available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. x–y of this issue

Re: Andrew Vickers, Sigrid V. Carlsson, Matthew Cooperberg. Routine Use of Magnetic Resonance Imaging for Early Detection of Prostate Cancer Is Not Justified by the Clinical Trial Evidence. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.04.016

Prebiopsy MRI: Through the Looking Glass

A diagnostic test can be defined as any test used to determine the presence, nature, or severity of a particular condition. In our technology-driven era, we may like to believe that the best diagnostic test is the one that provides the most details with the highest accuracy for the condition being investigated. However, the most sophisticated and precise test is useless if its results do not change patient management or improve relevant outcomes. In other words, it is the physician's responsibility to define the right level of detail of the diagnostic test, beyond which further magnification does not result in additional clinical consequences. This dilemma applies to many diagnostic tests used in urological practice (Does ultrasensitive prostate-specific antigen [PSA] detect relevant biochemical recurrence? Does novel imaging detect relevant metastasis?). It also applies to developments in prostate biopsy indication and procedure. Is the development aimed at providing the most accurate representation of the tissue of the whole gland, and particularly of the different prostate cancer (PCa) foci that may be present? Or is it (only) aimed at retrieving the necessary information to adequately risk stratify a patient for clinical decision-making?

In their Platinum Opinion paper, Vickers et al [1] argue that routinely performing magnetic resonance imaging (MRI) before a first set of prostate biopsies is not justified, which is in contradiction to clinical practice guidelines that now recommend using MRI in this setting on the basis of level 1 evidence [2]. Two main arguments against the use of MRI are provided: systematic biopsy (SB) provides sufficient detection of clinically significant PCa (csPCa), and the use of MRI lesion–targeted biopsy (TB) induces a grade migration that may lead to overtreatment. Does our new looking glass mostly cause tunnel vision?

First, although SB maintains added value in the population of biopsy-naïve patients [3–5], it seems difficult to believe that it provides adequate detection of csPCa. In the Danish cohort cited by Vickers et al, among patients with negative SB, the true 20-yr PCa-specific mortality at 20 yr was 5.2% [6]. The rate of 0.7% cited must be interpreted with caution, as these data only relate to a subgroup of patients with PSA $<$ 10 ng/mL, and PSA measurements at diagnosis were available for only 22% of the cohort. In the Göteborg screening trial, for men with negative SB in the first screening round and PSA levels of 3–10 ng/ml the 20-yr cumulative PCa mortality was 0.6%; for those with PSA $>$ 10 ng/mL the PCa mortality was 21.4% [7]. Metastasis and PCa mortality do occur after negative SB and an imperfect diagnostic strategy may be a cause.

Second, there is no doubt that use of MRI and TB increases the detection of grade group $\geq$2 cancers [3–5,8,9]. We agree with Vickers et al that the use of a more sensitive test may induce stage/grade migration due to the Will Rogers effect (Fig. 1). A grade group 2 cancer only detected at TB is on average a different tumour to a grade group 2 lesion already found at SB; it is likely to be on average smaller (and if risk is a combination of grade and tumour size, also of lower risk). Notably, stage/grade migration constantly occurred during the last 50 yr as the biopsy indication and technique evolved from digital rectal examination–guided biopsy to PSA-based transrectal ultrasound (TRUS)-guided six-core (sextant) lateralised biopsy, to TRUS-guided 12-core (or more) biopsy. The 2005 International Society of Urological Pathology (ISUP) reclassification of the Gleason grading system into grade groups led to another grade migration.

But a stage/grade shift is not a reason to abandon the MRI looking glass and stick to blind sampling of the gland, because it does not rule out the chance that additional csPCa will also be detected after MRI and TB. Not all grade group $\geq$2 cancers detected by MRI/TB and missed by SB are insignificant cancers. Improved prostate mapping using MRI and TB, by providing a more sensitive test for ISUP score (one of the most robust predictors of clinical outcomes), is

DOI of original article: https://doi.org/10.1016/j.eururo.2020.04.016.
https://doi.org/10.1016/j.eururo.2020.06.005

