

Patient Perspectives and Understanding of MRI-Directed Prostate Cancer

Diagnosis

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Multiparametric magnetic resonance imaging (mpMRI) has enhanced the risk stratification for men with suspected prostate cancer¹ and inevitable implementation challenges around pathway modification, capacity and quality control are well rehearsed.² Use of pre-biopsy prostate mpMRI is now well-established following publication of multiple Level 1 evidence trials,¹ however, views of men undergoing this pathway have not yet been explored, in-depth.

Some groups have started to explore the impact of this novel technology on men. Ullrich and colleagues surveyed a group of men in Germany (a proportion with prostate cancer, others without) on their views surrounding prostate mpMRI.³ The majority (68%) considered mpMRI to be useful for obtaining a prostate cancer diagnosis. However, only a minority of those surveyed (29%) had personally experienced mpMRI. Many who had not experienced mpMRI directly had little, if any, knowledge of the role of mpMRI in the new risk stratification process.³ Whilst a good start in understanding the impact on men, the work by Ullrich and colleagues does not give us enough detail to alter the manner in which this technology is both explained and delivered. Detailed exploration of men's perceptions on the use of mpMRI for prostate cancer diagnosis would provide valuable input on a number of remaining uncertainties, including:

What degree of accuracy of diagnosis do patients demand?

Pre-biopsy mpMRI detects the majority of significant prostate cancers, however, a small number (approximately 10–20%) are overlooked by this technique.⁴ As yet, the only reliable way of increasing detection rates is to offer men 5mm transperineal template sampling.¹ In PROMIS, the difference in detection rates of significant

disease between mpMRI and 5mm template sampling was 7% (17/230; 95% CI 4.4–12%).⁴ However, template sampling at this density is associated with known risks, principally, prolonged urinary retention (24%), detrimental impact on erectile function (decrease of IIEF-15 scores by 23%),⁵ and infection-related complications, however, these are lower than those of TRUS-guided biopsy (0% vs. 5%).⁶ Currently, we do not know the values and utilities that men express when choosing between the two, or the degree of error that they are willing to tolerate. Nor do we know the drivers in their decision-making, assuming they have access to valid information, presented in a manner that is easily understood.

Are men willing to forgo biopsy in the presence of a non-suspicious MRI?

Increasingly, men with ‘non-suspicious’ or ‘negative’ prostate mpMRI (i.e. Likert/PI-RADS scores 1–2) are offered omission or delay of immediate biopsy, on the basis of excellent sensitivity for significant disease.¹ We have recently demonstrated that this strategy is supported by favorable histopathological,⁴ molecular and genetic⁷ characteristics of mpMRI-invisible disease. However, as yet, it is not clear whether patients are willing to tolerate the incumbent risk of overlooking invisible significant cancer (approximately 10%) despite reassuring features,¹ or whether adjunctive strategies (e.g. use of PSA density thresholds, MDT discussion, or longitudinal PSA follow-up) would provide further security for them.

Is MRI-targeted prostate biopsy sufficient, or do patients seek concomitant systematic sampling?

Recent evidence has suggested that mpMRI-targeted biopsy detects more clinically significant prostate cancer than classical systematic TRUS-guided biopsy alone.^{1,4}

However, many clinicians still perform simultaneous systematic biopsies in addition to MRI-targeted biopsies, due to ongoing concern regarding mpMRI-invisible disease. Exploration of patient perceptions regarding biopsy strategy would elucidate whether men are supportive of MRI lesion-only targeting (with inherent risk of overlooking mpMRI-invisible cancer), or whether they would desire to have their entire prostate sampled, despite higher risks of detection of insignificant disease and biopsy-related side-effects.

What do we mean when we use the term ‘clinically significant’ prostate cancer?

