results from a randomized prospective study in biopsy-naïve patients with suspected prostate cancer. Eur Urol 2017;72:282-8.

21. Park BK, Park JW, Park SY, Kim CK, Lee HM, Jeon SS, et al. Prospective evaluation of 3-T MRI performed before initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-specific antigen and no previous biopsy. AJR Am J Roentgenol 2011;197:W876-81.

22. Panebianco V, Barchetti F, Sciarra A, Ciardi A, Indino EL, Papalia R, et al. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. Urol Oncol 2015;33:17.e1-7.

23. Arsov C, Rabenalt R, Blondin D, Quentin M, Hiester A, Godehardt E, et al. Prospective randomized trial comparing magnetic resonance imaging (MRI)-guided in-bore biopsy to MRI-ultrasound fusion and transrectal ultrasound-guided prostate biopsy in patients with prior negative biopsies. Eur Urol 2015;68:713-20.

24. Taverna G, Bozzini G, Grizzi F, Seveso M, Mandressi A, Balzarini L, et al. Endorectal multiparametric 3-tesla magnetic resonance imaging associated with systematic cognitive biopsies does not increase prostate cancer detection rate: a randomized prospective trial. World J Urol 2016;34:797-803.

25. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve men with elevated prostate-specific antigen: a large prospective multicenter clinical study. Eur Urol 2019;75:570-8.

26. Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège-Lechevallier F, et al.; MRI-FIRST Investigators. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019;20:100-9.

27. Bratan F, Niaf E, Melodelima C, Chesnais AL, Souchon R, Mège-Lechevallier F, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. Eur Radiol 2013;23:2019-29.

28. Kido A, Tamada T, Kanomata N, Yamamoto A, Miyaji Y, Nagai A, et al. Multidimensional analysis of clinicopathological characteristics of false-negative clinically significant prostate cancers on multiparametric MRI of the prostate in Japanese men. Jpn J Radiol 2019;37:154-64.

29. Chung DY, Koh DH, Goh HJ, Kim MS, Lee JS, Jang WS, et al. Clinical significance and predictors of oncologic outcome after radical prostatectomy for invisible prostate cancer on multiparametric MRI. BMC Cancer 2018;18:1057.

30. Borofsky S, George AK, Gaur S, Bernardo M, Greer MD, Mertan FV, et al. What are we missing? False-negative cancers at multiparametric MR imaging of the prostate. Radiology 2018;286:186-95.

31. Lee CH, Ku JY, Park WY, Lee NK, Ha HK. Comparison of the accuracy of multiparametric magnetic resonance imaging (mpMRI) results with the final pathology findings for radical prostatectomy specimens in the detection of prostate cancer. Asia Pac J Clin Oncol 2019;15:e20-7.

32. Kim JJ, Byun SS, Lee SE, Lee HJ, Choe G, Hong SK. A negative multiparametric magnetic resonance imaging finding does not guarantee the absence of significant cancer among biopsy-proven prostate cancer patients: a real-life clinical experience. Int Urol Nephrol 2018;50:1989-97.

33. Asvadi NH, Afshari Mirak S, Mohammadian Bajgiran A, Khoshnoodi P, Wibulpolprasert P, Margolis D, et al. 3T multi-

parametric MR imaging, PIRADSv2-based detection of index prostate cancer lesions in the transition zone and the peripheral zone using whole mount histopathology as reference standard. Abdom Radiol (NY) 2018;43:3117-24.

34. Le JD, Tan N, Shkolyar E, Lu DY, Kwan L, Marks LS, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol 2015;67:569-76.

35. Hansen NL, Kesch C, Barrett T, Koo B, Radtke JP, Bonekamp D, et al. Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy. BJU Int 2017;120:631-8.

36. Abd-Alazeez M, Ahmed HU, Arya M, Charman SC, Anastasiadis E, Freeman A, et al. The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level: Can it rule out clinically significant prostate cancer? Urol Oncol 2014;32:45.e17-22.