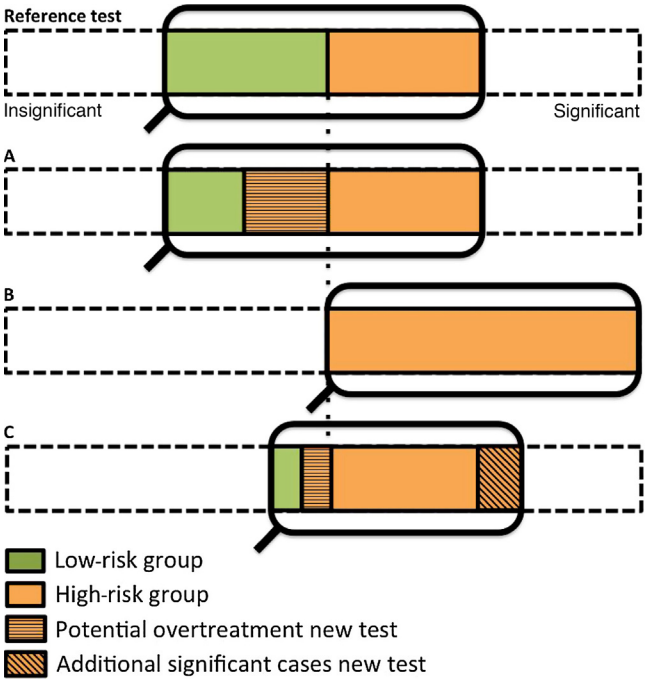

Fig. 1 – Schematic representation of different scenarios for a new diagnostic test versus a reference test. The low-risk group is considered for expectant management, while high-risk cases are considered for treatment. Reference test: established risk groups represent the significance of the disease. Insignificant cases are overdetected and significant cases are underdetected. Scenario A for the new test: stage shift only for the risk groups with no difference in the significance of the disease and a risk of overtreatment. Scenario B for the new test: no detection of insignificant disease and detection of only significant disease, which represents a perfect test. Scenario C for the new test: combined effect, with a lower rate of testing, a reduction in overdetection of insignificant disease, and improved detection of significant disease.

likely to provide additional parameters and allow further refinement of current risk groups using clinical outcomes of MRI-based diagnosed PCa [10].

While waiting for data for patients with TB-diagnosed PCa to mature, we believe that rather than rejecting MRI for biopsy-naïve patients, the urological community should adopt a pragmatic approach by mitigating the potential consequences of stage/grade migration. Thus, recognising that improved targeting could artificially inflate the ISUP grade of the tumours by focusing the sampling at areas of high-grade cancer, a recent ISUP consensus conference has already suggested the use of an aggregated ISUP grade summarising the results of all the targeted biopsy cores rather than the worst core from the same MRI-identified lesion [11]. In addition, results from TB should also not be interpreted as stand-alone but in the light of the clinical context, MRI parameters such as the apparent diffusion coefficient and tumour size, PSA density, and SB results. As a result, a greater proportion of grade group 2 cancers may become eligible for active surveillance [12].

An essential point not addressed by Vickers et al is that concordant studies suggest that a biopsy indication strategy combining high-quality MRI and clinical and biochemical data (such as PSA density) improves the selection for prostate biopsy [2]. TB has the potential to dramatically decrease the number of unnecessary biopsies and resulting postbiopsy complications. Although SB is currently still recommended in addition to TB, the strategy has the potential to also reduce diagnosis of grade group 1 cancers [2].

In conclusion, there is clear evidence that MRI and TB improve the detection of grade group $\geq$2 cancer over SB. This higher rate should be interpreted with care. Some detected cancers may correspond to small cancers as a result of stage/grade migration, while others may be aggressive tumours that would otherwise have been missed. The urological community should adapt risk classification in order to correctly separate the wheat from the chaff in the MRI era. Importantly, growing evidence suggests that MRI, in combination with clinical data, could also help in selecting patients with very low-risk cancer who do not need to undergo biopsy at all. The advantages of using prebiopsy MRI clearly outweigh the suggested harms.

