Prostate cancer visibility on multiparametric magnetic resonance imaging: high Gleason grade and increased tumour volume are not the only important histopathological features

Joseph M. Norris,[1,2,3*] Lina M. Carmona Echeverria,[1,3*] Benjamin S. Simpson,[1] Clare Allen,[4] Rhys Ball,[5] Veeru Kasivisvanathan,[1,2,3] Daniel Kelly,[6] Alex Kirkham,[4] Hayley C. Whitaker,[1] Alex Freeman,[5] Mark Emberton[1,2]

**joint first-name authors*

[1] UCL Division of Surgery & Interventional Science, University College London, London, UK

[2] London Deanery of Urology, London, UK

[3] Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK

[4] Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK

[5] Department of Pathology, University College London Hospitals NHS Foundation Trust, London, UK

[6] School of Healthcare Sciences, Cardiff University, Wales, UK

Correspondence to: Mr Joseph M. Norris BSc (Hons), MSc, BM BS, MRCS (Eng)

MRC Clinical Research Training Fellow, University College London

UCL Division of Surgery & Interventional Science, London, UK, W1W 7TS

Email: joseph.norris@ucl.ac.uk Phone: +44 7724022171 ORCID: 0000-0003-2294-0303

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Abbreviations: ADC, apparent diffusion coefficient; AE1/AE3, anti-pan cytokeratin; CD31, cluster of differentiation 31; DWI, diffusion weighted imaging; H&E, haematoxylin and eosin; mm, millimetre; mpMRI, multiparametric magnetic resonance imaging; *n*, number; *p*, probability value; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate serum antigen; SIR, signal intensity ratio; T2W, T2-weighted; vs., versus.

Gleason grade and tumour volume are strong determinants of prostate cancer conspicuity on multiparametric MRI (mpMRI) [1]. This is manifest by the high diagnostic sensitivity afforded by mpMRI for detection of 'clinically significant' disease, when significance is histopathologically defined by Gleason grade and cancer core length (within a biopsy core, as a proxy for tumour size). However, there is growing evidence to suggest that grade and size are not the only histopathological features that influence tumour visibility, or invisibility, on mpMRI.

Recently, Miyai and colleagues took a cohort of men undergoing radical prostatectomy (n = 59) for prostate cancer, and analysed the histopathological factors affecting tumour conspicuity on mpMRI. They standardised for tumour size, but not Gleason grade, and classified tumours as mpMRI-visible (PI-RADS score 3-5) or mpMRI-invisible (PI-RADS score 1-2). They then used a combination of expert pathological review, and semi-automated imaging analysis of cytokeratin (AE1/AE3) stained slides, to assess proportions of key histological components between the two groups. They found that mpMRI-visible tumours appeared to have higher 'architectural density' than mpMRI-invisible tumours, with an increased proportion of cancer cells (60.9% vs. 42.7%, $p < 0.0001$), a decreased proportion of stroma (33.8% vs. 45.1%, $p = 0.00089$), and a decreased proportion of luminal spaces (5.2% vs. 12.2%, $p < 0.0001$). Interestingly, despite not matching for cancer grade, they found no significant difference between Gleason grade group, or percentage of Gleason pattern 4, between mpMRI-visible and mpMRI-invisible tumours; however, these findings were limited by small sample size and radical prostatectomy population.

In another study, Borren and colleagues used a previously developed logistic regression model to calculate voxel-wise tumour probability and then correlated this with whole mount radical prostatectomy specimens (n = 12) [3]. They defined tumour voxels as mpMRI-visible (hypointense T2-weighted [T2W] images, low values on the apparent diffusion coefficient [ADC] map, and high values on K^{trans}) or mpMRI-invisible (non-hypointense T2W, high ADC, and low K^{trans}). Cell density was derived from digital scans of haematoxylin and eosin (H&E) slides, and anti-CD31 antibodies were used to assess microvessel density. They found that mpMRI-visible tumours tended to have higher density in both domains, compared to mpMRI-invisible tumours (cell density: 3560 cells/mm^2 vs 2910 cells/mm^2; microvessel density: 115 vessels/mm^2 vs 90 vessels/mm^2). Additionally, they found that the cellular and vascular density of mpMRI-invisible tumours was similar to that of benign peripheral zone tissue, perhaps alluding to potential mechanisms of tumour invisibility on mpMRI, especially on sequences reliant upon tissue density and diffusion of water (for example, the diffusion weighted imaging [DWI] sequence). These findings reiterate the conclusions from Miyai, stressing the probable importance that tissue density plays in prostate cancer conspicuity of mpMRI; however, the significance this has on diagnosis or prognosis, has not yet been explored.