37. Dal Moro F, Zecchini G, Morlacco A, Gardiman MP, Lacognata CS, Lauro A, et al. Does 1.5 T mpMRI play a definite role in detection of clinically significant prostate cancer? Findings from a prospective study comparing blind 24-core saturation and targeted biopsies with a novel data remodeling model. Aging Clin Exp Res 2019;31:115-23.

38. Hansen N, Patruno G, Wadhwa K, Gaziev G, Miano R, Barrett T, et al. Magnetic resonance and ultrasound image fusion supported transperineal prostate biopsy using the Ginsburg protocol: technique, learning points, and biopsy results. Eur Urol 2016;70:332-40.

39. Mortezavi A, Märzendorfer O, Donati OF, Rizzi G, Rupp NJ, Wettstein MS, et al. Diagnostic accuracy of multiparametric magnetic resonance imaging and fusion guided targeted biopsy evaluated by transperineal template saturation prostate biopsy for the detection and characterization of prostate cancer. J Urol 2018;200:309-18.

40. Tsivian M, Gupta RT, Tsivian E, Qi P, Mendez MH, Abern MR, et al. Assessing clinically significant prostate cancer: diagnostic properties of multiparametric magnetic resonance imaging compared to three-dimensional transperineal template mapping histopathology. Int J Urol 2017;24:137-43.

41. Drost FH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev 2019;4:CD012663.

42. van der Poel HG, van den Bergh RCN, Briers E, Cornford P, Govorov A, Henry AM, et al. Focal therapy in primary localised prostate cancer: the European Association of Urology position in 2018. Eur Urol 2018;74:84-91.

43. Scheltema MJ, Tay KJ, Postema AW, de Bruin DM, Feller J, Futterer JJ, et al. Utilization of multiparametric prostate magnetic resonance imaging in clinical practice and focal therapy: report from a Delphi consensus project. World J Urol 2017;35:695-701.

44. Azzouzi AR, Emberton M; PCM301 study investigators. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer – authors' reply. Lancet Oncol 2017;18:e188.

45. Le Nobin J, Rosenkrantz AB, Villers A, Orczyk C, Deng FM, Melamed J, et al. Image guided focal therapy for magnetic resonance imaging visible prostate cancer: defining a 3-dimensional treatment margin based on magnetic resonance imaging histology co-registration analysis. J Urol 2015;194:364-70.

46. Eifler JB, Feng Z, Lin BM, Partin MT, Humphreys EB, Han M, et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. BJU Int 2013;111:22-9.

47. Augustin H, Auprich M, Mannweiler S, Pachernegg O, Al-Ali BM, Pummer K. Prostate cancers detected by saturation repeat biopsy impairs the Partin tables' accuracy to predict final pathological stage. BJU Int 2012;110:363-8.

48. Yu JB, Makarov DV, Sharma R, Peschel RE, Partin AW, Gross CP. Validation of the partin nomogram for prostate cancer in a national sample. J Urol 2010;183:105-11.

49. Bhojani N, Salomon L, Capitanio U, Suardi N, Shariat SF, Jeldres C, et al. External validation of the updated partin tables in a cohort of French and Italian men. Int J Radiat Oncol Biol Phys 2009;73:347-52.

50. de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM. Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. Eur Urol 2016;70:233-45.

51. Gandaglia G, Ploussard G, Valerio M, Mattei A, Fiori C, Roumiguié M, et al. The key combined value of multiparametric magnetic resonance imaging, and magnetic resonance imaging-targeted and concomitant systematic biopsies for the prediction of adverse pathological features in prostate cancer patients undergoing radical prostatectomy. Eur Urol 2019. doi: 10.1016/j.eururo.2019.09.005 [Epub].