Appendix A. Members of the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel who contributed to group authorship of this letter

Erik Briers, Hasselt, Belgium

Thomas Van den Broeck, Department of Urology, University Hospitals Leuven, and Laboratory of Molecular Endocrinology, KU Leuven, Leuven, Belgium

Philip Cornford, Royal Liverpool and Broadgreen Hospitals NHS Trust, Liverpool, UK

Marcus G. Cumberbatch, Academic Urology Unit, University of Sheffield, Sheffield, UK

Maria De Santis, Charite Universitätsmedizin, Berlin, Germany, and Department of Urology, Medical University of Vienna, Vienna, Austria

Stefano Fanti, Department of Nuclear Medicine, Policlinico S. Orsola, University of Bologna, Bologna, Italy

Nicola Fossati, Unit of Urology/Division of Oncology, Urological Research Institute, IRCCS Ospedale San Raffaele, and Università Vita-Salute San Raffaele, Milan, Italy

Giorgio Gandaglia, Unit of Urology/Division of Oncology, Urological Research Institute, IRCCS Ospedale San Raffaele, and Università Vita-Salute San Raffaele, Milan, Italy

Nikolaos Grivas, Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands

Jeremy Grummet, Department of Surgery, Central Clinical School, Monash University, Caulfield North, Victoria, Australia

Thomas B. Lam, Academic Urology Unit, University of Aberdeen, and Department of Urology, Aberdeen Royal Infirmary, Aberdeen, UK

Michael Lardas, Department of Urology, Leto Hospital, Athens, Greece

Matthew Liew, Department of Urology, Wrightington, Wigan and Leigh NHS Foundation Trust, Wigan, UK

Lisa Moris, Department of Urology, University Hospitals Leuven, and Laboratory of Molecular Endocrinology, KU Leuven, Leuven, Belgium

Please cite this article in press as: van den Bergh RCN, et al. Re: Andrew Vickers, Sigrid V. Carlsson, Matthew Cooperberg. Routine Use of Magnetic Resonance Imaging for Early Detection of Prostate Cancer Is Not Justified by the Clinical Trial Evidence. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.04.016. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.06.005

Malcolm D. Mason, Division of Cancer & Genetics, School of Medicine Cardiff University, Velindre Cancer Centre, Cardiff, UK

Nicolas Mottet, Department of Urology, University Hospital, St. Etienne, France

Daniela E. Oprea-Lager, Department of Radiology & Nuclear Medicine, Amsterdam University Medical Centers, VU University Medical Center, Amsterdam, The Netherlands

Guillaume Ploussard, Department of Urology, Clinique La Croix du Sud-St. Jean Languedoc, and Institut Universitaire du Cancer, Toulouse, France

Ivo G. Schoots, Department of Radiology & Nuclear Medicine, Amsterdam University Medical Centers, VU University Medical Center, Amsterdam, The Netherlands

Derya Tilki, Martini-Klinik Prostate Cancer Center and Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Henk G. van der Poel, Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands

Thomas Wiegel, Department of Radiation Oncology, University Hospital Ulm, Ulm, Germany

Peter-Paul M. Willemse, Department of Urology, University Hospital Groningen, Groningen, The Netherlands

Conflicts of interest: Erik Briers has received grant and research support from IPSEN and the European Association of Urology, and Bayer; is an ex officio board member for Europa UOMO; is an ethics committee and advisory group member for REQUITE; is a patient advisory board member for PAGMI; and is a member of SCA and EMA PCWP. Philip Cornford is a company consultant for Astellas, Ipsen, and Ferring; has received company speaker honoraria from Astellas, Janssen, Ipsen, and Pfizer; has participated in trials run by Ferring; and has received fellowships and travel grants from Astellas and Janssen. Maria De Santis is a company consultant for Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Eisai Inc., ESSA, Ferring, GSK, Incyte, IPSEN, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SeaGen, Shionogi, Synthon, Takeda, Teva, OncoGenex, and Sandoz; receives speaker honoraria from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Ferring, GSK, IPSEN, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, Synthon, and Takeda; participates in trials run by Technical University Munich, Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Eisai Inc., Ferring, GSK, IPSEN, Incyte, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SOTIO, and Cancer Research UK; and as a member of the EORTC GU group participates in various trials. She has received research grants from Pierre Fabre Oncologie and travel grants from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreaon, Ferring, GSK, IPSEN, Incyte, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SeaGen, Shionogi, Synthon, Takeda, and Teva/OncoGenex. Stefano Fanti is a company consultant for Bayer and ANMI; has received speaker honoraria from Bayer, Genzyme, ANMI, and GE Healthcare; and participates in trials by Amgen, Bayer, BMS, Genzyme, Janssen, Merck, and Novartis. Jeremy Grummet has received a speaker honorarium from Mundipharma, a travel grant from Astellas, and a research grant from Cancer Australia. He is the owner of MRI PRO Pty Ltd., an online training platform. Thomas B. Lam is a company consultant for and has received company speaker honoraria from Pfizer, GSK, Astellas, and IPSEN. Malcolm D. Mason is a company consultant for Ellipses Pharma and Oncotherics. Nicolas Mottet is a company consultant for Janssen, GE, BMS, Sanofi, and Astellas; has received speaker honoraria from Astellas, Pierre Fabre, Steba, Janssen, and Ferring; and has received fellowships and travel grants from Astellas, Ipsen, Sanofi, Janssen, and Roche. Derya Tilki has received a speaker honorarium from Astellas and a travel grant from Janssen. Henk G. van der Poel is a company consultant for Intuitive Surgical; has participated in trials for Astellas and Steba Biotech; and has received grant and research support from Astellas. Thomas Wiegel is an advisory board member for IPSEN; receives company speaker honoraria from IPSEN and Hexal; is a member of the Janssen Steering Committee; and has participated in the ATLAS/AUO trial. The remaining authors have nothing to disclose.'