There is no current, universally agreed definition of clinically significant prostate cancer (by urologists and patients alike). Ideally, such a definition would be calibrated on prognostic significance. In other words, prostate cancer that was deemed to be clinically significant might be associated with a 5% greater chance of resulting in a prostate cancer-related death, if left untreated. Instead, the community has landed on the presence of any Gleason pattern 4 (on prostate biopsy) as constituting clinical significance. The most common manifestation of ‘any’ Gleason pattern 4 is secondary pattern 4, with the proportion of pattern 4 constituting 10% or less of all the cancer present. It is worth noting, that cancer of this type was not associated with prostate cancer related-death in the 29-year update of the SPCG-4 study.⁸ As such, it would be interesting to speculate where patients, if asked, would place the bar on risk that they might deem to be clinically important or significant. Indeed, the definition of ‘significance’ is likely to vary from man-to-man, with some placing emphasis on quality-of-life, above longevity. It is now prudent for us to explore and recognise this, as our chosen diagnostic strategy is inherently linked to the definitions

chosen for disease significance. It is also worth reflecting that definitions of clinical significance are likely to differ between urologists and their patients, with surgeons likely favouring 'objective' metrics of significance (e.g. statistical likelihood of metastasis) and patients favouring 'subjective' values (e.g. careful balance of quantity and quality of life).

Are men willing to undergo 'biparametric' MRI without Level 1 evidence demonstrating equivalence?

Multiparametric MRI has traditionally involved delivery of gadolinium as part of the dynamic contrast enhanced (DCE) MRI sequence, however, recent evidence has suggested that the DCE component of mpMRI may be unnecessary for accurate pre-biopsy tumor detection. Furthermore, contrast administration is associated with a roster of potential challenges, including, gadolinium-allergy, cerebral deposition, systemic fibrosis, and technical difficulties in image acquisition and reporting. At present, we lack Level 1 evidence to support removal of the DCE sequence (to create so-called 'biparametric' MRI) for prostate cancer diagnosis, however, at this early pivotal stage, ascertaining patient perceptions of biparametric MRI would be informative, particularly for delivery of clinical trials in this field.

To address the paucity of research in this area, each of these aforementioned themes should now be explored at depth, using systematic, mixed-methods research, with anticipation of a wide-range of attitudes towards outcomes of diagnosis and treatment.⁸ This work would allow exploration of issues that truly matter to patients, and would provide a dedicated evidence-base, demonstrating views held by men who experience prostate mpMRI, and would inform further

development of the current clinical pathway and future research in this field – and for once, this would truly put patients at the centre of the diagnostic process.

References

1. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet*. 2017;389: 815–822
2. Kim SJ, Vickers AJ, Hu JC. Challenges in adopting level 1 evidence for multiparametric magnetic resonance imaging as a biomarker for prostate cancer screening. *JAMA Oncol*. 2018;4:1663–1664
3. Ullrich T, Schimmöller L, Oymanns M, Blondin D, Dietzel F, Kirchner J, et al. Current utilization and acceptance of multiparametric MRI in the diagnosis of prostate cancer. A regional survey. *Rofo*. 2018;190:419–426
4. Norris JM, Carmona Echeverria LM, Bott SRJ, Brown LC, Burns-Cox N, Dudderidge T, et al. What type of prostate cancer is systematically overlooked by multiparametric magnetic resonance imaging? an analysis from the PROMIS cohort. *Eur Urol*. 2020;78:163–170
5. Miah S, Eldred-Evans D, Simmons LAM, Shah TT, Kanthabalan A, Arya M, et al. Patient reported outcome measures for transperineal template prostate mapping biopsies in the PICTURE study. *J Urol*. 2018;200:1235–1240
6. Grummet JP, Weerakoon M, Huang S, Lawrentschuk N, Frydenberg M, Moon DA, et al. Sepsis and 'superbugs': should we favour the transperineal over the transrectal approach for prostate biopsy? *BJU Int*. 2014;114:384–388
7. Norris JM, Simpson BS, Parry MA, Allen C, Ball R, Freeman A, et al. Genetic landscape of prostate cancer conspicuity on multiparametric magnetic resonance imaging: a systematic review and bioinformatic analysis. *Eur Urol Open Sci*. 2020;20:37–47

8. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, et al.
Radical prostatectomy or watchful waiting in prostate cancer - 29-year follow-up. *N Engl J Med.* 2018;379:2319–2329
9. Norris JM, Kasivisvanathan V, Allen C, Ball R, Freeman A, Ghei M, et al.
Exploring patient views and acceptance of multiparametric magnetic resonance imaging for the investigation of suspected prostate cancer (the PACT study): a mixed-methods study protocol. *Methods Protoc.* 2020;3:26