

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/137710/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Norris, Joseph M., Carmona Echeverria, Lina M., Simpson, Benjamin S., Ball, Rhys, Freeman, Alex, Kelly, Daniel, Kirkham, Alex, Stavrinides, Vasilis, Whitaker, Hayley C. and Emberton, Mark 2021. Conspicuity of cribriform prostate cancer on multiparametric magnetic resonance imaging: the jury is still out. *BJU International* 127 (2), pp. 169-170. 10.1111/bju.15295

Publishers page: <http://dx.doi.org/10.1111/bju.15295>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



# Conspicuity of cribriform prostate cancer on multiparametric magnetic resonance imaging: the jury is still out

Joseph M. Norris<sup>a,b,\*</sup>, Lina M. Carmona Echeverria<sup>a</sup>, Benjamin S. Simpson<sup>a</sup>, Rhys Ball<sup>c</sup>, Alex Freeman<sup>c</sup>, Daniel Kelly<sup>d</sup>, Alex Kirkham<sup>e</sup>, Hayley C. Whitaker<sup>a</sup>, Mark Emberton<sup>a,b</sup>

<sup>a</sup> UCL Division of Surgery & Interventional Science, University College London, London, UK

<sup>b</sup> Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK

<sup>c</sup> Department of Pathology, University College London Hospitals NHS Foundation Trust, London, UK

<sup>d</sup> School of Healthcare Sciences, Cardiff University, Wales, UK

<sup>e</sup> Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK

\* Corresponding author. UCL Division of Surgery & Interventional Science, 3<sup>rd</sup> Floor, Charles Bell House, 43-45 Foley Street, London W1W 7TS, UK. Tel. +44 7724022171.

E-mail address: joseph.norris@ucl.ac.uk (J.M. Norris).

Article type: Research Letter.

Ethics: Not required.

Word count: 750 words.

Funding: Norris is funded by the Medical Research Council (MRC) (Grant Reference: MR/S00680X/1).

Keywords: Conspicuity; Cribriform; Multiparametric magnetic resonance imaging; Prostate cancer

Conflicts of Interest: Norris receives funding from the MRC. Simpson receives funding from the Rosetrees Trust. Whitaker receives funding from PCUK, the Urology Foundation and the Rosetrees Trust. Kirkham, Freeman and Emberton have stock interest in Nuada Medical Ltd. Emberton receives funding from NIHR-i4i, MRC, Sonacare Inc., Trod Medical, Cancer Vaccine Institute and Sophiris Biocorp for trials in prostate cancer. Emberton is a medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, GSK, Exact Imaging and Profound Medical. Travel allowance was previously provided from Sanofi Aventis, Astellas, GSK and Sonacare. Emberton is a proctor for HIFU with Sonacare Inc. and paid for training other surgeons in this procedure.

Abbreviations: T2W, T2-weighted imaging; ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; mpMRI, multiparametric magnetic resonance imaging; PI-RADS, Prostate Imaging–Reporting and Data System; PSAD, prostate specific antigen density.

Cribriform, from the Latin for 'sieve-like,' describes an aggressive prostate cancer pattern associated with poor prognosis, including biochemical recurrence after prostatectomy [1]. Following progressive integration of multiparametric magnetic resonance imaging (mpMRI) into risk stratification for suspected prostate cancer, there has been understandable concern that particular morphologies (including, intraductal, mucinous and cribriform) may have reduced visibility on mpMRI [2]. If undetected, mpMRI-invisible pathology may avoid biopsy interrogation, resulting in delayed presentation, management, and as such, adverse clinical outcome. However, evidence surrounding mpMRI conspicuity of cribriform disease is contradictory, and given the clinical importance of this phenomenon, warrants discussion.

The radiobiological mechanism of cribriform invisibility on mpMRI is unknown, however, overall reduced tissue density observed in cribriform cancer may partly explain this. Cribriform cancer is typified by numerous punched-out lumina, resulting in loosely-packed architecture and altered gland-to-stroma ratio. As such, lower density may result in less clearly-defined tumours on the anatomic T2-weighted (T2W) sequence. Furthermore, diffusion of water tissue may occur more readily in cribriform disease, resulting in reduced diffusion restriction, and thus, lower signal intensity on diffusion-dependent sequences, including diffusion-weighted imaging (DWI) and the apparent diffusion coefficient (ADC) map.

In a noteworthy study from Truong and colleagues [3], they took a cohort of men with suspected prostate cancer ( $n = 240$ ) and used a combination of biopsy and whole-mount prostatectomy pathology, correlated to mpMRI phenotype, to assess mpMRI visibility of cribriform disease. They compared cribriform detection by various biopsy approaches (MRI-targeted, systematic, and combined) and also compared lesion presence on mpMRI against prostatectomy, to infer that the majority of cribriform tumours (82.6%) were in fact non-visible to mpMRI.