References

[1] Vickers A, Carlsson SV, Cooperberg M. Routine use of magnetic resonance imaging for early detection of prostate cancer is not justified by the clinical trial evidence. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.04.016.

[2] Mottet N, Cornford P, van den Bergh RCN, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Arnhem, The Netherlands: European Association of Urology; 2020.

[3] Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev 2019;2019:CD012663.

[4] Rouviere O, Puech P, Renard-Penna R, et al. 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.

[5] van der Leest M, Cornel E, Israel B, 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-naive men with elevated prostate-specific antigen: a large prospective multicenter clinical study. Eur Urol 2019;75:570–8.

[6] Klemann N, Roder MA, Helgstrand JT, et al. Risk of prostate cancer diagnosis and mortality in men with a benign initial transrectal ultrasound-guided biopsy set: a population-based study. Lancet Oncol 2017;18:221–9.

[7] Palmstedt E, Mansson M, Franlund M, et al. Long-term outcomes for men in a prostate screening trial with an initial benign prostate biopsy: a population-based cohort. Eur Urol Oncol 2019;2:716–22.

[8] 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.

[9] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767–77.

[10] Ploussard G, Manceau C, Beauval JB, et al. Decreased accuracy of the prostate cancer EAU risk group classification in the era of imaging-guided diagnostic pathway: proposal for a new classification based on MRI-targeted biopsies and early oncologic outcomes after surgery. World J Urol. In press. https://doi.org/10.1007/s00345-019-03053-6.

[11] Van Leenders GJ, Van der Kwast T, Grignon D, et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. Am J Surg Pathol. In press.

[12] Ploussard G, Beauval JB, Lesourd M, et al. Active surveillance eligibility of MRI-positive patients with grade group 2 prostate cancer: a pathological study. World J Urol. In press. https://doi.org/10.1007/s00345-019-02973-7.

Please cite this article in press as: van den Bergh RCN, et al. Re: Andrew Vickers, Sigrid V. Carlsson, Matthew Cooperberg. Routine Use of Magnetic Resonance Imaging for Early Detection of Prostate Cancer Is Not Justified by the Clinical Trial Evidence. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.04.016. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.06.005

Roderick C.N. van den Bergh[a,*]
Olivier Rouvière[bc]
Theodorus van der Kwast[d]
on behalf of the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel[†]

[a]*Department of Urology, St. Antonius Hospital, Utrecht, The Netherlands*
[b]*Hospices Civils de Lyon, Department of Urinary and Vascular Imaging, Hôpital Edouard Herriot, Lyon, France*
[c]*Université de Lyon, Université Lyon 1, Faculté de Médecine Lyon Est, Lyon, France*
[d]*Department of Pathology, Erasmus University Medical Center, Rotterdam, The Netherlands*

*Corresponding author. Department of Urology, St. Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands.
Tel. +31 623 456800, Fax: +31 88 3203000.
E-mail addresses: roodvdb@hotmail.com (R.C. van den Bergh).
r.van.den.bergh@antoniusziekenhuis.nl (R.C. van den Bergh).
[†]Members of the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel who contributed to group authorship of this letter are listed in Appendix A.

June 4, 2020

Please cite this article in press as: van den Bergh RCN, et al. Re: Andrew Vickers, Sigrid V. Carlsson, Matthew Cooperberg. Routine Use of Magnetic Resonance Imaging for Early Detection of Prostate Cancer Is Not Justified by the Clinical Trial Evidence. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.04.016. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.06.005