In addition to tissue density, it appears that the histopathological subtype of prostate cancer also plays an important role in mpMRI-conspicuity. Ductal prostate cancer is a rare, aggressive and low PSA secreting subtype, that histopathologically may resemble endometrial uterine carcinoma, and appears to have a tendency to be mpMRI-occult. Schieda and colleagues investigated this by comparing the T2 signal intensity ratios (T2-SIRs) of various prostate cancers (including ductal) with the T2-SIRs of obturator internus muscles and normal peripheral zone tissue in men undergoing radical prostatectomy for prostate cancer (n = 11) [4]. They found a significant difference between T2-SIRs of ductal prostate cancer and traditional high-grade prostate cancer (T2-SIRs for muscle: 3.60 vs. 2.68 $p = 0.003$; T2-SIRs for normal peripheral zone: 0.66 vs 0.46, $p = 0.004$). However, they found no significant difference in T2-SIRs between ductal prostate cancer and traditional low-grade prostate cancer (T2-SIRs for muscle: 3.60 vs. 3.95, $p = 0.52$; T2-SIRs

for normal peripheral zone: 0.66 vs 0.73, p = 0.39) implying that ductal carcinoma may have a seemingly benign (or low-grade) appearance on the T2W sequence, which may account, in part, for mpMRI-inconspicuity.

Cribriform prostate cancer is another aggressive histopathological pattern that also appears to have an mpMRI-occult phenotype. To examine this, Truong and colleagues took 83 tumours from radical prostatectomy specimens (n = 22) and classed them as mpMRI-visible (PI-RADS score 3-5) or mpMRI-invisible (PI-RADS score 1-2) [5]. Within their cohort, the majority of cribriform pattern prostate cancers were mpMRI-invisible (66% vs 34%) and the size threshold for mpMRI-visibility was higher for cribriform tumours than for other architectural patterns. However, in contrast, Tonttila and colleagues showed that cribriform prostate cancer may in fact be mpMRI-visible [6]. They examined a cohort of men undergoing radical prostatectomy for prostate cancer (n = 124) and found that 89 of 124 cases (71%) contained cribriform or ductal pattern prostate cancer. Surprisingly, they found that preoperative mpMRI identified 86 of 95 tumours (90.5%) that contained any cribriform or ductal pattern (sensitivity: 90.5%, CI 82.5-95.6). The stark discrepancy in conclusions between Truong and Tonttila may be attributed to differences in histopathological reporting. In the Truong study, the 23 missed cribriform cases were pure cribriform pattern, whilst, in the Tonttila study, the nine missed cribriform cases actually contained less than 50% cribriform or ductal pattern (in other words, they were predominantly traditional pattern prostate cancers), suggesting that the true mpMRI-visibility status of these aggressive subtypes still warrants further evaluation.

In summary, it seems that we are now starting to appreciate the histopathological characteristics accounting for conspicuity of prostate cancer on mpMRI, beyond tumour grade and size (figure 1). The density of prostate tissue, and particular histopathological subtypes of prostate cancer appear to be important, however, further in-depth work is still required. Moreover, questions remain over the influence of concomitant prostatic features, such as luminal spaces, atrophy, inflammation, or pre-malignant changes. Finally, and perhaps most importantly, the diagnostic or prognostic implications of any of these histopathological facets have yet to be explored.

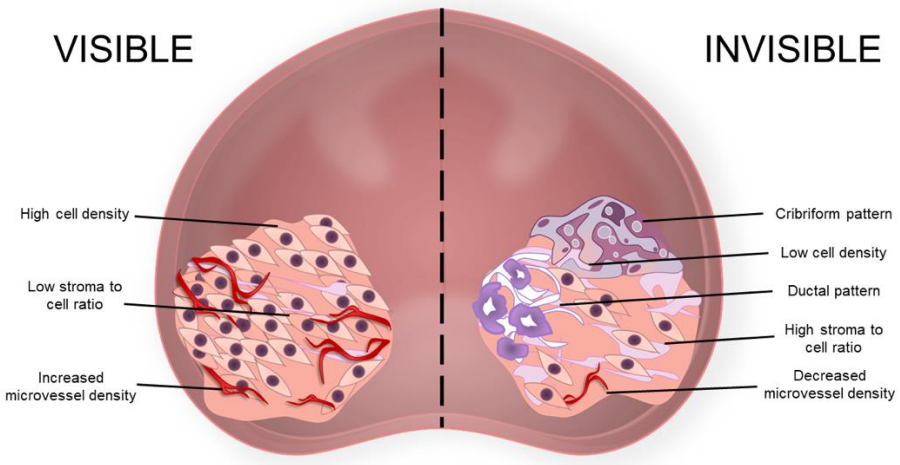

Figure 1. Summary of histopathological features of prostate cancer conspicuity on mpMRI.

Conflicts of Interest

None declared.

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