However, findings from Truong [3] have recently been contradicted by three further studies [4–6]. Using a similar approach, Prendeville and colleagues [4] examined a cohort of men with suspected prostate cancer ( $n = 154$ ) who underwent pre-biopsy mpMRI followed by targeted and systematic biopsy. In this cohort, cribriform/intraductal cancer was found in 23 cases, of which 96% (22/23) were visible on mpMRI ( $p < 0.001$ ). Furthermore, they found additional evidence to support conspicuity of cribriform disease, specifically, significant association with high Prostate Imaging-Reporting and Data System v2 (PI-RADS) scores ( $p = 0.008$ ) and reduced ADC values ( $p = 0.005$ ). Next, Tonttila and colleagues [5] took another cohort of men with prostate cancer ( $n = 124$ ) and found that 71% of cases (89/124) contained cribriform or intraductal disease. Again, in contrast to Truong [3], they found that preoperative mpMRI identified 90.5% of tumours (86/95) containing cribriform or intraductal disease [5]. Lastly, Gao and colleagues [6] took a cohort of men with prostate cancer ( $n = 215$ ) and assessed presence of cribriform disease diagnosed on both biopsy and whole-mount prostatectomy specimens. In their cohort, 51.2% of men (110/215) had cribriform cancer, and when compared to men without cribriform, were noted to have greater levels of tumour mpMRI conspicuity, as denoted by higher PI-RADS v2 scores ( $p < 0.001$ ), mpMRI lesion size ( $p < 0.001$ ) and prostate specific antigen density (PSAD;  $p = 0.001$ ).

Differences in results from Truong [3] and the three subsequent trials [4–6] are considerable, and may be attributable to varied histopathological classification. Truong and colleagues drew attention to 'pure' cribriform tumours (that did not contain other patterns) [3], whilst the other investigators considered cribriform disease when mixed other morphologies, including, intraductal carcinoma [4,5], or simply any other cancer pattern [6]. Scientifically, analysis of pure cribriform is commendable, however, the latter approach

(assessing mixed disease) is arguably more pragmatic and representative of clinical practice. Furthermore, both cribriform and intraductal cancer are known to have similar prognostic profiles [1], and as such, may not require discretisation in the manner performed by Truong and colleagues [3].

So, how can this uncertainty be resolved? Two major solutions: generation of new trial data, or statistical summation of extant studies. A trial in which detailed mpMRI-correlated pathology accounted for both cribriform proportion and conspicuity (and the interrelation of these two features) would help bring clarity to this issue, but would have understandable methodological challenges. Alternatively, with an acceptable heterogeneity level, meta-analysis of extant trials would produce an overarching answer to this question, however, the small number of appropriate existing studies might limit this approach.

The majority of evidence now appears to suggest that cribriform cancer is reassuringly conspicuous on prostate mpMRI. However, given a persistent level of uncertainty, it seems prudent to produce a consensus on this issue, with the important diagnostic and treatment implications associated with potential non-detection of this aggressive disease entity.

### **Conflicts of Interest**

Norris receives funding from the MRC. Simpson receives funding from the Rosetrees Trust. Whitaker receives funding from PCUK, the Urology Foundation and the Rosetrees Trust. Kirkham, Freeman and Emberton have stock interest in Nuada Medical Ltd. Emberton receives funding from NIHR-i4i, MRC, Sonacare Inc., Trod Medical, Cancer Vaccine Institute and Sophiris Biocorp for trials in prostate cancer. Emberton is a medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, GSK, Exact Imaging and Profound Medical. Travel allowance was previously provided from Sanofi Aventis, Astellas, GSK and Sonacare. Emberton is a proctor for HIFU with Sonacare Inc. and paid for training other surgeons in this procedure.

### **Acknowledgements**

Joseph M. Norris would like to acknowledge funding from the Medical Research Council (MRC) (Grant Reference: MR/S00680X/1).

## References

- [1] Kweldam CF, Wildhagen MF, Steyerberg EW, et al. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. *Mod Pathol* 2015;28:457–64.
- [2] Norris JM, Carmona Echeverria LM, Bott SRJ, et al. What type of prostate cancer is systematically overlooked by multiparametric magnetic resonance imaging? an analysis from the PROMIS cohort. *Eur Urol* 2020 Aug;78:163–70.
- [3] Truong M, Feng C, Hollenberg G, et al. A comprehensive analysis of cribriform morphology on magnetic resonance imaging/ultrasound fusion biopsy correlated with radical prostatectomy specimens. *J Urol* 2018;199:106–13.
- [4] Prendeville S, Gertner M, Maganti M, et al. Role of magnetic resonance imaging targeted biopsy in detection of prostate cancer harboring adverse pathological features of intraductal carcinoma and invasive cribriform carcinoma. *J Urol* 2018;200:104–13.
- [5] Tonttila PP, Ahtikoski A, Kuisma M, et al. Multiparametric MRI prior to radical prostatectomy identifies intraductal and cribriform growth patterns in prostate cancer. *BJU Int* 2019;124:992–8.
- [6] Gao J, Zhang Q, Fu Y, et al. Combined clinical characteristics and multiparametric MRI parameters for prediction of cribriform morphology in intermediate-risk prostate cancer patients. *Urol Oncol* 2020;38:216–24.