Prostate Cancer Visibility on Multiparametric Magnetic Resonance Imaging: High Gleason Grade and Increased Tumour Volume are Not the Only Important Histopathological Features

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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; PZ, peripheral zone; T2W, T2-weighted; vs., versus.

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Multiparametric magnetic resonance imaging (mpMRI) has excellent pre-biopsy sensitivity for detection of clinically significant prostate cancer, and this now places mpMRI at the forefront of our risk stratification process. Despite this, it appears that not all significant cancers are detected by mpMRI. We know that Gleason grade and tumour volume are strong determinants of conspicuity on mpMRI, which works to our benefit, as it means that small, low-grade cancers can be avoided, whilst high-risk tumours can be detected [1]. However, beyond this, there are likely additional factors that influence tumour visibility on mpMRI. Here, we explore histopathological features (beyond grade and volume) associated with tumour conspicuity on mpMRI.

Recently, Miyai and colleagues took a cohort of men undergoing radical prostatectomy (n=59) for prostate cancer and analysed histopathological aspects affecting tumour conspicuity on mpMRI. They restricted analysis to tumours measuring 10-20mm and classified cancers 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), decreased proportion of stroma (33.8% vs. 45.1%, p=0.00089) and decreased proportion of luminal spaces (5.2% vs. 12.2%, p<0.0001); which was reiterated by multivariate analysis. Interestingly, despite not matching for grade, they found no significant difference between grade group or percentage of Gleason pattern 4, between mpMRI-visible and mpMRI-invisible tumours; however, this is limited by small sample size and selection bias associated with radical prostatectomy. Association of increased tissue density and tumour visibility on mpMRI has biological plausibility – MRI-signal generated on the diffusion-weighted imaging (DWI) sequence reflects restricted diffusion of water, which would likely be further restricted in tissue with high architectural density.

In another study, Borren and colleagues used a previously developed logistic regression model to calculate voxel-wise tumour probability and correlated this with whole mount radical prostatectomy specimens (n=12) [3]. They defined tumour voxels as mpMRI-visible (hypointense T2-weighted [T2W], low values on apparent diffusion coefficient [ADC] mapping 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, cellular and vascular density

of mpMRI-invisible tumours was similar to benign peripheral zone tissue, alluding to potential mechanisms of tumour invisibility on mpMRI, especially on MRI sequences reliant upon tissue density and diffusion of water. These findings recapitulate conclusions from Miyai, stressing the importance that density plays in conspicuity on mpMRI. Again, there is biological plausibility in association of microvessel density and tumour visibility on mpMRI; in this instance, MRI-signal generated on the dynamic contrast enhanced (DCE) sequence reflects tumour vascularity, which would likely be greater in tissue with higher microvessel density.

Beyond density, it appears that histopathological-subtype also plays an important role in mpMRI-conspicuity. Ductal prostate cancer is a rare, aggressive and low PSA-secreting subtype that pathologically resembles uterine carcinoma and appears to have tendency toward mpMRI-invisibility. Schieda and colleagues investigated this by comparing the appearance of T2W MRI sequences of various cancers and normal tissues (including, ductal cancer, prostate peripheral zone [PZ] and muscle; *n*=11) [4]. They found significant differences in MRI-appearances of ductal cancer and traditional high-grade cancer (T2W-signal intensity of each compared to muscle: 3.60 vs. 2.68, p = 0.003, respectively; T2W-signal intensity of each compared to PZ: 0.66 vs 0.46, p = 0.004, respectively). However, using this approach, they found no significant differences between ductal cancer and traditional low-grade cancer (compared to muscle: 3.60 vs. 3.95, p=0.52, respectively; compared to PZ: 0.66 vs 0.73, p=0.39, respectively). This implies that ductal carcinoma may have a seemingly benign or indolent appearance on T2W MRI sequences, which may in part account for the mpMRI-invisibility, and again this could reflect lower levels of tissue density in this subtype.

Cribriform cancer is another aggressive histopathological pattern that also appears to have an mpMRI-invisible 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 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 71% of cases (89/124) contained cribriform or ductal pattern prostate cancer. Surprisingly, they found that preoperative mpMRI identified 90.5% of tumour (86/95) containing 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, we are beginning to appreciate the histopathological characteristics associated with prostate cancer conspicuity on mpMRI, beyond tumour grade and size (figure 1). Density of tissue and histopathological subtype appear to be crucially 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 and pre-malignant changes. Finally, and perhaps most importantly, the diagnostic and prognostic implications of these histopathological components have yet to be explored.

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

Conflicts of Interest

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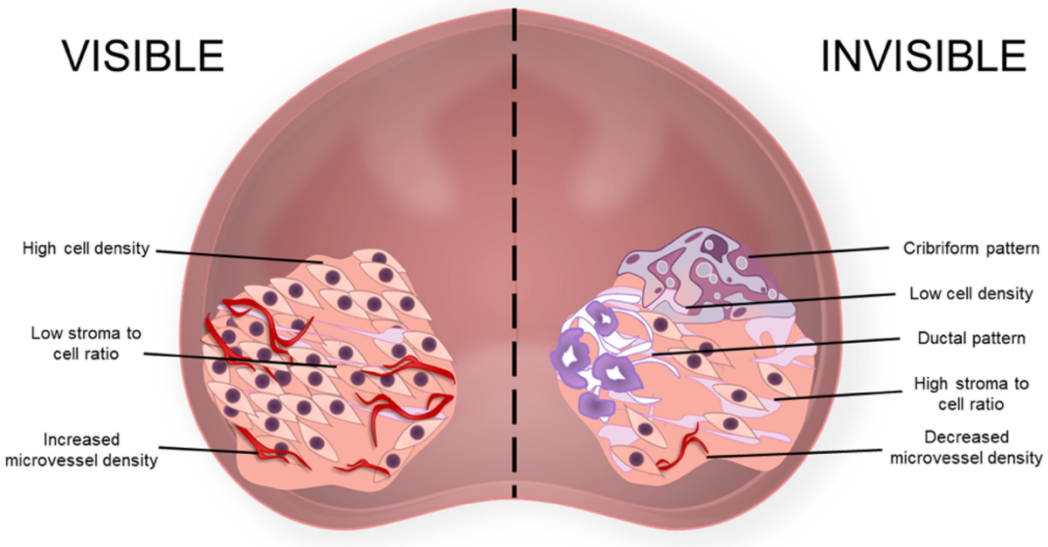

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