52. Mehralivand S, Shih JH, Harmon S, Smith C, Bloom J, Czarniecki M, et al. A grading system for the assessment of risk of extraprostatic extension of prostate cancer at multiparametric MRI. Radiology 2019;290:709-19.

53. Rayn KN, Bloom JB, Gold SA, Hale GR, Baiocco JA, Mehralivand S, et al. Added value of multiparametric magnetic resonance imaging to clinical nomograms for predicting adverse pathology in prostate cancer. J Urol 2018;200:1041-7.

54. Martini A, Gupta A, Lewis SC, Cumarasamy S, Haines KG 3rd, Briganti A, et al. Development and internal validation of a side-specific, multiparametric magnetic resonance imaging-based nomogram for the prediction of extracapsular extension of prostate cancer. BJU Int 2018;122:1025-33.

55. Zanelli E, Giannarini G, Cereser L, Zuiani C, Como G, Pizzolitto S, et al. Head-to-head comparison between multiparametric MRI, the partin tables, memorial sloan kettering cancer center nomogram, and CAPRA score in predicting extraprostatic cancer in patients undergoing radical prostatectomy. J Magn Reson Imaging 2019;50:1604-13.

56. Ma S, Xie H, Wang H, Yang J, Han C, Wang X, et al. Preoperative prediction of extracapsular extension: radiomics signature based on magnetic resonance imaging to stage prostate cancer. Mol Imaging Biol 2019. doi: 10.1007/s11307-019-01405-7 [Epub].

57. Feng TS, Sharif-Afshar AR, Wu J, Li Q, Luthringer D, Saouaf R, et al. Multiparametric MRI improves accuracy of clinical nomograms for predicting extracapsular extension of prostate cancer. Urology 2015;86:332-7.

58. Truong M, Hollenberg G, Weinberg E, Messing EM, Miyamoto H, Frye TP. Impact of Gleason subtype on prostate cancer detection using multiparametric magnetic resonance imaging: correlation with final histopathology. J Urol 2017;198:316-21.

59. Tonttila PP, Ahtikoski A, Kuisma M, Pääkkö E, Hirvikoski P, Vaarala MH. Multiparametric MRI prior to radical prostatectomy identifies intraductal and cribriform growth patterns in prostate cancer. BJU Int 2019;124:992-8.

60. Dong F, Yang P, Wang C, Wu S, Xiao Y, McDougal WS, et al. Architectural heterogeneity and cribriform pattern predict adverse clinical outcome for Gleason grade 4 prostatic adenocarcinoma. Am J Surg Pathol 2013;37:1855-61.

61. Houlahan KE, Salmasi A, Sadun TY, Pooli A, Felker ER, Livingstone J, et al. Molecular hallmarks of multiparametric magnetic resonance imaging visibility in prostate cancer. Eur Urol 2019;76:18-23.

62. Chua MLK, Lo W, Pintilie M, Murgic J, Lalonde E, Bhandari V, et al. A prostate cancer "nimbosus": genomic instability and SChLAP1 dysregulation underpin aggression of intraductal and cribriform subpathologies. Eur Urol 2017;72:665-74.

63. Abouassaly R, Klein EA, El-Shefai A, Stephenson A. Impact of using 29 MHz high-resolution micro-ultrasound in real-time targeting of transrectal prostate biopsies: initial experience. World J Urol 2020;38:1201-6.

64. Eure G, Fanney D, Lin J, Wodlinger B, Ghai S. Comparison of conventional transrectal ultrasound, magnetic resonance imaging, and micro-ultrasound for visualizing prostate cancer in an active surveillance population: a feasibility study. Can Urol Assoc J 2019;13:E70-7.

65. Lughezzani G, Saita A, Lazzeri M, Paciotti M, Maffei D, Lista G, et al. Comparison of the diagnostic accuracy of micro-ultrasound and magnetic resonance imaging/ultrasound fusion targeted biopsies for the diagnosis of clinically significant prostate cancer. Eur Urol Oncol 2019;2:329-32.